Approach to the Patient: Transgender Youth: Endocrine Considerations

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Compelling studies have demonstrated that "gender identity"—a person's inner sense of self as male, female, or occasionally a category other than male or female—is not simply a psychosocial construct, but likely reflects a complex interplay of biological, environmental, and cultural factors. An increasing number of preadolescents and adolescents, identifying as "transgender" (a transient or persistent identification with a gender different from their "natal gender"—ie, the gender that is assumed based on the physical sex characteristics present at birth), are seeking medical services to enable the development of physical characteristics consistent with their affirmed gender. Such services, including the use of agents to block endogenous puberty at Tanner stage 2 and subsequent use of cross-sex hormones, are based on longitudinal studies demonstrating that those individuals who were first identified as gender-dysphoric in early or middle childhood and who still meet the mental health criteria for being transgender at early puberty are likely to be transgender as adults. Furthermore, onset of puberty in transgender youth is often accompanied by increased "gender dysphoria"—clinically significant distress related to the incongruence between one's affirmed gender and one's "assigned (or natal) gender." Studies have shown that such distress may be ameliorated by a "gender-affirming" model of care. Although endocrinologists are familiar with concerns surrounding gender identity in patients with disorders of sex development, many providers are unfamiliar with the approach to the evaluation and management of transgender youth without a disorder of sex development. The goals of this article are to review studies that shed light on the biological underpinnings of gender identity, the epidemiology and natural history of transgenderism, current clinical practice guidelines for transgender youth, and limitations and challenges to optimal care. Prospective cohort studies focused on long-term safety and efficacy are needed to optimize medical and mental health care for transgender youth. (***J Clin Endocrinol Metab*** **99: 4379–4389, 2014)**

Case Presentations

Case 1

Patient 1 is a 13-year-old phenotypic male who was referred to the Child and Adolescent Gender Center (CAGC) Clinic with gender dysphoria. The parents report that as early as 3 years of age, the patient stated, "I am a girl" and asked why he had a penis if he was a girl. The patient subsequently insisted on a girl's name and the use of the female pronoun and would only wear girls' clothing. The parents acquiesced to the patient's requests while at home but initially insisted on a male presentation outside of the home. The patient experienced significant anxiety and depression throughout the middle childhood years, which worsened with the onset of puberty. Medical and mental health histories were otherwise unremarkable. By searching for information on the Internet, the family became aware of the CAGC and asked their pediatrician to initiate a referral so the patient could receive "pubertal blockers." After a series of mental health evaluations from a qualified child psychologist/gender specialist at the

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Abbreviations: AR, androgen receptor; BMD, bone mineral density; BSTc, central part of the bed nucleus of the stria terminalis; CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; DEXA, dual-energy x-ray absorptiometry; DSD, disorder of sex development; FTM, female-to-male; GID, gender identity disorder; GnRH, gonadotropin releasing hormone; INAH 3, interstitial nucleus of the anterior hypothalamus 3; MTF, male-to-female; SOC, standards of care; T, testosterone.

CAGC, it was determined that the patient had severe gender dysphoria and would likely benefit from putting puberty "on hold" to provide an additional period of time for self-awareness and understanding. In addition, the family interacted with a CAGC advocacy specialist who worked with the child's school to provide training for teachers, parents, and students to establish a safe and tolerant environment for the patient. Physical examination demonstrated normal male genitalia with Tanner stage 2 pubic hair and early pubertal testes (5 cc, bilaterally). The remainder of the physical examination was entirely within normal limits. The patient and family were advised of the potential risks (including likely effects on bone mineralization and on fertility) and benefits of pubertal suppression with gonadotropin releasing hormone (GnRH) agonists. Baseline laboratory studies confirmed that the patient was in early puberty. Serum calcium, phosphorous, alkaline phosphatase, and 25-hydroxyvitamin D were all in the normal range. Bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA) scan was 0.5 SD below that of an age-matched reference population for whole body, lumbar spine, and proximal femur. GnRH agonist treatment was prescribed; however, despite multiple appeals, this medication was denied by the family's insurance company.

Case 2

Patient 2 is a 16-year-old phenotypic female referred to the CAGC with long-standing gender dysphoria and a stated preference to be referred to with the male pronoun. In retrospect, the patient felt that he had "always been a boy" but did not reveal these feelings to family or friends for fear of rejection. The onset of puberty was accompanied by significant anxiety and depression, prompting referral to a therapist who was not knowledgeable about gender dysphoria in adolescents and thought the patient was likely "gay." The patient felt less anxious after decisions to wear a binder to hide the breasts and to wear loose-fitting "masculine" clothing. However, recurring monthly menses were accompanied by heightened anxiety. The patient became increasingly depressed and contemplated suicide. The patient eventually told his parents that he was not gay, but realized he was "transgender." The patient was subsequently referred to the CAGC for evaluation and management. Medical and mental health histories were otherwise unremarkable. Physical examination revealed Tanner 5 breasts and pubic hair and normal pubertal external female genitalia; the remainder of the physical examination was unremarkable. Mental health assessment confirmed that the patient was transgender with severe gender dysphoria. After detailed discussions with the medical team, in conjunction with ongoing mental health support, the patient and family opted for treatment with GnRH agonists to suppress the hypothalamic-pituitary-gonadal axis, with cessation of menses. Shortly thereafter, with continuing GnRH agonist therapy, the patient was treated with increasing doses of testosterone (T), achieving T blood levels in the mid-normal range for adult males. The patient's gender dysphoria and suicidal ideation fully resolved, and the depression was markedly reduced.

Background

Definitions

Although a person's "sex" refers to the physical attributes that characterize biological maleness or femaleness (eg, the genitalia), "gender identity" refers to a person's fundamental, inner sense of self as male or female (and is not always binary). The medical and mental health literature contain ample references to "gender assignment"/"natal gender" (1–3) on the one hand, and to "sex assignment"/"birth sex"/"sex of rearing" (2–5) on the other, sometimes leading to confusion. The gender assignment (or natal gender) is based on the "initial assignment as male or female," usually at birth (1), which, in turn, in the absence of a disorder of sex development (DSD), is typically based on the appearance of the external genitalia. Although sex of rearing can be assigned at birth, gender identity can only be assumed, and not, in fact, known until an individual achieves a particular level of psychological development and self-awareness. "Transgender" has been defined somewhat differently by the American Psychiatric Association and by the World Professional Association for Transgender Health (WPATH). In the former, transgender refers to a person who transiently or persistently identifies with a gender different from their natal gender (1). As defined in the standards of care (SOC) from WPATH, transgender (adjective) describes "a diverse group of individuals who cross or transcend culturally defined categories of gender" (6). In the WPATH SOC, "transsexual" (adjective) describes "individuals who seek to change or have changed their primary and/or secondary sex characteristics through feminizing or masculinizing medical interventions (hormones and/or surgery), typically accompanied by a permanent change in gender role" (6). Transsexual has also been used to describe a person who identifies as a member of the gender opposite to that assigned at birth (7, 8), but who has not necessarily sought medical and/or surgical interventions. In contrast, "gender-conforming" (sometimes used interchangeably with "cisgender") refers to a person whose gender identity is congruent with the natal gender. "Gender behavior"

(sometimes referred to as "gender role") is not equivalent to gender identity (7, 8). In fact, most youth with gender-nonconforming behavior will not turn out to have a transgender identity (9, 10). Previously referred to as "gender identity disorder" (GID) in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV, this term has now been replaced with "gender dysphoria" in DSM-5, with distinct diagnostic criteria for "gender dysphoria in children" and "gender dysphoria in adolescents and adults" (specifying with or without a DSD) (1). Replacing "disorder" with "dysphoria" depathologizes the transgender identity and focuses instead on dysphoria as the clinical problem (1). It should be noted that most patients with gender dysphoria do not have a DSD. Whether in children or adolescents, a core feature of gender dysphoria is "a marked incongruence between one's experienced/expressed gender and assigned gender" of at least 6-month duration (1). "Sexual identity" (or "sexual orientation") is often confused with "gender identity." Both are distinct aspects of human development. While sexual identity pertains to the individuals to whom one is sexually attracted, gender identity indicates who one "is" as male, female, or somewhere on the gender continuum. Just as gender-conforming individuals may have a heterosexual, homosexual, or bisexual orientation, the same holds true for transgender individuals.

Prevalence of transgenderism/transsexualism

Limited data exist regarding the prevalence of transgenderism/transsexualism. Recent data for natal adult males suggest a prevalence ranging from 1:7000 to 1:20 000, and for natal adult females a prevalence ranging from 1:33 000 to 1:50 000, and these are thought to represent "modest underestimates" (1). In The Netherlands, among the population age 15 years and older, a prevalence of 1:11 900 for male-to-female (MTF) and 1:30 400 for female-to-male (FTM) transsexualism has been reported (11). Such data were derived from patients diagnosed as transsexual by mental health professionals (11). Prevalence estimates in Singapore and Thailand were significantly higher (12, 13). Equivalent studies in North America have not yet been reported. However, a recent report from Massachusetts suggests that the prevalence of transgenderism may be more common than previously thought. In a survey of 18 to 64 year olds (n = 28 662) in a "representative household sample" carried out between 2007 and 2009, participants were presented with a commonly accepted definition of transgender and were provided with more detailed information if requested (14). Of those surveyed, 131 (0.5%) self-identified as transgender (14). Although prevalence data for younger transgender adolescents are lacking, multidisciplinary clinics for transgender youth and adolescents in Europe and North America have seen a steadily increasing demand for services in recent years (15–18), with a ratio of phenotypic males to females close to 1:1 (17).

Psychiatric co-morbidities and impact of family support

Transgender youth and adolescents are at significantly increased risk for life-threatening behaviors. Interviews of transgender youth in New York City (n = 55; MTF = 31, FTM = 24) demonstrated that 45% had experienced suicidal ideation, whereas 26% had attempted suicide (19). A recent report from Ontario, Canada, of transgender youth and young adults ages 16 to 24 years (n = 84) assessed the impact of the degree of parental support on mental health outcomes (20). Satisfaction with life and self-esteem were significantly greater in transgender youth whose parents were "very supportive" vs those whose parents were "somewhat to not at all supportive" (20). In addition, depression and suicide attempts were significantly decreased in transgender youth whose parents were supportive in comparison to those whose parents were not supportive (20). However, even with supportive parents, transgender youth still have a significant risk for depression (20), perhaps in part from their experience of transphobia from members of their communities and a feeling that they don't fit in.

Current Concepts of the Biology of Gender Identity

Numerous studies from a variety of biomedical disciplines— endocrine, genetic, and neuroanatomical— have begun to shed light on the biological underpinnings of gender identity. Results of these studies support the concept that gender identity is not simply a psychosocial construct, but likely reflects a complex interplay of biological, environmental, and cultural factors.

Although most transgender patients do not have a DSD, studies of gender identity outcome within the endocrine discipline have been principally carried out in patients with a variety of DSDs, primarily exploring the role of prenatal and postnatal androgens in gender identity development. For example, studies in 46,XX patients with "classical" congenital adrenal hyperplasia (CAH) caused by mutations in *CYP21A2*, resulting in 21-hydroxylase deficiency and varying degrees of genital masculinization, demonstrate a greater than expected number of patients with gender dysphoria, "atypical gender identity," or who were transgender (21–23). In an interview study of 43 patients ages 3–18 years, gender identity scores indicated

that 11.6% of patients had scores outside the range of control girls; no correlation was found between gender identity and degree of genital virilization or age of genital surgery (21). In a larger meta-analysis of 250 patients with 46,XX 21-hydroxylase deficiency leading to virilizing CAH and who were raised female, 94.8% of patients reported a female gender identity without gender dysphoria, whereas 5.2% reported either a male gender identity or gender dysphoria (22). As with an earlier study (21), there was no apparent correlation with the degree of genital masculinization and gender identity outcome (22). A study of adult women with classical 21-hydroxylase deficiency demonstrated a relationship between severity of disease and gender identity outcome. Of 42 patients with the salt-wasting form, three (7.1%) either had gender dysphoria or had changed gender to male; no gender dysphoria was seen in less severely affected individuals (23). These and other studies demonstrate that most 46,XX patients with virilizing CAH from 21-hydroxylase deficiency appear to have a female gender identity. However, the finding that 5.2–11.6% of such patients have gender dysphoria, an atypical gender identity, or are transgender would appear to be much more common than expected based on the reported prevalence of FTM transsexualism, implying that there is some role for prenatal/postnatal androgens in gender identity outcome (21–23). It is noteworthy that in 46,XX individuals with virilizing CAH from 21-hydroxylase deficiency, prenatal androgens are more likely to affect gender behavior and sexual orientation than gender identity (24, 25).

The potential effects of prenatal and postnatal androgen exposure on gender identity outcome and "gender role change" have also been explored in other hormonal and nonhormonal DSDs. For example, in 5α-reductase-2 deficiency among 46 XY individuals raised female, a gender role change from female to male (typically after puberty) was reported in 56–63% of the patients (26). Gender role changes from female to male were also reported in 39–64% of 46,XY individuals raised female with 17β-hydroxysteroid dehydrogenase-3 deficiency (26). In the largest series of patients with 5α-reductase-2 and 17β-hydroxysteroid dehydrogenase-3 deficiency reviewed by Cohen-Kettenis (26), individuals undergoing gender role change from female to male had intact testes, implying a potential role of prenatal as well as postnatal androgen exposure in gender identity outcome (27, 28). Among "nonhormonal" DSDs, gender identity outcome has been studied in patients with cloacal exstrophy, penile ablation, and penile agenesis (29, 30). A study of patients with 46,XY cloacal exstrophy reported that the majority (eight of 14) who had undergone neonatal sex reassignment to female (castration) subsequently declared a male gender identity and that two patients raised as males remained male (29). However, this study has been criticized for methodological concerns in the assessments of gender identity and gender dysphoria (30). A literature review of patients with 46,XY cloacal exstrophy found that of 51 patients assigned female, the majority (65%) were living as female, whereas 14% were living as female but with possible gender dysphoria, and approximately 22% were living as male (30). In addition, of 16 males with penile agenesis assigned female at birth and of seven males with penile ablation reassigned to female in infancy or early childhood, the majority were living as female (30).

Taken together, these studies of gender identity outcome in hormonal and nonhormonal DSDs indicate that gender identity is not solely dependent on prenatal and postnatal androgen exposure; however, the occurrence of gender identity change (in comparison to the natal gender) at a rate significantly higher than would be expected in the general population supports some role of prenatal and possibly postnatal androgens in gender identity development. It should be noted that potential limitations of all these survey/questionnaire-based studies to assess gender identity include a person's degree of self-awareness and one's willingness to disclose this information in the study context.

In contrast to studies that support some role of androgens in male gender identity, a case report in a 46,XY individual with complete androgen insensitivity syndrome (CAIS) challenges the concept that androgen receptor (AR) signaling is required for male gender identity development (31). Although individuals with CAIS typically have unambiguous female genitalia and a female gender identity, an individual with CAIS, associated with an unambiguous female phenotype and an *AR* gene mutation resulting in a premature stop codon, was found to have a male gender identity (31). The authors acknowledge that this patient may have had a postzygotic de novo *AR* gene mutation (the mother's DNA was not available) and could theoretically have brain mosaicism (with a normal AR in the brain); however, this was considered unlikely given that the same *AR* gene mutation was found in both the patient's blood and fibroblasts (31).

With respect to genetics and gender identity, heritability of transsexualism has been suggested from studies describing concordance of transsexualism in monozygotic twin pairs and in father-son and brother-sister pairs (32, 33). A larger study of survey responses from parents of twins (96 monozygotic pairs and 61 dizygotic pairs, ages 7–14 y) demonstrated a 2.3% prevalence of clinically significant GID (34) (based on DSM-IV criteria). These authors reported that heritability accounted for 62% of the variance for GID in their twin sample (34). A more recent

study supporting a role for genetic factors in gender identity outcome demonstrated a 39.1% concordance for GID (based on DSM-IV criteria) in 23 monozygotic female and male twin pairs, with no concordance in 21 same-sex dizygotic female and male twin pairs or in seven opposite-sex twin pairs (35). With respect to specific genes, association studies with transsexualism have been inconsistent and lacking strong statistical significance. In one study of 29 MTF transsexuals and 229 male controls, an association was found with a longer dinucleotide CA repeat in intron 5 of the *ERβ* gene in the transsexuals vs controls ($P = .03$), but no associations were found with polymorphisms in the *AR* (CAG repeat length) and the aromatase (*CYP19*) (TTTA repeat length) genes (36). A larger study (112 MTF transsexuals and 258 male controls) did not find an association of transsexualism with the *ERβ* gene or the *CYP19* gene but did find that the MTF transsexuals had a longer trinucleotide CAG repeat in exon 1 of the *AR* gene vs controls ($P = .04$) (37). A study from Japan (74 MTF and 168 FTM transsexuals with 106 male and 169 female controls), however, did not find any significant associations of transsexualism with polymorphisms in five candidate genes (the same polymorphisms noted above for *AR*, *CYP19*, and *ERβ*, as well as polymorphisms in *ERα* and the progesterone receptor) (38). A single study reported a positive association between a single nucleotide polymorphism in the *CYP17* gene and FTM transsexuals but not in MTF transsexuals (39).

With respect to a neurobiological basis for transsexualism, numerous studies have reported brain differences in transsexual individuals vs controls. It is well-established that there are "sexually-dimorphic" brain structures— eg, cell groups in the anterior hypothalamus (eg, interstitial nucleus of the anterior hypothalamus 3 [INAH 3]) and the central part of the bed nucleus of the stria terminalis (BSTc) that have different morphological characteristics in males and females (40, 41). In addition, there is some evidence for a "sexual-orientation dimorphic" brain structure. In 1991, it was reported that the INAH 3, which, in addition to being twice as large in heterosexual men vs women, was also found to be twice as large in heterosexual men vs homosexual men (40). This study was criticized for its relatively small sample size, potential influence of HIV on INAH 3 size, and the fact that the characterization for INAH 3 in the initial study was only for volume and not cell number. A subsequent study with a larger sample size (particularly for controls) confirmed that INAH 3 was significantly larger in presumed heterosexual males vs presumed heterosexual females and demonstrated that INAH 3 was not affected by HIV status (42). However, no difference was found in INAH 3 neuronal number based on sexual orientation, although there was a trend for decreased volume and increased cell density in the INAH 3 of homosexual vs heterosexual men (42).

Recent studies have supported the concept that there may also be "gender-dimorphic" brain structures, which segregate not according to physical sex but rather according to gender identity (41, 43). The BSTc, known to be larger in men than in women (independent of sexual orientation), had a female appearance in a group of MTF individuals (41, 43). Potential limitations of this study were a small sample size and the fact that many of the MTF individuals had received estrogen treatment (43). Of note, however, were the findings observed in several controls. A male with a feminizing adrenal tumor producing high blood levels of estrogen nonetheless had the male BSTc pattern, as did two T-deficient males who were orchidectomized for prostate cancer; furthermore, a female with a virilizing adrenal tumor producing high blood levels of androstenedione and T nonetheless had the female BSTc pattern, as did an 84-year-old MTF individual who had never received any estrogen or antiandrogen treatment (43). Despite the above-noted study limitations, the inclusion of critical controls with sex steroid variations and an untreated MTF individual lends some support to the concept that the observed BSTc differences in the transsexual individuals were intrinsic and not simply a consequence of sex steroid milieu (43). However, it should be noted that the sexually dimorphic differentiation of the BSTc in humans is not present until puberty, in contrast to rats, where such differences in the BST occur in the early postnatal period and apparently require perinatal differences in T levels (44, 45). Given that many transgender adolescents experience significant gender dysphoria before puberty (and before sex differences in BSTc volume emerge), the relationship between BSTc volume and gender identity would appear to be unclear.

Subsequent studies have explored brain differences in transsexual adults who had not yet received cross-sex hormone treatment (46–49). One study of gray matter volumes by magnetic resonance imaging noted that the right putamen volume was sexually dimorphic and reported that the volume of the right putamen in MTF individuals was larger than in control males and within the average range for control females (46). A subsequent study, however, did not confirm these findings but reported that the putamen volume in MTF individuals was smaller than in both male and female cisgender controls (49). With respect to sexually dimorphic white matter structures (eg, parts of the superior longitudinal fasciculus), magnetic resonance imaging studies using fractional anisotropy found that patterns in transsexual individuals were closer to individuals who had the same gender identity rather

than the same physical sex (47). In addition, in studies where hypothalamic blood flow was activated by smelling odorous steroids in a sexually dimorphic manner, the response in MTF individuals not yet treated with cross-sex hormones (estrogens) was closer to that of control women than control men (48). A potential limitation in the gray and white matter studies is related to brain functional plasticity. It has been demonstrated that changes in both white matter microstructure and gray matter can be induced by training/experience in healthy human adults (50, 51); thus, it would be difficult to know with certainty whether any observed brain differences between transgender and cisgender individuals are intrinsic or a consequence of experience.

Natural History of Transgenderism in Youth/Adolescents

Longitudinal studies have demonstrated that most gender-dysphoric prepubertal youth will no longer meet the mental health criteria for gender dysphoria once puberty has begun (9, 10). Although gender "fluidity" may be a contributing factor, the lack of persistence of gender dysphoria in most gender-dysphoric prepubertal youth undoubtedly reflects the heterogeneous nature of this group. In fact, many such individuals will turn out to be homosexual (natal males, in particular) rather than transgender (1, 5, 9, 10). Recent studies have attempted to identify factors that predict gender dysphoria "persisters" vs "desisters" (52). Persisters reported relatively greater degrees of gender dysphoria and were more likely to have experienced social transition (to their affirmed gender) during childhood (52). Furthermore, persisters "believed they were" the other sex, whereas desisters "wished they were" the other sex (52). The limitations in prediction of persistence, coupled with the observation that most gender-dysphoric children will not become transgender adolescents or adults, have led some investigators to promote efforts to encourage gender-dysphoric children to accept their natal gender (53). In contrast, a model of care that "affirms" a child's gender expression is thought to have a more optimal mental health outcome (54). Long-term outcome studies are needed to resolve these differences in approach to the care of gender-dysphoric prepubertal youth.

Diagnostic and Therapeutic Strategies

Assessment

Although the symptoms of gender dysphoria will decrease or disappear in most gender-dysphoric youth after initiation of puberty, persistence of gender dysphoria implies a very high likelihood that such individuals will be transgender as adults; in fact, the emergence or worsening of gender dysphoria with onset of puberty is thought to have significant diagnostic value in the determination of being transgender (55). It is noteworthy, however, that with the advent of gender-affirming medical interventions (as detailed below), awareness of such treatment options may positively impact and, thus, limit the degree of dysphoria that might otherwise accompany the onset of puberty in a transgender individual. It is therefore essential that gender-dysphoric youth undergo a thorough psychodiagnostic evaluation by a qualified mental health provider. An important role of the mental health/gender specialist is not only to determine the presence or absence of gender dysphoria but also to evaluate for psychiatric comorbidities. Although there is an increased prevalence of autism spectrum disorder in clinically referred gender-dysphoric children in comparison to the general population (56) (and, conversely, increased "gender variance" in referred children with autism spectrum disorder) (57), most gender-dysphoric children and adolescents do not have an underlying severe psychiatric illness (55).

Management

Guidelines from The Endocrine Society (7) and the WPATH SOC (6) provide direction for the comprehensive management of two distinct pediatric transgender populations likely to seek medical services: an early pubertal group (Tanner 2/3) and a late pubertal group (Tanner 4/5).

Early pubertal transgender youth

Pioneering studies from The Netherlands, first published in 1998, have examined the consequences of pubertal suppression with a GnRH agonist (classically used for the treatment of precocious puberty) in early/midpubertal gender-dysphoric adolescents (58–61). The rationale for such fully reversible treatment is that additional time for gender exploration can be created without the pressure of ongoing pubertal development. Once completed, the physical changes of puberty cannot be reversed (by means other than surgical or, for voice, other than by voice training)—eg, low voice, Adam's apple, and facial features in phenotypic males and breast development in phenotypic females. Theoretically, preventing pubertal development that does not match a person's gender identity can lead to decreased gender dysphoria and can ultimately make the individual more "passable" as an adult. Subsequently, if the individual continues to identify as transgender, cross-sex hormones can be added while continuing GnRH agonist suppression of endogenous puberty, enabling the individual to experience only the physical changes of puberty that match the person's affirmed

Table 1. Hormonal Interventions for Transgender Adolescents (All Currently Off-Label for Gender Nonconforming/Transgender Youth)

A. Inhibitors of gonadal sex steroid secretion or action
  1. GnRH analogs: inhibition of the hypothalamic-pituitary-gonadal axis (FTM and MTF)
    a. Leuprolide acetate im (1- or 3-mo preparations) or sc (1-, 3-, 4-, or 6-mo preparations) at dose sufficient to suppress pituitary gonadotropins and gonadal sex steroids
    b. Histrelin acetate sc implant (once-yearly dosing, although may have longer effectiveness)
    c. Other options: goserelin acetate sc implant (4- or 12-wk preparations); nafarelin acetate intranasal (multiple daily doses) also available, but no reported use in this population
  2. Alternative approaches
    a. Medroxyprogesterone acetate orally (up to 40 mg/d) or im (150 mg every 3 mo): inhibition of hypothalamic-pituitary-gonadal axis and direct inhibition of gonadal steroidogenesis (FTM and MTF)
    b. Spironolactone (25 to 50 mg/d with gradual increase to 100–300 mg/d orally, divided into twice daily dosing): inhibition of T synthesis and action (MTF)
    c. Cyproterone acetate (gradual increase up to 100 mg/d orally; not available in United States): inhibition of T synthesis and action (MTF)
    d. Finasteride (2.5–5 mg/d orally): inhibition of type II 5 α-reductase, blocking conversion of T to 5α-dihydrotestosterone (MTF)
B. Cross-sex hormones
  1. MTF: estrogen-–17β-estradiol
    a. Transdermal: twice weekly patches (6.25 μg [achieved by cutting a 25-μg patch] with gradual increase to full adult dose)
    b. Oral/sublingual: daily (0.25 mg with gradual increase to full adult dose of 6–8 mg/d)
    c. Parenteral im (synthetic esters of 17β-estradiol): estradiol valerate (5–20 mg up to 30–40 mg/2 wk) or estradiol cypionate (2–10 mg/wk)
  2. FTM: testosterone
    a. Parenteral im or sc (synthetic esters of T): T cypionate or enanthate (12.5 mg/wk or 25 mg/2 wk, with gradual increase to 50–100 mg/wk or 100–200 mg/2 wk)
    b. Transdermal (consider once the full adult T dose has been achieved parenterally): patch (2.5–7.5 mg/d) or 1% gel (2.5–10 g/d of gel = 25–100 mg/d of T)

gender identity (6, 7). The Endocrine Society guidelines and WPATH SOC endorse the use of pubertal blockers (using GnRH agonists) at Tanner 2/3 in individuals experiencing a significant increase in gender dysphoria with onset of puberty (6, 7). Although age-specific guidelines for subsequent interventions are not delineated in the WPATH SOC, the Endocrine Society guidelines suggest that cross-sex hormones can be initiated at about the age of 16 years (the legal age for medical decision-making in some countries), whereas surgical procedures (with the exception of mastectomy) should be deferred until the individual is at least 18 years of age (7). The primary risks of pubertal suppression in these individuals include adverse effects on bone mineralization (which can theoretically be reversed with cross-sex hormone treatment), compromised fertility, and unknown effects on brain development (55, 59). It is important to ensure adequate intake of calcium and vitamin D, with routine monitoring of 25-hydroxyvitamin D levels. Despite the recommendation that cross-sex hormone treatment not be initiated before age 16 years, not only could delaying such treatment until that age be detrimental to bone health, but keeping someone in a prepubertal state until this age would isolate the individual further from age-matched peers, with potentially negative consequences for emotional well-being. Thus, gender centers at our institution and elsewhere are studying the impact of cross-sex hormone treatment initiation at 14 years of age (which approximates the upper end of the age range for normal pubertal onset in natal males and 1 year beyond the upper end of the age range in natal females). In this group, sex steroids are increased gradually over the course of 2–3 years.

Limited available outcome data support the above-noted Endocrine Society and WPATH recommendations. A prospective follow-up study from The Netherlands assessed 70 gender-dysphoric adolescents (33 MTF, 37 FTM), average age 13.65 years (range, 11.1–17 y) at initial assessment, who were Tanner stage 2–3, had lifelong gender dysphoria that increased with puberty, had stable psychological function, and were supported by their environment (59, 60). These adolescents were studied at the initiation of GnRH agonist treatment (mean age, 14.75 y), and approximately 2 years later, just before starting cross-sex hormones (60). Depressive symptoms decreased, general mental health functioning improved, no subjects withdrew from pubertal suppression, and all went on to cross-sex hormone treatment (60). In a separate report, BMD in the lumbar spine, femoral neck, and total body was followed in a small number of gender-dysphoric adolescents during 2 years of GnRH agonist alone and for an additional 2 years of combination treatment with GnRH agonist and cross-sex hormones (59). BMD (g/cm^2) did not

change significantly during treatment with GnRH agonist alone, although z-scores decreased; during combination therapy with GnRH agonist and cross-sex hormones, absolute BMD increased, as did z-scores (59). A 22-year follow-up of the first described gender-dysphoric adolescent treated with GnRH agonist and cross-sex hormones reported overall psychological well-being with no clinical signs of adverse effects on brain development; furthermore, BMD was within the normal range for both sexes (61).

Late pubertal transgender youth

Not infrequently, some transgender adolescents first come to medical attention when they are late pubertal (Tanner 4/5). Such FTM individuals can be treated with T alone, whereas MTF individuals are optimally treated with an agent that blocks T secretion and/or action, concurrent with the use of estrogen (6, 7, 62, 63). Although too late to block endogenous pubertal development, GnRH agonists can nonetheless be used to suppress the hypothalamic-pituitary-gonadal axis, potentially enabling the use of lower doses of cross-sex hormones to induce phenotypic transition to the affirmed gender, thereby decreasing potential toxicities associated with cross-sex hormone treatment. In this older cohort (having already experienced the full or near-full puberty associated with their physical sex), cross-sex hormone regimens may be increased to full replacement doses over a shorter interval than used for the younger cohort that had been initially treated with pubertal blockers at Tanner 2/3. Although GnRH agonists are the preferred option for pubertal suppression in both the early and late pubertal individuals, this treatment is costly and often inaccessible. Table 1 lists options for pubertal suppression and cross-sex hormone treatment. With specific respect to estrogen treatment, 17β-estradiol (transdermal, oral, or parenteral) is preferred to conjugated (eg, premarin) or synthetic estrogens (eg, ethinyl estradiol), given that conjugated and synthetic estrogen levels cannot be monitored in the serum and that ethinyl estradiol (in comparison to 17β-estradiol) is associated with an increased risk for venous thromboembolic disease and death from cardiovascular causes (64, 65). MTF individuals treated with estrogen may have impaired insulin sensitivity and hyperprolactinemia (7). Principal risks associated with T treatment in FTM individuals include cystic acne, polycythemia, hypertension, an atherogenic lipid profile, and possible decreased insulin sensitivity (7). Surveillance recommendations for desired as well as adverse effects during treatment with pubertal blockers alone and in combination with cross-sex hormones are adapted from the current Endocrine Society guidelines (7) and are summarized in Table 2.

Table 2. Monitoring During Pubertal Suppression and During Cross-Sex Hormone Treatment

Measure	Frequency
A. Pubertal suppression	
1. Physical exam: height, weight, Tanner staging	T 0 and every 3 mo
2. Hormonal studies: ultrasensitive LH, FSH, estradiol/T	T 0 and every 3 mo
3. Metabolic: calcium, phosphorous, alkaline phosphatase, 25-hydroxyvitamin D (see also Ref. 6)	T 0 and yearly
4. Bone density: DEXA	T 0 and yearly
5. Bone age	T 0 and yearly
B. Cross-sex hormone treatment in previously suppressed patients or in late pubertal patients not previously suppressed	
1. Physical exam: height, weight, Tanner staging, blood pressure (for FTM, in particular); monitor for adverse reactions	T 0 and q 3 mo[a]
2. Hormonal studies: ultrasensitive LH, FSH, estradiol/T	T 0 and q 3 mo[a]
If MTF, also monitor Prolactin	T 0 and yearly
3. Metabolic: calcium, phosphorous, alkaline phosphatase, 25-hydroxyvitamin D, complete blood count, renal and liver function, fasting lipids, glucose, insulin, glycated hemoglobin	T 0 and q 3 mo[a]
If MTF on spironolactone, serum electrolytes (potassium)	T 0 and q 3 mo[a]
4. Bone density: DEXA (if puberty previously suppressed)	T 0 and yearly[b]
5. Bone age (if puberty previously suppressed)	T 0 and yearly[b]

Modified from W. C. Hembree, et al: Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94:3132–3154 (7), with permission. © The Endocrine Society.

[a] Every 3–12 months after the first year.

[b] Until puberty is completed.

It should be noted that some Tanner 4/5-transgender adolescents present for medical services before 16 years of age. As with the group treated with GnRH agonists at early puberty, we and others are studying the consequences of cross-sex hormone treatment at 14 years of age. Occasionally, some gender-dysphoric youth first come to medical attention when they are Tanner 4/5, but $<$ 14 years of age. Such individuals would be candidates for pubertal blockers (eg, to stop menses in an FTM adolescent), but without supportive outcome data, not currently candidates for cross-sex hormone use under most circumstances.

It is essential that any use of pubertal blockers and cross-sex hormones includes an informed consent process and a discussion about implications for fertility. Transgender adolescents may wish to preserve fertility, which

may be otherwise compromised if puberty is suppressed at an early stage and the patient completes phenotypic transition with the use of cross-sex hormones.

Controversies and Areas of Uncertainty/ Barriers to Ideal Practice

The ability to provide optimal health care to gender-dysphoric/transgender youth is limited by areas of uncertainty, controversies, and barriers to state-of-the art practice. Only limited safety and efficacy data currently exist, with virtually no published data on the use of pubertal blockers in gender-dysphoric individuals < 12 years of age or cross-sex hormones in transgender youth < 16 years of age. Furthermore, randomized controlled trials for hormonal interventions in gender-dysphoric youth have not been considered feasible or ethical (66). The clinical practice guidelines that currently exist are based on best available evidence, with significant reliance on expert opinion. A 2011 report from the Institute of Medicine of the National Academies in the United States has endorsed the need for prospective, longitudinal safety and efficacy studies of medical interventions in gender-nonconforming/transgender youth (67). Barriers to implementation of current clinical practice guidelines include the fact that pubertal blockers and cross-sex hormone treatments are off-label in gender-dysphoric youth and are expensive, and coverage is often denied by insurance companies. Furthermore, whereas an increasing number of clinical programs have emerged in recent years, there are many geographic regions in which such services do not exist, limiting access to care and often requiring patients and families to travel long distances. In addition, access to optimal care may be limited by a lack of training of providers and by prejudice and misunderstanding on the part of family, community, and medical and mental health professionals.

Returning to the Patients

Despite insurance denials after multiple appeals, our 13-year-old Tanner 2/3 gender-dysphoric MTF patient and family were determined to have access to pubertal suppression with GnRH agonist therapy. They decided against alternative approaches to block T production or action and instead purchased the least expensive GnRH agonist option out of pocket. The patient's gender dysphoria has markedly reduced since initiating pubertal suppression.

Our 16-year-old Tanner 5 transgender FTM patient has continued to do well on GnRH agonist treatment to suppress the hypothalamic/pituitary/ovarian axis and on weekly sc T injections for phenotypic transition. Monitoring at 3-month intervals has thus far shown no toxicities associated with hormonal interventions; the gender dysphoria and suicidal ideation continue to be fully resolved, and the patient's depression continues to be reduced.

Conclusions

Transgender youth represent an often marginalized and misunderstood population. Compelling studies have demonstrated that gender identity is not simply a psychosocial construct, but likely reflects a complex interplay of biological, environmental, and cultural factors. The recent replacement of "disorder" with "dysphoria" in DSM-5 removes the connotation that a transgender identity itself is pathological and focuses instead on dysphoria as the clinical concern. The best available evidence indicates that mental health comorbidities in gender-dysphoric youth significantly diminish or resolve when such individuals are subject to a gender-affirming model of care, optimally delivered in a multidisciplinary clinical setting. Prospective cohort studies focused on long-term safety and efficacy are needed to optimize medical and mental health care for transgender youth.

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