Review Article

Transgender in pediatrics: a narrative review

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Background and Objective: In recent decades, we have seen a significant increase in the number of younger patients with gender incongruence. This can partially be explained by the access to information about gender identity on social media, television, and other mass media. Healthcare personnel, particularly pediatrician, need to be educated on the identification, support, and appropriate referrals of these patients to clinicians and mental health providers with experience in gender matters. In this manuscript, we present current knowledge of gender dysphoria in the pediatric population and recommended evaluation and management.

Methods: We searched in PubMed for relevant English literature published between 1995 and 2021 and reviewed peer-reviewed journal articles including reviews, case reports, and guidelines regarding gender dysphoria and transgender, and present data from our pediatric gender clinic.

Key Content and Findings: Early identification and referrals for evaluation and management of gender incongruent youth help avoid the development or worsening of gender dysphoria, depression, and/or suicidal ideation commonly observed when patients do not receive timely diagnosis and care. Treatment with puberty blockers and affirming hormones, when indicated, has shown significant improvement in the psychological wellbeing of these patients.

Conclusions: The development of multidisciplinary teams, including mental health providers, pediatric endocrinologists, adolescent medicine, plastic surgeons, and urologists, should be encouraged in large pediatric centers. Active research on the current management and long-term safety and consequences of these treatments needs to be performed.

Keywords: Gender dysphoria; gender incongruence; transgender; affirming hormones; puberty blockers

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Introduction

Since ancient times, groups that do not follow the binary representation of gender have been identified. More than 4,000 years ago in the Sumerian culture, the priests of gala dressed and behaved as females, and used female names (1). People who identified as a third gender are a historical part of most communities on earth and many exist in current times. In some cultures, they have a special place in society and their traditions are respected. They have used different terminologies to identify themselves as "transgender" people. One example is the Hijras in the Indian subcontinent. The Hijras are officially recognized as a third gender and referenced in the Kama Sutra. They are born as males and some of them go through a rite that includes the removal of their male genitalia (2). We can also observe this

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in other cultures, such as the Fa'afafine of Polynesia, the ladyboys and the tomboys of Thailand, and the Takatapui of New Zealand (3). Of note, most of these groups are comprised of individuals that were born male. However, the Balkan sworn virgins are assigned female at birth. Later in life, after vowing a life of celibacy, they choose to live as males. This is a tradition over 500 years old, principally in the mountains of Albania. However, these virgins do not appear to change their gender due to dysphoria. There are various motives that explain why they become virgins, such as to please their parents, to avoid unwanted marriages, or to inherit the family wealth (4).

The formal clinical management of transgender patients began in Germany. At the beginning of the 20th Century, the German sexologist Magnus Hirschfeld co-founded the Institute for Sexual Science for the study and support of gay, lesbian, and transgender people. In 1906, Karl Baer, a German-Israeli author and social worker, became one of the first people to have sex affirming, female to male surgery, and had full legal acceptance of his gender identity (5). In 1922, with the support of doctors from the Hirschfeld's Institute, Dora Richter, one of the Institute's employees, became the first known trans woman to undergo removal of the penis and had a vaginoplasty (6). One of the most famous patients was Lili Elbe (fictionalized in the movie "The Danish Girl"), who had a total of five genital affirming surgeries (7).

In the United States (U.S.), Alan Hart was the first affirmed male person to undergo gender transition in 1917. However, Christine Jorgensen was the first American to announce publicly her gender reassignment in 1952. This was just a few years after having been a soldier in WWII. She became a leading advocate for the transgender movement in U.S. Testosterone became available in 1935 and diethylstilbestrol in 1938, offering more treatment options to people with gender incongruence.

Over the past two decades, we have witnessed a significant increase in the number of patients with gender incongruence in our pediatric practices in the U.S., and in Europe. Thanks to the publication of guidelines by the World Professional Association for Transgender Health (WPATH) and the Endocrine Society, the evaluation and management of patients with gender incongruence have been standardized and, over the past decade, the number of gender clinics has increased significantly. With the support of the American Academy of Pediatrics presenting literature on comprehensive care for transgender and gender-diverse children and adolescents, access to information on gender incongruence by general pediatricians has been facilitated. The ultimate goals of care for our pediatric patients are emotional well-being and decreasing the potential development of psychological pathologies related to gender incongruence. With this review we aim to provide a better understanding of gender dysphoria definition, evaluation and management.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-66/rc).

Methods

We searched the database PubMed (pubmed.ncbi.nlm.nih.gov) with the searching terms and formula as follows: (gender dysphoria) AND ((adolescents) OR (children) OR (pediatric)) AND ((affirming hormones) OR ("puberty blockers") OR (surgery) OR (management)). We included peer-reviewed journal articles including reviews, case reports, and guidelines regarding gender dysphoria and transgender published between 1995 to 2021. Additionally, we are presenting data from our pediatric gender clinic. Excluded articles were (I) duplicate articles, (II) articles not in English language, and (III) articles not available electronically (*Table 1*).

Definitions

According to DSM-5 guidelines, gender dysphoria in children is defined as:

- A definite difference between one's experienced/expressed gender and the one assigned at birth, of at least 6 months in duration.
- At least 6 of the following accompanying sub criteria:
  - (I) Strong desire to be of the other sex or insistence that they belong to the other sex.
  - (II) Strong preference for cross dressing and dislike or refusal to wear clothing associated with one's assigned gender.
  - (III) Fantasizing about playing opposite gender roles.
  - (IV) Preference for toys, games, or activities of the opposite sex.
  - (V) Rejection of toys, games, or activities of one's assigned gender.
  - (VI) Preference for playmates of the other sex.
  - (VII) Dislike of one's own sexual anatomy.
  - (VIII) Desire to acquire the primary and/or secondary sex characteristics of the opposite sex.

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	01/05/2021–01/10/2021
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters). Note: please use an independent supplement table to present detailed search strategy of one database as an example	Gender dysphoria, gender incongruence, transgender, affirming hormones, puberty blockers, pediatrics
Timeframe	1995–2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	We included peer-reviewed journal articles (reviews, case reports, and guidelines regarding gender dysphoria and transgender) and excluded articles in languages other than English
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Selection was conducted independently by the authors.

- ❖ Gender dysphoria leads to clinically significant distress and/or social, occupational and other functional impairment, with increased risk of suffering distress or disability.
- ❖ Subtypes: with or without defects in sex development.

According to the DSM-5, gender dysphoria in adolescents and adults has the same definition but for adults only requires a minimum of two of the six accompanying sub criteria:

(I) A marked difference between one's experienced/expressed gender and primary and/or secondary sexual characteristics (or in early adolescence, anticipated sexual characteristics).

(II) Strong desire to be rid of one's primary and/or secondary sexual characteristics because of a marked incongruence with one's experienced/expressed gender (or in early adolescence, desire to prevent the development of anticipated sexual characteristics).

(III) Strong desire for the primary and/or secondary sexual characteristics of the opposite gender.

(IV) Strong desire to be of other gender different from one's designated gender.

(V) Strong desire to be treated as other gender different from one's designated gender.

(VI) Strong conviction that one has the typical feelings and reactions of other gender different from one's designated gender.

- ❖ Gender dysphoria leads to clinically significant distress and/or social, occupational and other functional impairment, with increased risk of suffering distress or disability.
- ❖ And gender dysphoria has two subtypes: with or without differences in sexual development (8).

To be transgender is not considered a psychiatric condition anymore, as previously defined in the mental health section in the ICD-9 and ICD-10. The diagnosis of gender dysphoria has changed on the ICD-11 to "gender incongruence", and it is included in a new sexual health section. It will be in effect on January 1st, 2022. Other relevant definitions of terms are listed in *Table 2* (9).

It has been noted that children who are supported in their gender identity early on, do not develop gender dysphoria. For this reason, the diagnosis has been modified to gender incongruence (10,11).

Epidemiology

The prevalence of gender incongruence has increased over the past decade. It is estimated in the U.S. that approximately 150,000 children and adolescents from 13 to 17 years identify as transgender (12). In the pediatric population over the past decade, the number of assigned females with gender dysphoria has increased to two to four times higher than assigned males (13). The prevalence of gender incongruence is approximately 0.6% in the U.S.; however, this varies by state. The largest populations of transgender youth are found in California, Texas, New York, and Florida. The smallest populations of trans youth are found in North Dakota, Vermont, and Wyoming (12). In more socially conservative states, the prevalence is lower than in those that are more progressive. Of note, the prevalence reported in the DSM-5 is far lower than current reports. It is possible that readily available access

Table 2 Terminology

Sex: characteristics that define biological maleness or femaleness, as sex-determining genes, sex chromosomes, H-Y antigen, gonads, sex hormones, internal and external genitalia, and secondary sexual characteristics
Biological sex: physical aspects of maleness or femaleness
Sex designated at birth: the sex assigned at birth based on external genitalia
Sexual orientation: enduring physical or emotional attraction to another person
Gender identity: also known as experienced gender. One's internal sense of gender
Gender identity disorder: term used in the past for gender dysphoria or gender incongruence
Gender incongruence: term used when the gender identity does not match with the sex designated at birth
Gender variance: same as gender incongruence
Gender reassignment: also known as gender-affirming treatment. Hormonal or surgical therapy for those who want to match their bodies with the experienced gender
Cisgender: individual whose gender identity corresponds with the sex assigned at birth
Transgender: individual whose gender identity differ from the sex assigned at birth
Transgender male: also called "female to male". Person assigned as female at birth but who identifies as a man
Transgender female: also called "male to female". Person assigned as male at birth but who identifies as a woman
Transition: process during which a transgender person changes their physical, social and/or legal characteristics to match their gender identity

to information about gender identity and media exposure to people with gender incongruence have allowed people to put a name to their feelings. Commonly, adolescents and young adults report that it was only when they learned of gender dysphoria on a TV program or the internet, that they were able to explain their own feelings, often experienced over several years.

In 2019, we evaluated our cohort of 158 patients with gender incongruence in Miami. At that time 67.7% of our patients were affirmed males (female to male), 29.7% affirmed females (male to female), and 2.5% identified as non-binary. The median age of onset for symptoms of gender dysphoria was 7 years in affirmed females, and 9 years in affirmed males (14).

Development of gender identity

Gender identity is determined by biological, environmental, and cultural factors (15). After the publication of the human genetic sequencing in 2000, we have learned that most human traits are not produced by the variation of a single gene. Rather, it is likely that multiple genes are involved in the development of gender identity. Moreover, the fact that gender is experience across a wide spectrum makes it more difficult to identify genetic markers for non-binary individuals. A study comparing 23 monozygotic female and male twins, and 21 dizygotic female and male twins, showed that when one twin had gender dysphoria, of the monozygotic twins, 39.1% (9 out of 23) were concordant for gender dysphoria, vs none of the dizygotic twins (16). In adolescents, studies have reported heritability of gender dysphoria to be between 38–47% in natal females, and 25–43% in natal males, whereas in adults, estimates ranged between 11–44% and 28–47% respectively (17).

A whole exome sequencing test (WES) involving 13 affirmed males and 17 affirmed females found 21 variants in 19 genes associated with estrogen receptor activated pathways of sexually dimorphic brain development which may be related to gender dysphoria (18). A genetic study evaluating repeat length polymorphisms or single nucleotide polymorphisms in 380 transgender women and 344 control cisgender males, showed a significant association between gender dysphoria and estrogen receptor alpha (*ER* α), steroid 5-α reductase (*SRD5A2*), and steroid sulfatase (*STS*) alleles, as well as *ER* α an sulfotransferase *(SULT2A1*) genotypes. The researchers concluded that gender dysphoria may have an oligogenic component involving several genes related to sex-hormone

signaling (19). Studies in postmortem hypothalamic tissue have shown that the infundibular kisspeptin system has a female-typical expression in trans females (20). It is also known that some patients with genetic conditions producing disorders of sex development have higher risk of changing their assigned gender later in life. Patients with 46,XY karyotype and 5α-reductase deficiency or 17β-hydroxysteroid dehydrogenase type 3 deficiency, have a risk of 50% and 33% respectively of changing their gender if raised as females (21). The fact that a significant proportion of patients with the same condition did not develop gender dysphoria support the theory that social factors may play a role in the development of gender identity as well. In a recent descriptive literature review on gender dysphoria in patients with the 46,XX karyotype and congenital adrenal hyperplasia, 9.6% of patients raised as females, and 18.4% of patients raised as males, developed gender dysphoria (22).

Evaluation

Children start expressing their gender as early as 2 years of age; however, gender identity may evolve later in life. A significant number of children report wanting to belong to the opposite gender and/or have phases of cross dressing. However, these ideas or behaviors are transient in over 85% of cases (described by some as "desisters") (23). Children with persistent, consistent, and insistent feelings have higher chances of permanent gender dysphoria (described by some as "persisters"). For pre-teens with gender incongruence, the period between 10 and 13 years of age is considered to be of critical importance in determining if dysphoria will continue or resolve. This is because by this time they start to develop secondary sexual characteristics, begin entering romantic and sexual relationships, and establish a comfort level with their gender (24). Worsening of gender dysphoria with the onset of puberty has diagnostic value when assessing a patient for gender incongruence. Pediatricians should be able to identify children and adolescents with gender incongruence, as they are often the first and only health care provider having routine contact with them. It is recommended to offer a third choice for gender, other than male or female, in the office's intake forms. Pediatricians should start assessing gender identity at all annual visits once the child is reaching adolescence, or before if there are cues that the child has gender incongruence. It should be explained to the family that some questions may be uncomfortable, but are part of the routine psychological/well-being evaluation of every child. Then the pediatrician can ask the question directly about how the patient feels being a girl or a boy, and how they feel with their body and the changes happening. Upon physical examination there are some findings that may prompt further exploration, such as the use of chest binders, tight sport bras, very loose shirts in girls, cross dressing, and scars from cutting on arms or legs. It is important to be sensitive during the physical exam and avoid making the patient feel uncomfortable.

Once the child is suspected of having gender incongruence, he/she should be referred to a mental health professional with experience in sexual orientation and gender incongruence. There are multiple support groups online that can help identify those providers in the area where the family lives. In the U.S., there are more than 50 centers that offer medical transgender care. These centers can orient families about the steps in the evaluation process and assist in identifying suitable providers. A mental health professional with training and experience in child and adolescent gender development should confirm the diagnosis and assess, in the case of a child entering puberty, the readiness for blocking puberty, and guide the process of hormone affirmation. It is also essential to evaluate psychiatric comorbidities. Data shows that 40% of transgender patients have at least one suicide attempt in their past, a rate nine times higher than reported in the general population in the U.S. (4.6%) (25). Among our patients, the prevalence of psychiatric comorbidities was 78.5%, depression being the most frequent diagnosis (66.5%), followed by anxiety (33.5%). Psychiatric comorbidities were more common among affirmed males (84.1% *vs.* 66%). History of suicidal ideation in our population was significantly higher than reported in other studies and was more common among affirmed males (70.1%) than affirmed females (49%) (14).

Evaluation should also include assessment of home and school/work environment, and sources of support. Transgender individuals are at increased risk of emotional and physical violence, substance abuse, and high-risk sexual behavior compared to cisgender individuals. It is recommended to periodically assess safety concerns, risky sexual behavior, bullying, and partner violence (25).

Once the mental health professional considers that the child/adolescent is ready to start puberty blockers and/or the hormone affirmation process, the patient should be referred to a specialist with knowledge and experience in the management of this condition. Pediatric endocrinology and adolescent medicine are the most common specialties

offering hormone treatment to these patients. The mental health professional should write a letter according to the WPATH recommendations, stating that the patient meets criteria for gender incongruence and is ready to start treatment with puberty blockers and/or affirming hormones.

Management

For several years, there were no principles or guidelines on how to offer transgender patients the therapeutic options they were looking for. In 1979, the WPATH published the first version of the Standards of Care (SOC) for gender nonconforming patients. The aim of the SOC is to provide evidence-based clinical guidelines for health professionals who are willing to work together with transgender patients to maximize their overall health, psychological well-being, and self-fulfillment. The WPATH-SOC are periodically updated and revised, the seventh and latest revision published in September of 2011 (26). The Endocrine Society also published guidelines for the evaluation and management of transgender patients for the first time in 2009 and the updated version in 2017 (9). The current recommendations are based on these guidelines.

Treatment management varies according to the patient's emotional/psychological condition, age, pubertal stage, family expectations, cultural preferences, insurance coverage, and availability of services in the community. Treatment should always be individualized. For some patients, mental health therapy may be enough to alleviate their dysphoria, others may need mental health therapy and hormone treatment, and the majority will be looking to have hormone treatment and affirming surgeries.

Some adolescents start to experience gender dysphoria with the onset of puberty. It was shown that an early intervention may reduce psychological comorbidities and may give adolescents more time to explore their gender identity before choosing more permanent treatment options (27).

In 1998, there was a first report on the use of gonadotropin-releasing hormone analogs (GnRHa) to stop pubertal development in an affirmed male to avoid non-desired secondary sexual characteristics and physical changes and facilitate the process of gender affirmation (28). Since then, the use of GnRHa, also known as puberty blockers, have been part of the ideal management of youth patients with gender dysphoria. The first protocol using GnRHa was developed in the Netherlands and it is sometimes referred to as "the Dutch" protocol. This protocol determined that after psychological evaluation, adolescents with gender dysphoria were eligible to be treated with GnRHa starting at age 12 years, cross-sex hormones at age 16 years, and gender affirming surgery at age 18 years. Outcomes from this protocol showed that after gender reassignment in younger adults, the gender dysphoria resolved and psychological functioning improved. Their well-being did not differ from that of cisgender individuals of the same age (29).

The Endocrine Society guidelines and WPATH-SOC recommend the use of pubertal blockers with GnRH agonists at Tanner stages 2–3 in adolescents experiencing severe gender dysphoria (26). They can also be used in late puberty to suppress uncomfortable secondary sex characteristics such as menstrual periods in affirmed males or beard/moustache development in affirmed females. Some practitioners use puberty blockers in affirmed females to be able to use lower doses of estradiol during the first stages of hormone affirmation. In *Table 3* we present the criteria to start treatment with pubertal blockers. Before starting any of these medications, the child should be evaluated by a mental health professional with expertise in gender, and the child and family need to sign consents that detail administration and side effects of medications.

The principal concern with using GnRHa to temporarily halt puberty is related to fertility. Not allowing gonads to go through their normal process of maturation makes it impossible to collect eggs or sperm for freezing and future use. Presently, there are no available methods to collect eggs or sperm from patients who are prepubertal or in early puberty. Ovarian and testicular cryopreservation are experimental methods at this time. Another important side effect of GnRHa is related to bone health. A recent study showed that bone mineral density decreases during GnRHa treatment and increases during gender-affirming hormone treatment. Although it recovers among affirmed boys, it continues to be low among affirmed females after 3 years of treatment with estradiol (30).

Multiple formulations of GnRHa are available on the market. Long acting intramuscular and subcutaneous preparations of leuprolide and histrelin have been used for several years for the management of precocious puberty in children. A histrelin implant, replaced annually, has been used successfully. However, when preparations approved for children are not covered by insurance, off-label adult preparations have been used with positive results. A recent study in young patients with gender incongruence compared

Table 3 Criteria for pubertal suppression treatment in gender nonconforming adolescents

The following has been confirmed by a mental health professional
The adolescent has demonstrated a long-lasting and intense pattern of gender dysphoria
The gender dysphoria worsened with the onset of puberty
Any coexisting psychological, medical, or social problems that could interfere with treatment adherence have been addressed
The adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment
The adolescent has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility, and has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process
A pediatric endocrinologist or other clinician experienced in pubertal assessment agrees with the indication for GnRH agonist treatment, has confirmed that puberty has started in the adolescent (Tanner stage 2), has confirmed that there are no medical contraindications to GnRH agonist treatment

GnRH, gonadotropin releasing hormone.

Table 4 Criteria for hormonal treatment in gender nonconforming adolescents

The following has been confirmed by a mental health professional
Persistence of gender dysphoria
Coexistence of psychological, medical, or social problems that could interfere with treatment have been addressed
The adolescent has sufficient mental capacity to estimate the consequences of the treatment
The adolescent has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility) and has given informed consent and the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process
A pediatric endocrinologist or other clinician experienced in pubertal induction agrees with the indication for sex hormone treatment, and has confirmed that there are no medical contraindications to sex hormone treatment

the use of a histrelin implant approved for pediatric use that delivers 65 mcg/day of histrelin with a similar implant indicated for adults that delivers 50 mcg/day, and showed no differences in puberty suppression between implants (31). Puberty blockers are used until cross hormone treatment is able to suppress undesired gonadal hormone production. In affirmed females, this is often achieved with higher doses of estradiol. In affirmed males, treatment with testosterone stops periods in the majority of patients, but it does not decrease estrogen levels to prepubertal levels in most patients. Although treatment with androgen blockers decreases the action of testosterone, these are not as effective at suppressing testosterone production as GnRHa medications. For this reason, to avoid the use of high doses of estradiol, it is ideal to continue GnRHa until the patient is able to undergo gonadectomy.

When the adolescent or young adult is ready for affirming hormone therapy (see *Table 4*), the family should obtain a letter from the mental health professional with gender expertise who has been taking care of the patient. This letter should confirm that the child meets diagnostic criteria for gender incongruence and is ready for affirming hormone treatment. Most providers require the patient and parents or legal guardians sign consent forms that describe and discuss administration and side effects of the medications. Puberty suppression is fully reversible. Their use allows time for the child, their family, and the mental health specialist to determine readiness to start gender affirming hormones, which produce physical changes that are only partially reversible. The patient and family need to be well informed about the consequences of these treatments including future fertility and specific hormone side effects, including acne, libido changes, alterations in facial appearance and body fat distribution, cardiovascular and thromboembolic risks, among others. It is recommended for them to sign consent forms

Table 5 Hormone regimen for affirming females

Drug	Dosage
Oral	
Estradiol	2.0–6.0 mg/day
Transdermal	
Estradiol transdermal patch	0.025–0.2 mg/day
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 weeks; 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/day
Cyproterone acetate	25–50 mg/day
GnRH agonist	3.75–15 mg SC monthly; 11.25–30 mg SC every 3 months

GnRH, gonadotropin releasing hormone; IM, intramuscular; SC, subcutaneous.

Table 6 Hormone regimen for affirming males

Drug	Dosage
Transdermal	
Testosterone gel 1.6%	50–100 mg/day
Testosterone transdermal patch	2.5–7.5 mg/day
Parenteral	
Testosterone enanthate or cypionate	50–200 mg SC or IM every 1–2 weeks
Testosterone undecanoate	1,000 mg every 12 weeks

IM, intramuscular; SC, subcutaneous.

acknowledging these points. The recommended age to start affirming hormones varies according to different sources. However, the 2017 Endocrine Society Guidelines state that while treatment may be started before age 16 years, there is a dearth of literature regarding initiating treatment before age 13.5–14 years.

Female affirming hormone treatment (*Table 5*)

Before starting treatment with estradiol, past medical history and family history of hypercoagulability/clotting should be explored. If positive, laboratory evaluation to determine causes of hypercoagulability and/or an evaluation by hematology should be done before starting treatment. To best imitate normal breast development, affirmed females should be started on low doses of estradiol, increasing the dose gradually every 3 to 6 months. Starting with a higher estradiol dose will produce a tubular shape of the breasts. The use of progesterone, though not recommended in the 2017 Endocrine Society Guidelines, appears to help some patients due to more rapid feminization, decreasing endogenous testosterone production, optimizing breast maturation, increasing bone formation, improving sleep and vasomotor symptoms, and having positive cardiovascular effects (32). However, the reported positive effects of progesterone in breast development, bone health, breast cancer, and cardiovascular disease are questionable (33). Some clinicians add progesterone treatment when requested by the patient or when breast development is not satisfactory on estradiol alone.

If the patient is already in advanced puberty, the use of puberty blockers is optional. Most providers use spironolactone or bicalutamide to decrease the action of testosterone. Spironolactone increases urination and produces depressive symptoms in some patients. Hyperkalemia is a potential, but uncommon side effect that has been reported among adolescent affirmed females during the first 6 months of treatment and resolves upon follow up measurements independent of the dose used (34). The use of bicalutamide, which is a potent androgen receptor blocker, is preferred by some clinicians due to its higher potency compared to spironolactone and cyproterone acetate (not available in the U.S.), and because it produces gynecomastia, which is a positive side effect in this particular situation. Gynecomastia is likely secondary to aromatization of higher levels of testosterone to estrogen. Of note, gynecomastia is also a reported side effect from spironolactone but is more significant with bicalutamide. One issue with bicalutamide is the need for frequent evaluation of liver function tests due to its potential liver toxicity (35).

Male affirming hormone treatment (*Table 6*)

When the child has been treated with a GnRHa, testosterone should be started at a low dose to imitate the normal process of puberty. Testosterone cypionate and enanthate are the most commonly used parenteral preparations in the U.S. Subcutaneous (SQ) administration has shown to be as effective as intramuscular (IM) (36). Occasionally, patients have localized erythema at the site of the injection, which resolves after switching to another

Table 7 Criteria for gender-affirming surgery

Persistent, well-documented gender dysphoria
Legal age of majority in the given country
Having continuously and responsibly used gender-affirming hormones for 12 months (if there is no medical contraindication to receiving such therapy)
Successful continuous full-time living in the new gender role for at least 12 months
If significant medical or mental health concerns are present, they must be well controlled
Demonstrable knowledge of all practical aspects of surgery (e.g., cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

preparation with a different carrier oil (cypionate or enanthate). SQ or IM injections can be administered every 2 weeks, but some patients prefer weekly injections to avoid mood changes resulting from fluctuations in testosterone levels when administered every 2, 3, or 4 weeks. Some patients prefer using gels or creams, but these preparations are often more expensive and not covered by insurance. Also, if stringent hand hygiene is not followed after application, or if the area of application is unprotected, testosterone can be absorbed through the skin of close contacts. Testosterone pellets, which last 4 to 6 months, may also be used. Some patients like them, however problems with scarring and extrusion are occasional complaints. Recently, the use of testosterone undecanoate oral capsules was approved in the U.S. However, there is no experience in the management of gender incongruence with this preparation. Other parenteral and topical preparations of testosterone are available but less frequently used in the pediatric population. When patients are in mid or late puberty, they may be started on higher doses of testosterone. Due to the high degree of dysphoria often associated with menstrual periods, treatment with progestins to stop periods can alleviate the psychological distress. In our practice, we do not require a letter or consent forms to start these medications due to the safety and reversible effect profile. We usually start with norethindrone 5 mg PO daily taken at the same time every day. If periods continue after 2–3 months, we increase the dose to 10 mg. If the patient continues having periods with 10 mg daily, we switch them to medroxyprogesterone 10 mg daily.

Surgery for sex reassignment (*Table 7*)

In our experience, with over 300 pediatric patients, all affirmed males with Tanner stage 4–5 breasts wished to have chest-affirming surgery. Also, a majority of our affirmed male patients would like to have genital-affirming surgery, if the cosmetic outcome, surgical complexity, and costs were not a deterrent. Approximately half of our affirmed female patients wished to have genital affirming surgery.

In general, it is required to have a letter of readiness from a mental health professional with experience in gender care prior to chest affirming surgery. For genital affirming surgery, two letters of readiness are required from two different mental health professionals who have independently evaluated the patient. Genital affirming surgery is done after the patient has reached the legal age of adulthood, in the U.S., this age corresponds to 18 years. Some surgeons start performing chest affirming surgery at age 16 years, particularly when patients have severe dysphoria related to their chest appearance.

A prospective follow-up study from The Netherlands assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (I) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (II) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (III) 1 year after "gender-reassignment surgery" (average age of 20.7 years). Despite a decrease in depression and an improvement in general mental health functioning, gender incongruence persisted through pubertal suppression, as previously reported. However, following sex hormone treatment and gender- reassignment surgery, gender incongruence resolved and psychological functioning steadily improved. Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long term follow-up of individuals managed

Table 8 Fertility preservation options for transgender individuals

Affirmed males	Affirmed females
Prepubertal	Prepubertal
Ovarian tissue cryopreservation (experimental)	Testicular tissue cryopreservation (experimental)
Post pubertal	Post pubertal
Oocyte cryopreservation	Sperm cryopreservation
Embryo cryopreservation	Embryo cryopreservation

according to currently existing clinical practice guidelines for transgender youth (29). In our cohort, the degree of dysphoria improved from 8/10 (no dysphoria =0 and maximum dysphoria =10) before starting affirming hormones, to 4/10 after affirming treatment was established in both affirmed males and affirmed females, and to 2/10 after chest affirming surgery among affirmed males (14). Our patients with gender affirming genital surgery had total resolution of their gender dysphoria (unpublished data).

A metanalysis including almost 8,000 transgender patients who underwent some type of gender affirmation surgery found a very low prevalence of regret of less than 1% (0.6% in trans females and 0.3% in trans males) (37).

Fertility

Collection and freezing of eggs, sperm, and embryos are frequently performed procedures. However, as previously discussed, when puberty blockers are used before the development of an advanced stage of puberty when sperm or eggs can be collected and frozen, the preservation of fertility potential is more difficult. However, as of the writing of this manuscript, over 130 births have been reported from cryopreserved ovarian tissue that was reimplanted into the patient following oocyte retrieval and *in vitro* fertilization. These procedures have been practiced mainly on patients undergoing chemotherapy and/or radiotherapy for treatment of cancer (38). Prepubertal testes from rhesus macaques have been removed, cut into small pieces, proven to be immature, and later transplanted back, with successful production of viable sperm and offspring (39). In a different procedure, skin fibroblasts from mice were transformed into stem cells, later differentiated to eggs, and successfully produced offspring (40). Currently, this technology is potentially viable for humans (41). Although most trans youth are not interested in fertility preservation when beginning pharmacological puberty suppression and gender affirmation, most adult transgender individuals report wanting to have the possibility of having children. Fertility preservation is cumbersome and expensive at this time, but technology is improving the odds of fertility and costs may decrease once these technologies become more commonly used and readily available (*Table 8*).

Conclusions

Due to the recent increase in the number of gender incongruent youth, pediatricians, mental health specialists, and all healthcare personnel need to be educated and trained to interact with and care for these particularly vulnerable populations. Healthcare institutions need to offer formal training to their personnel in communicating with these patients and their families. Additionally, they should provide gender neutral bathrooms, and use preferred names and genders in documentation and identification wristbands. Healthcare providers must be considerate and sensitive in their interactions and physical evaluation of their trans patients. Limitations in the understanding of treatment and long-term consequences of these treatments need to be discussed in depth before starting any pharmacological therapy. Factors that increase the risk of patients changing course with their gender identity need to be identified and discussed with patients and families prior to employing gender affirming medications and surgery. High quality research is necessary to answer several questions and optimize the physical and mental health of gender incongruent patients. To improve communication, accessibility to care, and overall outcomes, multidisciplinary gender clinics that provide mental health care, along with clinical and surgical services, are recommended.

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