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Advances in the Care of Transgender Children and Adolescents

Daniel E Shumer, MD, MPH[1], **Natalie J Nokoff, MD**[2], and **Norman P Spack, MD**[3]

[1]Assistant Professor, Department of Pediatrics and Communicable Diseases, Division of Pediatric Endocrinology, University of Michigan Health Systems, Ann Arbor, MI

[2]Fellow, Department of Pediatrics, Division of Pediatric Endocrinology, University of Colorado School of Medicine, Aurora, CO

[3]Senior Associate, Endocrine Division, Boston Children's Hospital, Boston, MA; Associate Clinical Professor of Pediatrics, Harvard Medical School, Boston, MA

Abstract

Children and adolescents with gender dysphoria are presenting for medical attention at increasing rates. Standards of Care have been developed which outline appropriate mental health support and hormonal interventions for transgender youth. This article defines terminology related to gender identity, reviews the history of medical interventions for transgender persons, outlines what is known about gender identity development, and reviews mental health disparities faced by this patient population. We provide an overview of medical management options for transgender adolescents meeting diagnostic criteria for gender dysphoria including pubertal suppression, cross-sex hormones, longitudinal screening and anticipatory guidance. We describe current challenges in the field and provide information about how care is currently being provided in the US and Canada. We conclude with 5 brief case examples.

Keywords

Gender dysphoria; transgender; gender identity; adolescent; child

Introduction

The World Professional Association for Transgender Health (WPATH) first published Standards of Care for the heath of transsexual, transgender, and gender-nonconforming people in 1980, with the 7th Edition released in 2012.[1] In 2009, The Endocrine Society issued a clinical practice guideline for the treatment of transsexual persons, including support for pubertal suppression and cross-sex hormones in carefully screened and supported transgender adolescents.[2] In the 35 years since the publication of the first edition of the WPATH standards, transgender issues have emerged from the periphery of the general

Corresponding author: Daniel E Shumer, MD, MPH, Assistant Professor in Pediatrics, Division of Pediatric Endocrinology, University of Michigan, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5175, Phone: 734-764-5175, Fax: 734-615-3353.

conscious to a center stage cultural, human rights, and medical topic in both lay media and scientific inquiry.[3,4] Gender management clinics have emerged to assess, support, and provide medical treatment for transgender adolescents across Europe and North America.[5–9] As transgender issues continue to emerge to the forefront of the public consciousness, the public is expecting knowledgeable, competent, and comprehensive mental health and medical care. Yet, only a minority of medical schools offer curriculum related to transgender-specific care.[10] This mismatch between provider education and patient expectation has left providers and health systems struggling to develop appropriate clinical care systems. This article will define critical terminology in the field, describe what is known about gender identity development, outline the current mental health disparities faced by transgender persons in general and youth specifically, address current guidelines regarding medical treatment of the pediatric transgender patient, highlight persisting challenges and barriers to care, and conclude with case examples.

Definitions and Epidemiology

Gender identity describes one's internal feeling of gender, for example, boy or girl, man or woman, agender (identifying as having no gender), or a non-binary understanding of one's gender. This is in contrast to *biologic sex*, which is describes the chromosomal, hormonal, and anatomic determinants which result in characterizing people as male or female. A *transgender* person feels a discrepancy between their sex assigned at birth and their gender identity.[11] The term *cisgender* has subsequently been introduced to describe individuals who have a gender identity congruent with or the same as their sex assigned at birth. *Gender role* or *gender expression* describes how a person presents themselves as masculine or feminine in the context of societal expectations. *Gender attribution* describes the process whereby other observers view a person as masculine or feminine. For example, a transgender woman who appears masculine due to the development of male secondary sex characteristics may have a male *gender attribution* and struggle with "passing" as an affirmed woman. Finally, *sexual orientation* describes the persons one finds sexually desirable, for example, homosexual, heterosexual, bisexual, pansexual or asexual.[12]

Gender dysphoria in childhood and *gender dysphoria in adolescents and* adults are defined in the Diagnostic and Statistical Manual of Mental Health Disorders, Fifth Edition (previously referred to *gender identity disorder in previous editions*).[13,14] Both children and adolescents meet diagnostic criteria for gender dysphoria if they experience a marked difference between their experienced and assigned gender which persists for at least 6 months, and causes significant distress or impaired functioning.[14] A *transsexual* person, as defined by the WPATH Standards of Care, 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."[1]

As evidenced by the American Psychiatric Association's decision to remove the stigmatizing word "disorder" from the lexicon, replacing *gender identity disorder* (GID) with *gender dysphoria*, there has been evolving depathologization for those whose gender identity differs from their sex assigned at birth. The idea that *gender identity* exists on a continuum and that

gender diversity should be celebrated has gained cultural traction and has resulted in greater acceptance of gender non-conforming people in certain communities. See Table 1 for a list of commonly used terms.

The prevalence of gender dysphoria has been difficult to estimate. A calculated prevalence from the Netherlands in 1996 suggested 1 per 11,900 natal Dutch males and 1 per 30,400 natal Dutch females were transsexual.[15] However, the frequency of new referrals to pediatric gender programs suggests that these numbers understate the current prevalence in the US. In addition, the proportion of natal male and natal female referrals appears to be closer to 1:1, conflicting with Dutch epidemiologic data.[5] In dramatic contrast to the Dutch data, a recent survey of 28,662 adults in Massachusetts found 0.5% self-identifying as transgender.[16] We suggest that as societal acceptance of gender diversity continues to advance and as barriers to care are removed, the transgender population will grow dramatically.

Historical Perspectives

Prior to the isolation of sex hormones, their development into an injectable or oral compound to be administered, and development of surgical techniques, there were no options to change one's secondary sex characteristics. Charles-Édouard Brown-Séquard was among the first to conceptualize that hormones, or substances, may be secreted by a gland and enter the bloodstream to affect distant organs. He claimed to have injected himself with an extract derived from dog and guinea pig testes.[17]

Testosterone was discovered in 1935[18] and was synthesized from cholesterol soon after.[19] Estrone was isolated in 1929–1930 from the urine of pregnant women in the US[20] and Germany[21] with the discovery of estriol shortly afterwards.[22] Progesterone was discovered in 1934 by multiple groups.[23,24] The first orally active progestin was synthesized in 1938 and named "ethisterone" and was significantly androgenic.[25] The same group later synthesized estradiol, termed "ethynylestradiol,"[26] which was widely used for decades including in the care of transgender women.[27]

Magnus Hirschfeld was a Jewish German physician and sexologist who is known for advocating for the rights of homosexuals in turn-of-the century Germany. He coined the term "transvestite" and opened the Institute for Sexual Research in 1919.[28]

The first "modern" orchidectomy was performed in 1930 for a Danish natal male who sought a sex change. She then went a penectomy, implantation of ovarian tissue and vaginoplasty.[29] There are older examples from history, for example, the Hijiras, an Indian Caste of men who lived as women and underwent ritual castration or a surgery performed in Australian aboriginal men to create a rudimentary vagina.[30] There were additional published cases of penectomy for gender dysphoria in the 1940s–1950s in Germany.[30]

The first widely published case in of a transgender female in the United States was Christine Jorgensen, who appeared on the front page of the *New York Daily News* on December 1, 1952.[31] Christine, formerly George, served in World War II and after returning from war, started taking feminizing hormones. She underwent castration and sex reassignment surgery in Denmark, and later had a vaginoplasty in the United States.[32]

The earliest case reports in the medical literature of surgical treatment of a transgender individual were in Germany in 1940s[33] and in JAMA in 1953 by Danish physicians.[34] A 24 year old natal male presented with a desire to more fully live as a woman and was treated with estradiol monobenzoate injections and oral ethinyl estradiol. Per the patient's wishes, she underwent castration after permission was granted by the Danish Ministry of Justice.[34] Following the initial operation, the patient had a penectomy and plastic surgery of the scrotum to construct "labia-like formations." A vaginoplasty was not performed and not desired by the patient. The authors were ahead of their time, calling upon the "medical profession and authorities" to show a "more positive attitude toward the efforts at easing and facilitating the daily life of the victims of genuine transvestism" with an outline of suggestions to make this possible,[34] which resonate with current recommendations.

Harry Benjamin was a German-born sexologist and endocrinologist who knew Magnus Hirschfeld and became widely known for his 1966 book, The Transsexual Phenomenon.[35] He treated Christine Jorgensen. In 1979, the Harry Benjamin International Gender Dysphoria Association was formed, now re-named the World Professional Association for Transgender Health. The first "standards of care" were published in 1979, now in their 7th version.[1]

The first female-to-male (FTM) sex reassignment surgeries were performed at Johns Hopkins in 1966 after the Gender Identity Clinic was formed. The psychologist and sexologist John Money helped found the clinic and was later widely criticized for the John/Joan case.[36] Thousands of gender affirmation surgeries were later performed by Dr. Stanley Biber in Trinidad, Colorado, which was later coined, the "sex change capital of the world." He performed his first sex reversal surgery in 1969 at his patient's request and after learning from sketches of surgical procedures.

In the 1980s, GnRH agonists were first used for the treatment of central precocious puberty,[37] and would prove to be a key treatment option for younger transgender patients. Prior to the late 1990s, treatment of children or adolescents with gender dysphoria was not considered. In 1998, Drs. Cohen-Kettenis and van Goozen in the Netherlands published a report of a FTM transgender patient treated with triptorelin, a GnRH agonist, starting at age 13 years.[38] The Dutch practice methods of using pubertal suppression followed by cross-sex hormones for transgender adolescents subsequently became incorporated into the WPATH and The Endocrine Society Standards of Care.[1,2]

The Development of Gender Identity

Expectant parents can now learn the chromosomal sex of their fetus with first trimester cell free fetal DNA and the anatomic sex on the second trimester ultrasound.[39] Many parents then spend the next few months preparing a nursery adorned in pink or blue, excited to welcome their new son or daughter into the world. The baby is born into a gendered world, where boys and girls dress differently and are often encouraged to pursue gender-specific games or styles of play. While these stereotypical gender roles vary by culture and change over time, the different expectations of boys and girls are thought to impact the development of gender identity. Children as young as 2 years learn to label themselves as a boy or a girl,

and by age 4–5, are able to understand that gender is a stable and lasting aspect of their identity.[40] Boys and girls have group differences in toy preference by as early as 12 months and can label other children as boys or girls by age 2.[41]

Development of gender identity development is complex, and likely a multifactorial process involving genetic, hormonal, and environmental factors. John Money and Anke Ehrhardt proposed the idea of brain sex,[42] which has drawn controversy.[43] Several brain structures appear to be sexually dimorphic,[44] which has led researchers to study whether transgender individuals have brain structures that more closely align with their affirmed gender. In one study, the volume of the bed nucleus of the stria terminalis in male-to-female (MTF) transgender persons was equivalent to the volume found in cisgender women.[45] However, others argue that such “dimorphisms” are better thought of as small differences with significant overlap.[43]

Studies of heritability of transgender identity have suggested that genetic factors may contribute to gender development. For example, in a recent review of twin studies, of 23 monozygotic male and female twin pairs where at least one twin met criteria for GID, 9 twin pairs (39.1%) were concordant for GID.[46] Studies have failed to firmly establish causative genes.[6]

The hormonal milieu of the developing fetal brain and its role on later gender identity has been another area of active research. Much of this research has been driven by the study of persons with disorders of sex development (DSD). Sex hormones, primarily androgens and estrogens, affect sex-specific changes in the developing fetus. During fetal life and infancy there are significant sex-specific differences in the normal concentrations of these hormones. It has been posited that these differences may contribute to group differences in behaviors observed between males and females later in life.[47,48] Populations of patients with various DSDs have served as natural experiments for this hypothesis. For example, infants with a 46,XX karyotype and congenital adrenal hyperplasia are most often raised as girls but have had fetal exposure to higher than normal concentrations of circulating androgens. In a meta-analysis, 5% of those assigned and raised female had gender dysphoria or a male gender identity, suggesting that prenatal androgen exposure may influence the development of a male-typical gender identity.[49] In another example, of 14 patients with 46,XY karyotype and cloacal extrophy raised female, 8 (57%) subsequently affirmed a male gender identity.[50] These and other studies (see Rosenthal[6] for a more complete review) suggest that the prenatal hormonal milieu, especially fetal androgen exposure, may play a role in gender identity development. Yet, the vast majority of transgender persons do not have an identified DSD or endocrinopathy.

Finally, individual environmental factors may influence the development of gender dysphoria. It has been suggested that the social relationship between the parent and infant[41] and cognitive learning about parental expectations and societal norms[51] contribute to gender development in all children. The observation that children with autism spectrum disorder (ASD) are disproportionately affected by gender dysphoria has contributed to the discussion of environmental factors and gender identity. Children with ASD may, as a result of social

cognitive impairment, feel less societal pressure to conform to their assigned sex at birth which may manifest as persistence of gender dysphoria.[52]

Children referred for assessment due to gender non-conformity may demonstrate gender non-conforming behaviors at a very young age, sometimes as early as 3 years.[53] Others persons may disclose a transgender identity later in adolescence or adulthood, without a history of gender non-conformity in early childhood.[6,54] Young children who are gender non-conforming or who identify as transgender may or may not continue to identify as transgender as adolescents and adults. In fact, there is evidence to suggest that for a majority of young children with cross-gender identity, this identity does not persist into adolescence; at the time of puberty their transgender identity may desist and perhaps evolve into a gay or lesbian sexual orientation.[55,56] However, those who have persistence of transgender identity and/or worsening of gender dysphoria in puberty are thought to be much less likely to identify as cisgender as adolescence continues. Clinicians can use worsening gender dysphoria at the onset of puberty as a diagnostic tool of persistent transgender identity and as a criterion for eligibility for medical intervention.[57,38]

There have been efforts to identify factors to differentiate prepubertal children who will persist in their transgender identity during adolescence and adulthood versus those who will desist. In a study of 53 adolescents in the Netherlands, those who persisted versus desisted in their gender identity had similar gender variant expression in childhood. Yet, those who experienced increased dysphoria in adolescence, starting between 10–13 years, were more likely to have a stable transgender identity. Important factors in early adolescence included: the social environment, feelings toward pubertal changes, and the emergence of sexual attraction.[58] Additional study of desistance versus persistence suggested that children who persist may have more severe symptoms of gender dysphoria in childhood and are more likely to undergo a social transition in childhood (live as the affirmed gender).[59] The uncertainty of future persistence, coupled with the idea that acceptance of a transgender identity in early childhood may be associated with persistence of transgender identity in adolescence and adulthood has led to controversy regarding the appropriate counseling and mental health treatment strategies for prepubertal children with gender dysphoria.

Mental Health

Transgender persons continue to be disproportionately affected by bias, persecution, and harassment,[60] and have alarmingly high rates of depression, anxiety, self-harm behaviors and suicidality. A staggering 41% of transgender adults have attempted suicide. Rates of suicide attempt are higher among non-white transgender adults, those who are unemployed or underemployed, poor, less educated, and young.[61] Transgender youth who experience verbal and physical abuse are more likely to attempt suicide,[62] and transgender individuals are disproportionately victimized by physical abuse.[63] Transgender youth also have higher rates of alcohol, tobacco, cannabis, and other drug use,[64] and MTF persons, in particular, have higher rates of sex work and HIV.[65] In a recent study of mental health disparity, transgender youth had two- to threefold increased risk of depression, anxiety disorder, suicidal ideation, suicide attempt, self-harm behaviors, and utilization of both inpatient and outpatient mental health services compared to cisgender youth.[66]

The 2011 National School Climate Survey of LGBT youth surveyed over 8,500 students ages 13–20 years in the US, 700 of whom identified as transgender. Eighty percent of the transgender students reported feeling unsafe at school because of their gender expression and over half of gender nonconforming students had experienced verbal harassment. School policies that affect transgender students include school dress codes, gender segregated sports and physical education, gender segregated bathrooms and locker rooms, gendered pronouns, and binary-only options on school forms.[67]

It is therefore not surprising that youth presenting to gender management clinics are disproportionately affected by mental health comorbidities. At Boston Children's Hospital's Gender Management Services program, patients had a high prevalence of diagnosed psychiatric comorbidities (44%), history of self-mutilation (21%), history of psychiatric hospitalization (9%), and history of suicide attempt (9%).[5] Among 101 transgender youth ages 12–24 followed at the Center for Transyouth Health and Development at Children's Hospital Los Angeles, 15% had mild depression, 9% had moderate depression, and 11% had severe depression as rated on the Beck Depression Inventory. Half reported having thoughts about suicide, while 30% had attempted suicide.[64] As noted above, rates of ASD disorder may also be elevated among children and adolescents presenting with gender dysphoria, with a rate of 7.8% reported from the gender program in the Netherlands, a rate exceeding that in the general population.[68]

There is a lack of consensus among mental health providers regarding the goals of mental health treatment in pre-pubertal children.[12] Some argue that therapeutic goals should focus on reduction in dysphoria and acceptance of the biologic sex.[69] Affirmative approaches help families to support a child's transgender identity and assist children and families with the logistics of making a social transition.[70] There is less controversy about treatment goals for pubertal adolescents. Pubertal adolescents are less likely to desist, and supportive trans-affirmative mental health support is encouraged. The American Psychological Association recently published "Guidelines for Psychological Practice with Transgender and Gender Nonconforming People" containing 16 guidelines recommended for psychologists to assist with "culturally competent, developmentally appropriate, and trans-affirmative psychological practice."[71]

The WPATH Standards of Care and The Endocrine Society clinical practice guidelines describe comprehensive approaches aimed to mitigate mental health disparities and improve outcomes. Data from a pioneering Dutch group suggests that adolescents followed by a multidisciplinary gender team and treated with pubertal suppression followed by cross-sex hormones had improvement in psychological function with mental health outcomes in young adulthood similar to the general Dutch population.[72,73] The Endocrine Society guidelines recommend that children and adolescents with gender concerns be seen by a mental health professional with training in child and adolescent developmental psychology. The mental health professional should: 1) determine whether the individual fulfills DSM criteria for gender dysphoria; 2) inform the individual with respect to possibilities and limitations of sex reassignment and other treatments; and 3) assess for potential psychological comorbidities.[2] The WPATH Standards of Care requires adolescents meet eligibility and readiness criteria before proceeding with hormone treatments; medical interventions can be initiated only after

a referral from a qualified mental health professional.[1] Many multidisciplinary clinics require such documentation before hormones are prescribed. However, mental health providers with expertise in this area are limited, and many transgender youth may not have access to such providers given location, insurance coverage and cost.

Sex Differentiation and Normal Puberty

Testosterone and estrogen are produced in the testes and ovaries beginning in early fetal life. Testosterone production in the fetus, and its subsequent conversion to dihydrotestosterone, leads to virilization of genital tissues and development of male genitalia. Absence of testosterone results in female external genitalia.[74]

After the “mini-puberty” of infancy, sex hormone production within the gonads enters a quiescent stage.[75] There is little difference in the hormonal milieu between prepubertal males and females, therefore, hormonal interventions are not indicated in prepubertal transgender children. The transgender prepubertal child can instead focus on better understanding their gender identity with the aid of a mental health professional and their family. When a prepubertal child makes a social transition, presenting themselves as their affirmed gender, their ability to “pass” as their affirmed gender is aided by the fact that they have not yet developed secondary sex characteristics.

Puberty, the life stage characterized by the development of secondary sex characteristics, begins with the activation of the gonadotropin releasing hormone (GnRH) pulse generator within the hypothalamus. Pulsatile GnRH leads, in turn, to pulsatile production luteinizing hormone (LH) and follicle stimulating hormone (FSH) within the anterior pituitary gland. LH inspires production of testosterone in testicular Leydig cells. It also leads to production of androgens in ovarian theca cells, which are then converted to estrogen. FSH causes germ cell maturation and testicular enlargement in males and the growth and recruitment of ovarian follicles in females.[76,77] Male puberty, driven by testosterone and dihydrotestosterone, is characterized by enlargement of the testes and phallus, development of facial and body hair, enlargement of the larynx and deepening of the voice, increase of lean muscle to fat ratio, and skeletal changes such as masculinization of the facial bones and jaw and widening of the shoulders. In female puberty, estrogen production results in development of glandular breast tissue and redistribution of fat to the buttock and hips. Ovarian and endometrial development leads to menarche.[78]

The onset of central puberty can be assessed clinically by the development of testicular enlargement and breast budding in biologic males and females respectively. The beginnings of testicular enlargement and thinning of the scrotal skin in biologic males, and the development of breast budding in biologic females, are hallmarks of sexual maturity rating or SMR (Tanner stage) 2. Pubic hair development and the development of apocrine body odor may develop prior to central puberty as a result of adrenal androgen production. These changes by themselves should not be considered evidence of central puberty.[79,80] The average age of onset of puberty is 10–11 years in females and age 11–12 years in males. Height velocity increases during puberty and peaks about 2.5 years after the start of the pubertal growth acceleration.[81] In biologic males, characteristics significantly affecting

gender attribution, such as facial hair development, completion of voice change, and masculinization of facial bones, occur later in puberty compared to genital development. The lateness of these changes within normal male puberty provides incentive for pubertal suppression in MTF individuals presenting in late puberty. In FTM individuals, breast development typically progresses from SMR 2 to 5 (fully developed) within 4–5 years and menses typically begin 2–2.5 years after breast budding.[78]

Overview of Medical Management

The WPATH standards of care and The Endocrine Society clinical practice guidelines both recommend the diagnosis of gender dysphoria be made by a mental health professional with expertise in gender identity prior to considering a hormonal intervention.[1,2] Some multidisciplinary gender programs employ mental health professionals to perform assessments for referred patients; other programs rely on community-based mental health providers to make the diagnosis of gender dysphoria.[82] Primary goals of medical interventions include: (1) prevention of the development of unwanted secondary sex characteristics of the biologic sex, and (2) promotion of the development of desired secondary sex characteristics of the affirmed gender. Broader objectives include reduction in dysphoric feelings, reduction in co-morbid depression, anxiety and suicidality, and enhanced ability to “pass” as the affirmed gender with subsequent improvement in quality of life and general functioning.

Prevention of the Development of Unwanted Secondary Sex Characteristics

Medical interventions that suppress sex hormone production, or that block sex hormone action, work to prevent the development of undesired secondary sex characteristics of the biologic sex (Table 2). These interventions include pubertal suppression using GnRH agonists, reduction in biologic hormone production using progestins, and use of androgen receptor antagonists such as spironolactone.[6]

Use of a GnRH agonist to completely suppress puberty starting at SMR 2 followed by introduction of cross-sex hormones in later adolescence was first described by a pioneering gender center in Amsterdam, The Netherlands.[57,38] The rationale for using GnRH agonist medications to suppress puberty include the following: (1) it allows a transgender adolescent protected time to explore their gender identity with their mental health professional and family without continued progression into their biologic puberty; (2) halting progression of puberty appears to improve behavioral and emotional problems, and reduces depressive symptoms;[72] (3) preventing the development of secondary sex characteristics of the biologic puberty can improve the ability to pass as the affirmed gender and obviate the need for procedures such as masculinizing chest surgery in biologic females, and electrolysis of facial and body hair, feminizing facial surgeries, and voice therapy in biologic males.

For example, a FTM patient who starts on GnRH agonist medication at SMR 2, and then starts on testosterone in later adolescence, may not require masculinizing chest surgery and will also forgo menstruation. If suppression occurs at SMR 3 or 4, prior to full breast

development, a less invasive chest surgery (for example, through an areolar incision rather than an inframammary incision) may be considered. A FTM patient presenting after full breast development has occurred would get less benefit from GnRH agonist treatment. While a GnRH agonist would suppress dysphoric menses, other more cost effective interventions, such as treatment with a progestin, may accomplish a similar result.

For MTF, use of GnRH agonist medication prior to the development of male secondary sex characteristics can dramatically improve gender attribution, the ability to pass as the affirmed female gender. For example, a MTF who starts on GnRH agonist medication at sexual maturity rating 2, who continues on it as estrogen therapy is initiated in later adolescence, and then proceeds with gonadectomy and vaginoplasty after age 18, will never develop masculine facial and body hair, will not have a deep voice, and will not have masculinization of the facial bones and skeletal frame.[12]

Both WPATH and The Endocrine Society Guidelines recommend consideration of GnRH agonist therapy only after the start of puberty (SMR 2).[1,2] Use of pubertal suppression to prevent puberty from starting, starting at SMR 1, is not recommended. This is because persistence of gender dysphoria during early puberty can be used as an important diagnostic tool, predicting continued transgender identity in older adolescence and adulthood. Additionally, starting at SMR 1 would add unnecessary treatment and cost for a prepubertal patient not requiring pubertal suppression.

GnRH agonist medications have been used extensively in the pediatric age group for treatment of precocious puberty for over 25 years. They are considered safe and reversible medications.[83] In the transgender population, theoretical risks include reduction in bone mineral density z-score while on treatment. However, new evidence suggests bone density accrual improves after starting treatment with cross-sex hormones.[57] Although the effects of GnRH agonists are reversible, they are often started with the intent of initiating cross-sex hormones later on, and the combination of the two results in permanent and semi-permanent effects. It is important that families receive counseling regarding the fertility effects of GnRH agonists and cross-sex hormones. A child who starts on GnRH agonist therapy at SMR stage 2 and continues on the mediation as cross-sex hormones are introduced later in adolescence will never have spermatogenesis or menarche, and will not have the opportunity to bank gametes using cryopreservation. Yet for many patients and families, after appropriate informed consent, the benefits of pubertal suppression still outweigh the risks.[1,2] GnRH agonists can be continued during treatment with cross-sex hormones. For example, a MTF individual may be concurrently treated with a GnRH agonist and estrogen until gonadectomy is performed, at which point GnRH agonist therapy would no longer be needed. A FTM individual may use a GnRH agonist and testosterone until masculinizing chest surgery, at which point monotherapy with testosterone should suffice to prevent continued menstruation.

GnRH agonists provide a constant level of stimulation to the GnRH receptor and, as a result, inhibit the pulsatile secretion of LH and FSH from the anterior pituitary. Common forms of administration include an intramuscular injection administered every 30 or 90 days (leuprolide acetate) or a subcutaneous implant, replaced annually (histrelin acetate). In our

experience, histrelin acetate implants in either the pediatric preparation (distributed in the US as Supprelin®, designed to deliver 65 mcg per day of active medication) or adult preparation (distributed in the US as Vantas®, designed to deliver 50 mcg per day of active medication) are both effective at suppressing puberty in transgender adolescents for longer than one year. GnRH agonists can also be given as intranasal preparations; however, there are no reports of use of this preparation in transgender individuals. Choice of GnRH agonist preparation in the US is often based on availability, insurance coverage, patient age and patient and family preference. We have often used Vantas® in situations where insurance coverage is denied because it is more affordable for out-of-pocket payment compared to other preparations. The use of any GnRH agonist preparation for pubertal suppression in transgender adolescents is considered “off-label” in the US. The Food and Drug Administration has not listed gender dysphoria as a clinical indication for their use, despite the fact that this is current standard of care.

In addition to GnRH agonists, other medications that reduce the production of sex hormones or inhibit their actions can be useful in the transgender adolescent. Even prior to the development of GnRH agonist medications, progestins, more specifically medroxyprogesterone acetate, had been used in the treatment of precocious puberty to suppress sex hormone production.[84] Progestins, including medroxyprogesterone acetate and norethindrone, reduce the pulsatile release of LH and also directly inhibit sex hormone production at the level of the gonad.[6] Medroxyprogesterone acetate can be given as an intramuscular injection every 3 months (Depo-Provera®) or as a daily oral medication (Provera®), and norethindrone as a daily oral medication (as Micronor® or Aygestin®). In our experience, treatment with progestins have been especially helpful in a few specific situations: (1) in a FTM individual who has already completed breast development and started menstruating, but who is either too young or still in the process of considering treatment with testosterone. In this situation, treatment with a progestin can aid in reducing dysphoria by suppressing menses; (2) in a MTF individual who has started on cross-sex hormone therapy with estradiol and who cannot receive GnRH agonist therapy due to lack of insurance coverage. In this situation, if the estrogen monotherapy is insufficient to bring testosterone down to a level which would support normal breast development, use of estrogen therapy with concurrent use of a progestin can help to promote normal breast development and minimize further masculinization from testicular production of testosterone. Note that, conversely, a FTM individual on monotherapy with testosterone will most often have adequate suppression of menses and should not require pubertal suppression with GnRH or treatment with a progestin.

Finally, spironolactone is an oral medication most commonly used as a weak diuretic, which also acts as a weak androgen receptor antagonist. This medication can be used by MTF individuals to reduce effects of testicular androgen production.[6] We most commonly use spironolactone when the patient is troubled by the development of facial and body hair. While spironolactone will not cause regression of the terminal hair follicles, patients on spironolactone therapy may require less frequent shaving or electrolysis treatments. Cyproterone acetate is another antiandrogen medication not approved for use in the US, but used in MTF patients in other countries.[6]

Promotion of the Development of Desired Secondary Sex Characteristics

The use of hormonal interventions, often referred to as *cross-sex or gender affirming hormones*, to promote the development of desired secondary sex characteristics in transgender persons can be considered in carefully screened and counseled adolescents with gender dysphoria (Table 2). Specifically, the use of 17β-estradiol in MTF individuals, and testosterone in FTM individuals, are used to induce the development of the secondary sex characteristics of the affirmed gender. Broad goals of treatment are to improve psychological functioning and general well-being, and enhance the patient's ability to present as their affirmed gender in social life. The WPATH standards of care do not specify an age at which cross-sex hormones can be administered, but suggest that obtaining parental consent.[1] The Endocrine Society suggests that cross-sex hormones can be considered "around age 16."[2] In our practice, we have found that for many patients there is significant psychosocial risk in waiting until age 16 years to start cross-sex hormones if the patient is otherwise stable in their transgender identity. It is therefore our practice, and the practice of similar institutions, to consider cross-sex hormone treatment initiation as young as age 14 years.[5,6]

MTF individuals are treated with 17β-estradiol to induce female secondary sex characteristics. Treatment with 17β-estradiol will promote the development of breast tissue and development of a more feminine body habitus. These changes are more effective when testosterone production is reduced, either by using GnRH agonist medication or a progestin concurrently. Higher doses of 17β-estradiol would be required to produce feminizing changes if the testosterone concentration is in the normal male range.

17β-estradiol is available in oral, sublingual, transdermal, and intramuscular preparations.[6] We prefer to use oral or transdermal 17β-estradiol. In a patient who is concurrently being treated with GnRH agonist, we would use oral 17β-estradiol (Estrace®) 0.5 mg daily and increase gradually to 2 mg daily, with dose increases every 4–6 months, or transdermal 17β-estradiol (such as Climara® or Vivelle-Dot®) starting at 12.5 or 25 μg weekly. In our practice, adolescent patients on GnRH agonist therapy concurrent with 17β-estradiol are able to achieve normal breast development without need or desire for later breast modification surgery. Similar results may be possible using a combination of medroxyprogesterone and 17β-estradiol or norethindrone and 17β-estradiol. Without any concurrent suppression using GnRH agonist or progestin, patients require higher doses of estrogen to suppress testosterone production and overcome its androgenic effect on the breast tissue. Cosmetic results may be less favorable and higher dose estrogen therapy carries thrombogenic risk. Once a patient undergoes gonadectomy as part of gender confirmation surgery, monotherapy with 17β-estradiol is sufficient. Additionally, some centers use progesterone concurrently with estradiol to improve breast development, although the effects have not been adequately studied.

FTM individuals are prescribed testosterone to promote the development of male secondary sex characteristics. Testosterone is available via many different preparations including intramuscular, gels and creams, and patches. Testosterone for pubertal induction has classically been given as an intramuscular preparation (as testosterone cypionate or testosterone enanthate). Intramuscular testosterone, when used for male pubertal induction,

is often used starting at 25 mg every 2 weeks with gradual dose increases to 100–200 mg every 2 weeks. Many centers use testosterone cypionate or testosterone enanthate administered as a subcutaneous injection administered by the patient or his parent weekly. It can be started at 12.5–25 mg weekly increasing to 50–100 mg weekly.[6] Doses are adjusted to keep the testosterone concentration in the normal male range for age, and based on clinical response. The subcutaneous method allows for in-home administration after a brief in-office education on subcutaneous administration technique. Because testosterone for injection is suspended in oil, it does not draw readily through a standard insulin syringe. Instead, a thicker gauge needle, such as a 21-gauge-needed for drawing, and a 25-gauge needle for injecting, must be prescribed for administration.

Longitudinal Screening and Anticipatory Guidance

Patients being treated with pubertal suppression, spironolactone, 17β-estradiol, and/or testosterone require continued support from a mental health professional, longitudinal follow-up to assess clinical response and development of untoward side effects of treatment, and laboratory monitoring. Rosenthal suggests that patients undergoing pubertal suppression using GnRH agonist medication should have a physical exam including monitoring of height, weight, and pubertal staging, as well as biochemical assessment of puberty using LH, FSH and estradiol or testosterone measurement every 3 months and a bone age evaluation annually. Additionally, due to the delay in bone density accrual in patients undergoing pubertal suppression, it is advised to follow bone health using measurement of calcium, phosphorus, alkaline phosphatase, and 25-hydroxyvitamin D annually, as well as consideration for dual-energy X-ray absorptiometry (DEXA) annually.[6] Spironolactone can cause hyperkalemia, therefore, we obtain a baseline electrolyte panel and repeat with each dose adjustment and when obtaining other laboratory evaluations. In patients prescribed 17β-estradiol or testosterone, Rosenthal suggests clinical follow-up every 3 months to assess height, weight, blood pressure, and pubertal progression. At these visits, LH, FSH, and estradiol and/or testosterone can be assessed. In addition, he suggests following calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitmain D, complete blood count, renal function, liver function, fasting lipids, glucose, insulin and hemoglobin A1C, plus prolactin in male-to-female patients.[6] Patients who had puberty suppressed and who are subsequently being treated with cross-sex hormones can also be monitored for gains in bone density using DEXA.[6]

While long-term health data is sparse with regards to adolescents, some data exists in the adult transgender literature. In longitudinal studies of FTM adults, testosterone administration (250 mg IM every 2 weeks) is associated with lower high-density lipoprotein (HDL) and higher triglycerides after 6–12 months of treatment compared to baseline.[85–87] However, long-term testosterone administration does not appear to alter fasting insulin or glucose utilization in FTM adults compared to a pre-testosterone baseline assessment.[86] A Dutch study of FTM adults on testosterone did not suggest an increased incidence of cardiovascular events or increased mortality compared to the general population.[88]

Elevated blood pressure, fasting insulin and decreased insulin sensitivity have been reported in MTF adults treated with ethinyl estradiol.[86,87] Treatment of MTF adults with ethinyl

estradiol has also been associated with increased risk of cardiovascular death.[88] After 1990, 17β-estradiol was used in the Netherlands in favor of ethinyl estradiol due to its more favorable cardiovascular risk profile.

We advise discussing potential impairment to fertility, not only prior to starting cross-sex hormones, but also prior to starting pubertal suppression. Even though pubertal suppression using GnRH agonist medications by themselves do not impair future fertility, their use combined with cross-sex hormones does impair fertility. In our experience, many adolescent patients, even those who are not transgender, are often reticent to discuss their future fertility. The conversation can be more complex in transgender adolescents who may have some desire to have biologic children, but who bristle at the idea of using their own anatomy to accomplish this. If a patient has progressed far enough into natal puberty such that cryopreservation of sperm or oocytes is possible, this option should be discussed. Providers treating transgender adolescents should familiarize themselves with cryopreservation options in their community. The cost of preservation methods, especially the preservation of oocytes, is often a significant barrier.

Gender Affirmative Surgery

Mental health and medical providers caring for transgender adolescents should become familiar with common surgical interventions used in the transgender patient population, and should be knowledgeable about what surgical resources are available in the community. Surgical interventions used in transgender persons for the purposes of transition are often referred to as *gender affirmation* surgeries. Procedures may include genital surgeries, chest surgeries, and a variety of other gender affirming procedures. The most common surgical procedures performed in MTF individuals include breast augmentation surgery, genital surgery including penectomy, orchiectomy and vaginoplasty, facial feminization surgeries, voice surgery, thyroid cartilage reduction, and hair reconstruction. Electrolysis or laser hair removal is also commonly performed. In FTM individuals, surgical procedures include mastectomy, and genital surgeries including hysterectomy/salpingoophorectomy, metoidioplasty with phalloplasty, vaginectomy, scrotoplasty, and implantation of erectile and testicular prostheses. Genital surgeries are typically not recommended until the patient has reached legal age of majority. Chest surgery in FTM patients can be considered earlier.[1]

Outcomes

Treatment with pubertal suppression in transgender adolescents improves psychological functioning and decreases depressive symptoms, however it does not seem to eliminate gender dysphoria.[72] Long-term outcomes data from the Netherlands suggests that transgender persons treated with pubertal suppression, followed by cross-sex hormones and finally gender affirmation surgery in young adulthood yields positive outcomes with none regretting starting gender affirming medical treatments.[73] In a study primarily sampling from the US, FTM individuals reported diminished quality of life compared to cisgender males and females, however, those who have received testosterone report significantly higher quality of life compared to those who have not.[89]

More robust long-term outcomes data may be necessary for the WPATH and The Endocrine Society recommendations to be more fully adopted, embraced and refined. In addition, these interventions will remain “off-label” in the US until approved by the US Food and Drug Administration. That said, it is evident by the growing demand of these interventions and the increase in pediatric gender programs in the US, that gender affirming medical interventions for appropriately assessed patients has become the standard of care.

Challenges and Barriers to Care

The National Transgender Discrimination Survey Report on Health and Health Care in 2010 surveyed over 6,000 transgender adults in the U.S. and U.S. territories and found that transgender adults experience discrimination by medical providers, with 19% of respondents reporting that they have been refused care due to their gender identity. Over a quarter responded that they have been verbally harassed in a medical setting and over half had to teach their provider about transgender healthcare. Over a quarter reported postponing or delaying needed either preventive care or care when they were sick or injured.[61] Transgender individuals who belong to racial and ethnic minorities experience more discrimination.[90] Finally, insurance company denial of transgender-related interventions remains a significant barrier to care.[12] There have been efforts to improve resident and medical student education and comfort with taking care of transgender patients,[10,91] including a recent report by the Association of American Medical Colleges on implementation of curricular changes.[92]

Current Gender Management Programs in the US and Canada

A recent report provides descriptions and contact information for 35 gender programs in the US and Canada.[93] In addition to these programs, several other programs are known to exist by the authors. The descriptions of the various programs in this report makes clear that different centers have approached providing gender services to children and adolescents in diverse ways. For example, providers from the fields of pediatric endocrinology, adolescent medicine, gynecology, primary care, and nurse clinicians are working in these programs to provide hormonal interventions. Programs often employ mental health providers from the fields of social work, psychology and psychiatry to provide individual counseling, assessments, family therapy and/or group therapy. Some programs serve as a primary care medical home for patients, whereas others function as a consultative program.[93]

We suggest that other roles of multi-disciplinary programs could include: providing training programs for hospital staff and other members of the health system, advocating for changes to paper forms and the electronic medical record to make them more gender inclusive, providing education for medical students and trainees, promoting community partnerships, collaborating with and/or providing education to school systems, promoting research, and assisting with transition to adult care.

Case Examples

Patient 1

An 11-year-old biologic male presented to the pediatrician with concerns regarding gender identity. The child had been interested in stereotypically feminine toys and play from a very young age, and the parents had assumed that the child would grow up to be a gay man. However, more recently the child has clearly expressed a female gender identity to the parents. The child has declared herself to be transgender and insisted on use of female pronouns at home. The parents noted that school performance had suffered and the child has become withdrawn and depressed over the past year. The pediatrician referred the family to a mental health professional with experience in gender identity in children. After several sessions, the mental health professional confirmed a diagnosis of gender dysphoria and recommended referral to a medical clinic with experience in gender dysphoria. At the clinic, the child was found to be at SMR 2. After discussion of risks and benefits of intervention, the child and family elected to proceed with pubertal suppression. A bone age and DEXA were found to be normal for age, and 25-hydroxyvitamin D was slightly low. A histrelin acetate implant was placed and vitamin D supplementation was initiated. Pubertal suppression continued until age 14. By that time, the child had made a complete social transition, using a female name and pronouns at home and at school, and had been supported by ongoing therapy from her mental health professional. Oral 17β-estradiol was started and pubertal suppression with histrelin acetate was continued. The child proceeded through a normal female puberty on 17β-estradiol treatment. At age 18, she elected to have gender affirmation surgery including orchiectomy and vaginoplasty, at which point histrelin acetate was discontinued.

Patient 2

A 10-year-old biologic female with characteristically male interests and behaviors became distressed with the development of breast budding. The patient also disclosed a male gender identity to friends, and then to parents. After a diagnosis of gender dysphoria was made by a mental health professional, the child was referred to a gender program. The clinic physician confirmed breast maturity rating 2, and after discussion with the patient and family, suppression of puberty was initiated using leuprolide acetate, administered every 90 days. The treatment halted progression of breast development. At age 15, after the child had made a complete social transition, testosterone enanthate was initiated, administered subcutaneously weekly at home. At age 19, the patient elected to undergo hysterectomy/salpingoophorectomy and leuprolide acetate was discontinued.

Patient 3

A 15-year old biologic male with female affirmed gender identity presented to a gender clinic after being referred by their primary care physician and mental health professional for treatment of gender dysphoria. The adolescent was found to be at SMR 4. Goals of treatment were determined to be suppression of continued masculinization and promotion of feminization including breast development. The provider attempted to prescribe a GnRH agonist but it was rejected by the patient’s insurance. The provider instead prescribed

norethindrone to suppress androgen production, spironolactone to inhibit androgen action, and 17β-estradiol to promote breast development and feminization.

Patient 4

A 16-year-old biologic female presented to a gender clinic after receiving a diagnosis of gender dysphoria by a mental health professional. The teen was especially dysphoric with monthly menses, but the family was uneasy about committing to irreversible therapy with testosterone. Treatment with norethindrone 5 mg oral daily was initiated, and the monthly menses were suppressed, with resulting improvement in well-being. At age 18, the patient had made a complete social transition and elected to start testosterone, prescribed at 50 mg subcutaneous weekly, at which point norethindrone was discontinued without subsequent return of menses on testosterone monotherapy.

Patient 5

A 12-year-old biologic male presented to the gender clinic after referral by a mental health professional. The child had been having dysphoric feelings about his male pubertal development, and was found to be at SMR rating 3. Treatment with a GnRH agonist was initiated. The child continued in therapy and by age 14 had developed a better understanding of their gender identity. The child accepts that they do not identity completely with a male or female gender identity, and begins to refer to themself as genderqueer. They prefer to be referred to using the them/they/their pronouns. After discussion with the family and mental health professional, the decision is made to withdraw the GnRH agonist medication and allow male puberty to progress with continued supportive counseling in place.

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Key points

- Children and adolescents with gender dysphoria are presenting for medical attention at increasing rates.
- Standards of Care have been developed which outline appropriate mental health support and hormonal interventions for transgender youth.

Table 1

Terminology Related to Gender Identity

Gender identity	An internal feeling of one's gender as a boy or man, girl or woman, no gender, or a non-binary understanding of one's gender
Biologic sex	The genetic, anatomic, and hormonal determinants of sex classified as male or female, or indeterminate due to a disorder of sex development
Transgender	Having a gender identity which is not congruent with one's biologic sex
Cisgender	Having a gender identity which is congruent with one's biologic sex
Transsexual	A term most often used to describe a transgender person who is or has transitioned using hormones and/or surgical procedures
Gender non-conforming	Describes a person who behaviors, actions, or interests do not conform to the societal expectations based on their biologic sex
Gender role	The stereotypical role which members of each biologic sex are expected to play based on societal norms or expectations
Gender dysphoria	A DSM-defined diagnosis describing distress caused by a incongruence between gender identity and biologic sex
Agender	A gender identity characterized by feeling no identification with being a boy or man, girl or woman, or any other gender identity
Gender fluid	Gender identity which varies over time
Genderqueer	A term used by people who do not classify themselves using conventional gender distinctoins, but may instead identify as neither gender, both genders, or a combinatoin of male and female genders
Gender attribution	How an observer decides which sex or gender they believe another person to be

Table 2

Medications used in the treatment of transgender adolescents

Prevention of the development of unwanted secondary sex characteristics			
Class of medication	**Medication names**	**Mechanism of Delivery**	**Mechanism of action**
GnRH agonists	Leuprolide acetate Histrelin acetate	IM injection SC implant	Inhibition of the HPG axis
Progestins	Medroxyprogesterone acetate Norethindrone	Oral or intramuscular injection Oral	Inhibition of the HPG axis
Androgen receptor inhibitors	Spironolactone Cyproterone acetate	Oral Oral or intramuscular injection	Inhibition of testosterone action
Promotion of the development of desired secondary sex characteristics			
Class of medication	Medication names	Mechanism of Delivery	Mechanism of action
Testosterone	Testosterone enanthate Testosterone cypionate Other testosterone	IM injection IM injection Transdermal gels and patches	Activation of androgen receptors
17β-estradiol	17β-estradiol	Oral or transdermal patch most common; also available as IM injection and sublingual	Activation of estrogen receptors

Abbreviations: IM: intramuscular; SC: subcutaneous; HPG: hypothalamic-pituitary-gonadal