Key Points

❖ Treatment of gender dysphoria with hormonal interventions in carefully assessed adolescents can reduce dysphoria, prevent development of unwanted secondary sex characteristics, and support development of desired secondary sex characteristics.

❖ Treatment requires collaboration between experienced mental health providers and medical providers.

❖ Pubertal suppression, a fully reversible intervention, can be considered at sexual maturity rating 2 (early puberty). This intervention can reduce dysphoria, prevent development of unwanted secondary sex characteristics, improve future gender attribution (“passability” as the affirmed gender), and obviate the need for some surgical interventions.

❖ Cross-sex hormones (17 beta-estradiol and testosterone) can be used to support the development of desired secondary sex characteristics in older adolescents with persisting gender dysphoria.

❖ Treatment of adolescents with hormonal interventions has unique surgical considerations. Medical providers caring for this patient population should familiarize themselves with the surgical options available to adolescents and adults with gender dysphoria.
Gender identity refers to a person's internal sense of gender (for example, boy, girl; man, woman; or a nonbinary identification such as genderqueer). A transgender person feels discordance between assigned biologic sex at birth and gender identity. Gender dysphoria refers to the discomfort felt as a result of this discordance. Gender dysphoria in childhood and gender dysphoria in adolescents and adults are defined separately in the Diagnostic and Statistical Manual of Mental Health Disorders, edition 5 (DSM-5), and in the previous edition was referred to as gender identity disorder. Children and adolescents are diagnosed with gender dysphoria if they have a significant difference between their experienced and assigned gender that has persisted for at least 6 months and causes significant distress or impairment in functioning. The change in terminology removes the stigmatizing word “disorder” and highlights that the dysphoria can improve with a variety of interventions, including counseling, cross-sex hormones, and gender affirmation surgery (GAS). Although there is an evolving deemphasis on the pathology of gender dysphoria and acceptance of gender identity diversity, transgender adolescents continue to be disproportionately affected by mental health comorbidities, such as anxiety, depression, self-harm, and suicidality. The World Professional Association for Transgender Health (WPATH) and the Endocrine Society provide clinical standards of care for treatment of the transgender adolescent.

The Transgender Child

Children are born into a gendered world, where boys and girls are often dressed differently and encouraged to participate in different types of play, and where men and women may traditionally assume different familial or occupational roles. In addition, stereotypical gender roles and gender behavior vary among different cultures and also change over time. Children 2 to 3 years of age are able to label themselves as boy or girl; by ages 4 to 5, they can understand the stability and lasting nature of gender. Gender-specific toy preference emerges as young as 12 months, and children can use gender labels (boy, girl) by 2 years of age. As young children begin to develop preferences in play and dress, these behaviors may appear very gender conforming, very gender nonconforming, or somewhere within this spectrum. Some gender nonconforming children may state a desire to be the other gender or express a feeling that they are the other gender, even by 3 years of age. Young children with cross-gender identification may become transgender adolescents; however, the evidence suggests that a larger percentage will not be transgender, and that individuals with a cross-gender identity in young childhood that later desists have high rates of identification as gay or lesbian.

Sex hormones, chiefly testosterone and estrogen, are steroids produced by the testes and ovaries that cause a multitude of effects that result in biologic differences between males and females. In fetal life and also in the first 6 to 12 months of postnatal life, there are significant differences in sex hormone levels in male and female fetuses and infants. The absence of testosterone production in fetal life results in normal female genitalia, whereas testosterone produced in the fetal testes is converted to dihydrotestosterone in the genital tissue, resulting in virilization of the external tissues into normal male genitalia. Differences in sex hormone levels during fetal life and infancy between the biologic sexes also likely play an important role in sexual differentiation in brain organization. These differences may be...
an important contributor to group differences in behaviors observed between males and females later in life.\textsuperscript{13,14}

In later childhood, as gender identity begins to manifest, the testes or ovaries have entered a quiescent stage with very little sex hormone production, and therefore there is little difference in the hormonal milieu between prepubertal male and female children (Figs. 14-1 through 14-3). Therefore hormonal intervention is not indicated for prepubertal children. Instead, the child and family can focus on mental health and logistical issues, such as addressing mental health comorbidities (for example, anxiety or depression) and deciding whether to make a social transition to the affirmed gender in young childhood. Although there is consensus that prepubertal children with gender dysphoria should be seen by a mental health professional with gender experience, there is not a consensus among mental health providers with respect to the goals of treatment.\textsuperscript{15} Some argue that because of the frequency of desistance later in adolescents, the therapeutic goals should focus on reduction in dysphoria through acceptance of the biologic sex.\textsuperscript{16} Another strategy focuses less on gender identity but rather on emotional, behavioral, and family problems that are co-occurring.\textsuperscript{17} Finally, affirmative approaches help families to support the child’s identified gender and assist children and families in making a social transition.\textsuperscript{18} When prepubertal children make a social transition, presenting themselves as their affirmed gender, their ability to “pass” is aided by the fact that they have not yet developed secondary sexual characteristics. This process of “passing” is also known as gender attribution, the process an observer undertakes when deciding what gender they believe another person is.\textsuperscript{15}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig_14-1.png}
\caption{Transgender children, all expressing a gender incongruent with their biologic sex. Before production of sex hormones, children are quite passable as either gender. [Courtesy of Sarah Wong from \textit{Inside Out: Portraits of Cross-gender Children}, 2011.]}
\end{figure}
Fig. 14-2  A prepubertal transgender boy. (Courtesy of Sarah Wong from Inside Out: Portraits of Cross-gender Children, 2011.)

Fig. 14-3  A prepubertal transgender girl. (Courtesy of Sarah Wong from Inside Out: Portraits of Cross-gender Children, 2011.)
Normal Puberty

Puberty, the life stage characterized by the development of secondary sexual characteristics, begins with the activation of the gonadotropin-releasing hormone (GnRH) pulse generator in the hypothalamus, which results in pulsatile luteinizing hormone (LH) and follicle-stimulating hormone (FSH) production within the anterior pituitary and secretion into the systemic circulation. LH in turn causes the production of testosterone in testicular Leydig cells and androgens in ovarian Theca cells, which are converted to estrogen within the ovary (Fig. 14-4). FSH causes germ cell maturation and testicular enlargement in males and the growth and recruitment of ovarian follicles in females.\textsuperscript{19,20} In males, testosterone and dihydrotestosterone cause the development of male secondary sexual characteristics and musculoskeletal changes, such as enlargement of the phallus, enlargement of the laryngeal prominence and deepening of the voice, development of facial hair, an increase in lean muscle relative to fat, widening of the shoulders, and masculinization of the facial bones and jaw. Testosterone production during puberty also causes accelerated growth within skeletal growth plates, the effect of which results in taller stature among men compared with women. In females, estrogen production causes the development of glandular breast tissue. This is followed by maturation of the vulva and vaginal epithelium, proliferation of the uterine lining with subsequent menstruation, distribution of body fat to the hips and buttocks, and skeletal growth, followed by closure of epiphyseal growth plates.\textsuperscript{21}

![Fig. 14-4](image-url) The hypothalamic-pituitary-gonadal axis.
The hallmark physical examination finding heralding the start of central puberty in males is testicular enlargement and in females development of breast buds. These early findings define testicular and breast sexual maturity rating (Tanner stage) 2. Pubic hair development, which may develop before central puberty as a result of adrenal androgen production, is not a reliable marker of activation of the hypothalamic-pituitary-gonadal axis. Th average timing of pubertal initiation has historically been age 10 to 11 years in females and age 11 to 12 years in males, with precocious puberty defined as initiation before age 8 years in females and age 9 years in males; however, new evidence suggests that normal central puberty may occur in the absence of pathology at ages younger than previous estimates.24 Peak height velocity occurs about 2½ years after the start of pubertal growth acceleration.25 In males, characteristics that significantly affect gender attribution, such as facial hair development, completion of voice change, and masculinization of facial bones, occur later compared with genital development. The lateness of these changes within normal male puberty provides an incentive for pubertal suppression in transgender males who present in late puberty. In females, breast development typically progresses from sexual maturity rating 2 to 5 (fully developed) within 4 to 5 years, and menses typically begins 2 to 2½ years after breast budding.21

Overview of Medical Management

Both WPATH and the Endocrine Society standards of care suggest that the diagnosis of gender dysphoria should be made by a mental health professional before consideration of hormonal intervention.5,6 Some pediatric centers perform mental health evaluations as part of a multidisciplinary gender team, emphasizing the role of mental health assessment and support in concert with medical treatment.26 The goals of hormonal treatment include prevention of the development or progression of unwanted secondary sex characteristics of the biologic sex and the induction of desired secondary sex characteristics of the affirmed gender. Broader goals of treatment include a reduction in dysphoric feelings, enhanced ability to "pass" as the affirmed gender, resulting in improved integration into society, and reduction in comorbid mental health outcomes such as anxiety, depression, and suicidality. Long-term outcome data from the Dutch group suggest improvement in psychological function in carefully selected adolescents treated with pubertal suppression followed by cross-sex hormones and a multidisciplinary team throughout treatment.27,28

Pubertal Suppression

The management sequence of treating early pubertal children with GnRH agonist medication to suppress puberty, followed by cross-sex hormones later in adolescence (Fig. 14–5), was first described by Cohen-Kettenis and colleagues29,30 at the Vrije University Medical Center in Amsterdam. Pubertal suppression allows a transgender child in early puberty the time to explore his or her gender identity without the continued influence of sex hormones, which can cause dysphoria and permanent changes to the body. Not only can puberty suppression reduce dysphoria, it can result in enhanced gender attribution later in adolescence and adulthood. It also can obviate the need for future surgical interventions. For females, if pubertal suppression is initiated at pubertal stage 2 breast development, masculinizing chest reconstruction may be avoided. If suppression occurs later but before full breast development with an inframammary fold, a less invasive chest surgery (for example, through an areolar incision rather than an inframammary incision) may be successful. For males, pubertal suppression before development of facial hair, voice deepening, and facial
and skeletal masculinization can dramatically enhance gender attribution. The need for such interventions as facial and chest electrolysis, vocal cord surgery or voice therapy, and facial feminization surgery can be eliminated. In addition, blunting of the testosterone-dependent growth acceleration with pubertal suppression in males can mitigate tall stature in transgender women.

Both WPATH and the Endocrine Society guidelines recommend initiation of GnRH agonist after the start of puberty (sexual maturity rating 2). In an effort to prevent puberty from beginning, treatment before the start of puberty is not recommended. This is likely because the persistence of gender dysphoria in the setting of exposure to early pubertal levels of sex hormones is an important diagnostic consideration.

GnRH agonist medications have been used extensively in this age group for the treatment of precocious puberty for more than 25 years and are considered safe and reversible. In the transgender population, theoretical risks include reduced bone mineral density accrual while the patient is receiving treatment (this has been found to improve after treatment with cross-sex hormones) and the unknown impact on brain maturation while the patient is on suppression. The concern about brain maturation may be overstated, given that this is not a significant concern for children with constitutional delay of puberty.

GnRH agonist medications work by inhibition of pulsatile LH and FSH secretion from the anterior pituitary gland. It can be administered as an injectable drug administered every 1 or 3 months (intramuscular leuprolide acetate) or as a subcutaneous implant recommended for replacement annually (histrelin acetate). Use of intranasal preparations of GnRH agonist for transgender patients has not been reported in the literature. In our experience, histrelin acetate administered in either the pediatric preparation (delivering 65 μg per day of active medication) or adult preparation (delivering 50 μg per day of active medication) is effective at suppressing puberty in transgender adolescents and remains effective longer than 1 year and usually more than 2 years. The choice of preparation is based on patient and family preference and can be affected by availability and insurance coverage. We
have found that in patients in whom insurance coverage is denied, the most cost-effective method of administration is to use the adult preparation of histrelin acetate. Use of GnRH agonist for pubertal suppression in transgender adolescents is considered off-label in the United States, because the Food and Drug Administration has not listed gender dysphoria as a clinical indication for use, despite the fact that this is the current standard of care.

In addition to GnRH agonists, other medications that reduce sex hormone production or action are often used in transgender adolescents. Progestins, such as medroxyprogesterone acetate or norethindrone (administered as a daily oral tablet or an intramuscular injection every 3 months), reduce the pulsatile release of LH and FSH from the anterior pituitary and also directly inhibit sex hormone production in the gonads. Progestins can be used in a menstruating FTM patient to suppress menses if the menses are causing significant dysphoria. In this patient group, which has often completed breast development, full suppression of puberty with a GnRH agonist is not required to achieve menstrual suppression. Instead, the less expensive progestins are a good alternative to minimize dysphoria. MTF patients can be similarly treated with progestins if GnRH agonists are unavailable or unaffordable. Treatment of MTF patients with progestins in early puberty can lower testosterone production and in late adolescence can allow lower, safer doses of estrogen to be used for a similar effect.32 As opposed to GnRH agonists, progestins may cause acne, nausea, and weight gain or bloating.

Spironolactone, an oral medication also used as a weak diuretic, is an androgen receptor antagonist used by MTF adolescents to reduce androgen effects.32 We commonly prescribe spironolactone when there is a desire to reduce growth of problematic facial and body hair in MTF patients who have already progressed to late male puberty. With treatment, hair becomes finer and more amenable to removal by electrolysis.

Cross-Sex Hormones

Cross-sex hormones, 17 beta-estradiol in MTF patients, and testosterone in FTM patients, are used to induce the development of gender-affirming secondary sex characteristics in the transgender adolescent. The WPATH standards of care do not specify an age at which cross-sex hormones can be administered but suggest that obtaining parental consent is preferred.5 The Endocrine Society suggests that cross-sex hormones can be considered at about 16 years of age.6 However, there is potential physical and psychosocial risk to patients who wait until age 16 to start cross-sex hormones if the patients are otherwise stable in their transgender identity. Therefore it is our practice and the practice of similar institutions to consider the initiation of cross-sex hormone treatment as young as age 14 years.32,33

MTF patients are treated with 17 beta-estradiol to induce female secondary sex characteristics, specifically breast development and feminine body habitus (Fig. 14-6). The medication is most commonly available in oral, sublingual, transdermal, and intramuscular preparations. We commonly use oral or transdermal 17 beta-estradiol, depending on patient preference. For the MTF patient, adequate suppression of intrinsic testosterone is important for optimal breast development. In our practice, adolescent patients receiving GnRH agonist therapy concurrent with 17 beta-estradiol are able to achieve normal breast development without the need or desire for later breast modification surgery. In suppressed patients, we start oral 17 beta-estradiol at 0.5 mg daily and gradually increase to 2 mg daily, with dose increases every 4 to 6 months (or transdermal 17 beta-estradiol starting at 25 μg weekly). Similar results may be possible with a
combination of a progestin and 17 beta-estradiol. Without suppression, patients require higher doses of estrogen to suppress testosterone production and overcome its androgenic effects on the breast tissue. Cosmetic results may be less favorable, and a higher dose of 17 beta-estradiol carries a thrombogenic risk. In addition, if an MTF patient undergoes gonadectomy as part of GAS, higher suppressive doses of 17 beta-estradiol are not required.

FTM patients develop male secondary sex characteristics from the effects of testosterone therapy (Fig. 14-7). Testosterone for pubertal induction has classically been given as an intramuscular preparation (as testosterone cypionate or testosterone enanthate), starting at 25 mg every 2 weeks, with gradual dose increases to 100 to 200 mg every 2 weeks. Our center and others have successfully used the same preparations administered as a subcutaneous weekly dose of 12.5 to 25 mg, increasing to 50 to 100 mg weekly with a 3 ml syringe and a ½-inch 25-gauge needle. Smaller-gauge needles, such as insulin syringes, are too narrow to draw up the viscous testosterone medication. The subcutaneous method allows home administration of testosterone after a brief in-office education on subcutaneous administration. Doses are adjusted to keep the testosterone level in the normal male range for age, and based on clinical response.
Transgender adolescents considering treatment with cross-sex hormones should be counseled about potential fertility impairment before initiation. If a patient has progressed far enough into natal puberty so that cryopreservation of sperm or oocytes is possible, this option should be discussed.

**Surgical Considerations**

Medical providers who treat adolescents should be familiar with the gender affirmation surgical options available to their patients and should help with referrals. Genital surgeries are typically not recommended until the patient has reached the legal age of majority; however, individual considerations, such as performing surgery at least 1 year before leaving home for college, may result in better compliance to postoperative care, such as vaginal dilations. Chest surgery in MTF patients can be considered earlier.

The sequence of pubertal suppression followed by cross-sex hormone administration has specific surgical implications. What is most evident is the potential elimination of the need for some surgical interventions. An FTM patient starting pubertal suppression at breast maturity rating 2 may not require a masculinizing chest surgery. A slightly later initiation of pubertal suppression (breast maturity rating 3 or 4) may facilitate a smaller procedure, such as a chest surgery through a periareolar incision instead of an inframammary incision. An MTF patient treated with 17 beta-estradiol concurrent with a GnRH agonist may not require breast augmentation surgery to achieve a fully developed chest. She also would not require facial or body electrolysis, facial feminization surgery, or vocal surgery or therapy.

An MTF patient who starts taking pubertal suppression treatments at sexual maturity rating 2 and proceeds to the age of majority without exposure to testosterone will have a much smaller scrotum and phallus than the typical MTF patient presenting for feminizing vaginoplasty. Therefore the surgeon may need to use tissue expansion or other techniques as part of the surgical planning. An FTM patient may require 1 year or more of testosterone treatment to achieve the clitoral enlargement necessary for masculinizing phalloplasty.

**Case Examples**

An 11-year-old biologic male with gender dysphoria presented for a well-child check; the child was determined to have a sexual maturity rating of 2, with testicular enlargement to 6 ml bilaterally. The patient had identified as female from a young age, and the parents, in coordination with a child psychologist versed in gender dysphoria, allowed her to make a complete social transition to female at 8 years of age. The development of testicular enlargement and impending puberty had caused anxiety and decline in school performance. The child was referred to a multidisciplinary gender center, where a mental health professional confirmed the diagnosis of gender dysphoria. The pediatric endocrinologist, confirming the sexual maturity rating 2 and early pubertal levels of LH, FSH, and testosterone, prescribed the GnRH agonist histrelin acetate. Bone health was supported with vitamin D supplementation to keep 25-hydroxyvitamin D within the normal range and with adequate dietary calcium intake. The histrelin acetate implant was replaced at 13 years of age at the first sign of measurable testosterone production. At 14 years of age, after a repeated psychological assessment, the patient started therapy with 17 beta-estradiol (0.5 mg per day orally). The dose was increased to 1 mg daily after 6 months and 2 mg daily after 12 months from initiation. The histrelin implant was replaced again at 15 and 17 years of age. Breast development progressed to sexual maturity rating 5 over 4 years. When she was 18 years old, the patient
was referred for feminizing vaginoplasty. A tissue expander was placed in the scrotum as part of the surgical planning. The gonads were removed during surgery, and the histrelin acetate implant was also removed. Treatment with 17 beta-estradiol continues as the patient’s care is transitioned to an adult provider.

A 15-year-old biologic female presented to the pediatric endocrinologist with her parents for consultation. The patient reported that she had always felt more male than female; however, she had tolerated the dysphoria until the recent development of menses. Over the past 6 months since menarche, she had become depressed and withdrawn and initiated arm-cutting behaviors. The patient began treatment with norethindrone to suppress menses and connected with a mental health professional to begin exploration of gender identity in more detail. Over the next 12 months, the patient’s menses remained adequately suppressed. The patient made a complete social transition to the new gender, male. At 16 years of age, he began treatment with 25 mg per week of subcutaneous testosterone enanthate, which was increased to 80 mg per week subcutaneously over 9 months. Norethindrone was discontinued on initiation of testosterone, and menses did not recur. At this dosage, the testosterone level was maintained in the middle of the normal male range for age. Within 12 months of starting testosterone, there was a noticeable voice change, hair growth on the face and chest, increase in strength, and a subtle masculinization of the facial bones. At 17 years of age, the patient elected to have masculinizing chest surgery. He had a hysterectomy, including removal of the cervix, at age 18 years, and is contemplating a future masculinizing phalloplasty.

A 10-year-old biologic female presented for evaluation to a gender clinic. She was always described as a “tomboy” with stereotypically masculine interests. However, recently she had expressed a male gender identity, and she was distressed about the new development of breast buds. Her parents were concerned about progression into puberty, given her new declaration of male identity. After a comprehensive assessment by a psychologist versed in gender, a diagnosis of gender dysphoria was made. She was treated with leuprolide acetate every 3 months, with adequate suppression of puberty and slight regression of breast buds. The child and her family connected with a local therapist, who helped them to explore her gender identity in greater detail during weekly sessions. Over 9 months, she was able to identify that she has a sexual attraction to females and identifies as a lesbian. Her gender identity lies somewhere on a spectrum between male and female but is more closely aligned with a female identity. She refers to herself as genderqueer and embraces the use of female pronouns when referring to herself. The decision was made to discontinue treatment with leuprolide acetate, and she continues through a normal female puberty.

A 15-year-old male presented to a gender clinic for evaluation with his mother. The child had announced a female gender identity to both parents at age 8 years. The announcement met with disapproval from the patient’s father, and the child was not allowed to present as female or attend therapy. Over the next 5 years, the child became anxious and depressed and had attempted suicide twice, prompting several inpatient psychiatric hospitalizations. At 13 years of age, the patient’s parents divorced, and the mother retained sole custody of the child. Over the past 2 years, the child has had extensive counseling and has made a social transition to female. The transition resulted in reduced symptoms of depression and anxiety; however, continued progression through male puberty has been extremely upsetting. The child was especially distressed about his changing voice, development of facial hair, and masculinization of the face. On examination he was found to be at sexual maturity rating 4, with incomplete development of facial and body hair and facial masculinization. After
receiving a letter of support from his treating therapist and undergoing a comprehensive gender assessment in the clinic, he was treated with histrelin acetate to suppress continued masculinization and spironolactone to reduce facial and body hair growth. Three months later, he began treatment with 17 beta-estradiol in a 25 mg transdermal patch weekly, which was increased to 100 mg weekly over 1 year. He continues to receive treatment with histrelin acetate, spironolactone, and 17 beta-estradiol into early adulthood and is considering feminizing vaginoplasty.

Conclusion

Gender dysphoria in children and adolescents should be managed thoughtfully, with attention to current best practices and standards of care. Adolescents with persisting gender dysphoria in early puberty can be treated with medications to suppress pubertal development. In older adolescents, cross-sex hormones can be considered. The timing of these interventions has important ramifications for future gender affirmation surgery. Providers in the field of gender affirmation surgery must understand the treatment options for adolescents and partner with pediatric clinics to help patients transition into surgical care programs as needed.

References
