

CLINICAL PRACTICE

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Care of Transgender Persons

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A healthy 19-year-old college student presents with the statement that he is transgender and wants to start hormone therapy. The sex recorded at birth was female, but he notes having identified as a boy for as long as he can remember. More recently, his treatment goals have become clearer, including a wish to begin medical treatment and to begin presenting as male. He has no medical or behavioral health concerns and takes no medications. How would you advise this patient?

THE CLINICAL PROBLEM

“GENDER IDENTITY” IS THE TERM USED TO DESCRIBE A PERSON’S sense of being male, female, neither, or some combination of both (Table 1). The terms “transgender,” “transsexual,” “trans,” “gender nonbinary,” “gender incongruent,” and “genderqueer” are adjectives for persons with gender identities that are not aligned with the sex recorded at birth. “Cisgender” is the term for persons who are not transgender — that is, persons whose sex recorded at birth aligns with their gender identity.

Transgender men have male gender identity and were recorded as female at birth. Transgender women have female gender identity and were recorded as male at birth. Gender nonbinary persons may identify as neither male nor female or as having features of both sexes. Gender expression relates to how a person communicates gender identity. Efforts to align physical characteristics with gender identity may be referred to as transition, gender affirmation, or gender confirmation.

Gender dysphoria is a mental health diagnosis that describes the discomfort felt by some persons when gender identity and sex recorded at birth do not align. Not all transgender persons have dysphoria. However, many U.S. insurance companies require a diagnosis of gender dysphoria for reimbursement of transgender medical and surgical interventions.¹ Despite the fact that being transgender is not a behavioral health condition, the codes for a transgender diagnosis are in the mental health section in the *International Classification of Diseases, 9th Revision* (ICD-9), and in the *10th Revision* (ICD-10). The plan for ICD-11 is to add the term “gender incongruence” to a new sexual health section and to remove the term “gender dysphoria” from the document.²

Although the mechanisms that inform gender identity are unknown, current data suggest a biologic underpinning programmed from birth.³⁻⁹ For example, there are reports of XY chromosome intersex persons raised as female who report male gender identity,^{4,5} and identical twin siblings of transgender persons are more likely than fraternal twin siblings of transgender persons to be transgender.⁶ Asso-

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KEY CLINICAL POINTS

CARE OF TRANSGENDER PERSONS

- Survey data indicate that approximately 0.6% of the U.S. population identifies as transgender.
- No medical intervention is indicated before puberty. When puberty begins, reversible therapy with a gonadotropin-releasing hormone agonist can delay puberty until a long-term treatment plan can be established.
- For transgender men, testosterone can be administered to achieve testosterone levels in the male range.
- For transgender women, estrogens lower testosterone levels through central suppression of the reproductive axis while having feminizing effects and protecting bone health.
- In transgender women, estrogen therapy is associated with an increased risk of venous thromboembolism. Concomitant treatment of transgender women with androgen-lowering agents (e.g., spironolactone) allows for administration of lower doses of exogenous estrogen.
- Surgery choice should be customized to patient goals, with consideration of associated risks and the patient's interest in fertility.

ciations between brain anatomy and gender identity have also been reported.⁹ Data from 2016 from the Behavioral Risk Factor Surveillance System at the Centers for Disease Control and Prevention suggest that in the United States approximately 0.6% of adults, or 1.4 million persons, identify as transgender.¹⁰ Many transgender persons experience barriers to health care access and medical mistreatment.¹¹⁻¹⁴ In a Web-based survey of more than 6000 transgender and gender-nonbinary persons, approximately 25% of respondents reported that they had been denied medical services and 30% reported that they had avoided care owing to fear of discrimination.¹² These barriers to care are thought to play a substantial role in the health disparities between transgender and cisgender persons, with higher rates of substance abuse, infection, mental health conditions, and cancer in transgender persons.^{11,12,15-17} Improvement in access to medical care will require the participation of more general providers outside specialized settings.¹⁸

STRATEGIES AND EVIDENCE

PRESENTATION AND ASSESSMENT

Children may label genders and articulate gender identity by 2 years of age.¹⁹ In surveys, up to 2.7% of children may report gender incongruence,²⁰ but many such children do not continue to do so later in life.²¹ The majority of transgender persons present to clinicians in late adolescence or adulthood. Whether the late presentation results from inability to articulate gender identity, failure to recognize gender incongruence, or outside pressure to conform is not known. Desire to avoid the “wrong puberty” may

be the catalyst for some adolescents to report their gender incongruence when they had not done so earlier.²² In retrospect, many transgender persons report that their awareness of their gender incongruence began before puberty.

Transgender identity is established on the basis of history alone; gender incongruence should be persistent, typically being present for years.²³ In addition to obtaining a social and sexual history, along with screening for infections if warranted by sexual history, clinician evaluation of transgender patients should include assessment of anxiety, depression, and suicidality, all of which are reported to be more common among transgender than cisgender persons.²⁴

Any provider able to identify mental health conditions that might confound assessment can determine whether an adult patient meets the criteria for treatment.²⁵ In rare instances, patients who present as transgender actually have obsessive compulsive disorder²⁶ or well-masked psychoses. Providers of mental health care should participate in the assessment of adults if a mental health condition is suspected or identified and participate routinely in the assessment of children and adolescents, who may articulate gender identity more heterogeneously.²⁵ Not all transgender persons seek medical intervention. In one online survey, just over half of transgender respondents reported having sought hormonal or surgical therapy.²⁷

GENERAL PRINCIPLES OF TREATMENT

There are several criteria for the prescription of hormone therapy. These include persistent gen-

der incongruence, capacity to make informed treatment decisions, and reasonable control of associated mental health conditions.

TRANSFEMININE (MALE-TO-FEMALE) HORMONE THERAPY

Conventional therapeutic goals for transfeminine hormone treatment are to reduce growth of facial hair, induce breast development, and induce redistribution of fat and muscle to a more feminine pattern. Initiation of hormone therapy after puberty will not affect height or voice. Because terminal hair on the face continues to grow without androgen stimulation, transgender women may require electrolysis or laser hair removal.

Absent data, the usual strategy involves the use of known physiologic information as a surrogate target to achieve hormone levels that match gender identity, moving testosterone levels from the male range (300 to 1000 ng per deciliter) to the female range (<50 ng per deciliter) and targeting estradiol levels in the range of 100 to 200 pg per milliliter while avoiding supraphysiologic levels (>200 pg per milliliter). Observational studies suggest that physical changes should be anticipated in 6 to 18 months. Although orchiectomy is the most effective means of decreasing testosterone levels, many transgender women instead opt for medical treatment.²⁸

Estrogens suppress androgen production through a central feedback mechanism while inducing feminization and protecting bone health. Commonly used estrogen regimens are reviewed in Table 2. Clinicians should consider relative contraindications to estrogen therapy that may affect treatment decisions, including a history of breast cancer, venous thromboembolic disease, cardiovascular disease, or cerebrovascular disease. Data largely derived from convenience samples from larger clinics with dozens to a few thousand patients²⁹ suggest that transgender women who receive hormone therapy may be at increased risk for deep venous thrombosis, pulmonary embolism, stroke, and myocardial infarction^{30,31} as compared with the expected rates among cisgender persons. It is not known whether these risks are greater than those reported among postmenopausal cisgender women who take exogenous estrogens. Data from transgender women are insufficient to inform associations between thrombosis risk and dose of hormones, blood levels of hormones,

Table 1. Definitions.

Sex and gender

Umbrella terms used to reference biologic characteristics, gender identification, and stereotypical behaviors considered male, female, or variation thereof

Gender identity

Internal sense of being male or female or identifying with both or neither

Transgender, transsexual, trans, gender nonbinary, gender incongruent, genderqueer

Adjectives for persons with gender identity not aligned with sex recorded at birth

Cisgender, nontransgender

Adjectives for persons with gender identity aligned with sex recorded at birth

Gender expression

Ways in which a person communicates gender identity to others

Gender-affirming or gender-confirming hormone treatment and surgery

Medical and surgical interventions for transgender persons performed to align appearance with gender identity

Gender dysphoria

Mental health term that refers to discomfort felt by some persons owing to lack of alignment between gender identity and sex recorded at birth

Sexual orientation

Term that characterizes pattern of romantic or sexual attraction to other people, independent of gender identity

Intersex

Term for conditions in which a person is born with reproductive or sexual anatomy that does not fit typical definitions of female or male. Also known as DSD (differences of sexual differentiation).

route of administration, or duration of therapy. However, the extrapolation of data from observational studies of postmenopausal cisgender women may support the strategy of reducing the estrogen dose or changing to transdermal estrogen preparations in transgender women of a similar age.^{32,33} Neither the World Professional Association for Transgender Health (WPATH) nor the Endocrine Society recommends the use of ethinyl estradiol because it appears to be particularly thrombogenic.^{23,25,34} Treatment generally includes other testosterone-lowering agents that allow for lower doses of estrogens. Estrogen and antiandrogen therapies are started together.

The most common adjunctive agents used to reduce androgen levels (Table 2) are the potassium-sparing diuretic spironolactone, which blocks the action of androgen at its receptor and decreases testosterone levels^{35,36}; the progestin cyproterone acetate, which is popular in Europe; and gonadotropin-releasing hormone (GnRH)

Table 2. Hormone-Treatment Regimens for Transgender Persons.

Medication	Dosage	Potential Adverse Events	Comments
Transfeminine persons			
Estrogens		Increased risk of thromboembolism in some patients	Although supporting data are inconsistent, some favor monitoring triglyceride levels; ethinyl estradiol is not recommended owing to possible increased risk of thrombosis.
Oral			
Estradiol (17β-estradiol)	Initial, 1–2 mg/day; adjust to 2–6 mg/day		Is most commonly used because of its low cost and availability and fact that serum levels can be monitored.
Conjugated estrogens	Initial, 1.25–2.5 mg/day; adjust to 5.0–7.5 mg/day		Blood levels cannot be measured with conventional assays, which may lead to supraphysiologic dosing; conjugated estrogens are generally not recommended when estradiol is readily available.
Transdermal			
Estradiol patch	Initial, 0.025–0.050 mg/day (new patch placed every 3–5 days); adjust to 0.1–0.2 mg/day	Skin reactions in some patients	May be associated with fewer adverse events than oral estrogen.
Parenteral			
Estradiol valerate	Initial, 5–10 mg intramuscularly every 2 wk; adjust to 10–20 mg every 2 wk		Can result in wide fluctuations in estradiol levels. An alternative preparation, estradiol cypionate, is less concentrated.
Androgen-lowering or inhibiting agents			
Spirolactone	Initial, 50 mg/day orally; adjust to 100–300 mg/day	Hyperkalemia, dehydration	Potassium level should be monitored when initiating therapy, when dose is changed, and annually thereafter.
Cyproterone acetate	Initial, 25 mg/day orally; adjust to 50 mg/day	Hyperprolactinemia and meningiomas in some patients	Not available in United States.
GnRH agonists (e.g., leuprolide)*	3.75–7.50 mg intramuscularly or subcutaneously every mo or 1.1.25–22.50 mg every 3 mo		Use may be limited by cost.
Transmasculine persons			
Testosterone		Erythrocytosis; acne may develop or be exacerbated	Erythrocytosis may be associated with polycythemia, in which case patients should be screened for tobacco use and sleep apnea.
Parenteral			
Testosterone enanthate or cypionate	Initial, 50 mg intramuscularly or subcutaneously weekly or 100 mg every 2 wk; adjust to 100 weekly or 200 mg every 2 wk		Subcutaneous and intramuscular injections have been shown to be equally effective; target levels are more easily achieved than with transdermal products; weekly administration diminishes periodicity. Levels should be monitored at peaks (at 24–48 hr after dosing) and troughs (immediately before next dose) or at the midpoint between doses.

Testosterone undecanoate	1000 mg intramuscularly every 12 wk	Oil embolism rare adverse event that requires REMS†
Transdermal or transbuccal		
Testosterone gel	Initial, 50 mg daily; adjust to 100 mg/day	Risk of transfer to others Uniform levels‡; target levels may be difficult to achieve, especially in larger persons.
Testosterone patch	Initial, 2 mg/day; adjust to 4–8 mg/day	Skin reactions in some patients Uniform levels‡; target levels may be more difficult to achieve, especially in larger persons.
Testosterone buccal patch	30 mg applied to gums every 12 hr	Inconvenience of buccal preparation may limit use.

* GnRH denotes gonadotropin-releasing hormone.

† Concerns regarding related risks of pulmonary oil microembolism and anaphylaxis have prompted the requirement for use of a Risk Evaluation and Mitigation Strategy (REMS) in the United States.

‡ Day-to-day levels of testosterone are more uniform with gels and patches than with injectable formulations, which have peaks and troughs.

agonists. Spironolactone is often administered at a higher dose for this indication than for hypertension treatment. Cyproterone acetate may suppress gonadotropins and act as an androgen-receptor antagonist. GnRH agonists suppress testosterone levels but are generally considered as second-line therapy owing to their high cost. Whereas other progestins (e.g., medroxyprogesterone acetate and micronized progesterone) can suppress gonadotropins and thus testosterone secretion, they are not recommended by the Endocrine Society. Medroxyprogesterone acetate has been associated with an elevated risk of cardiovascular disease and breast cancer in postmenopausal women who take conjugated estrogens,³³ and there is concern that the risk may extend to other progestins. Although the 5-alpha-reductase 2 inhibitor finasteride inhibits conversion of testosterone to the more potent dihydrotestosterone in some tissues (e.g., the prostate and scalp), it is not considered to be useful if testosterone levels are already in the female range.

A reported concern with hormonal therapy in transgender women is a rise in prolactin levels (and the potential for development of a prolactinoma). Thus, prolactin monitoring has been recommended.²⁵ However, reports of elevated prolactin levels are limited to clinics that use estrogen–cyproterone regimens. Findings from a retrospective study involving 98 patients who received an estrogen–spironolactone regimen did not show any cases of elevated prolactin levels at up to 6 years of follow-up.³⁷

TRANSMASCULINE (FEMALE-TO-MALE) HORMONE THERAPY

A conventional goal in transmasculine hormone therapy is to bring about physical changes that match gender identity through the administration of testosterone,³⁸ raising hormone levels to the male physiologic range (300 to 1000 ng per deciliter). After approximately 3 to 6 months of treatment, transgender men can anticipate cessation of menses, development of a deeper voice, and increases in facial and body hair, muscle mass, and sexual desire. Acne may develop or worsen transiently and should be treated if troublesome. Other changes may occur over longer periods, such as the development of a male hair pattern and clitoral enlargement.

Regimens include testosterone esters, gels, and patches (Table 2). Injectable testosterone

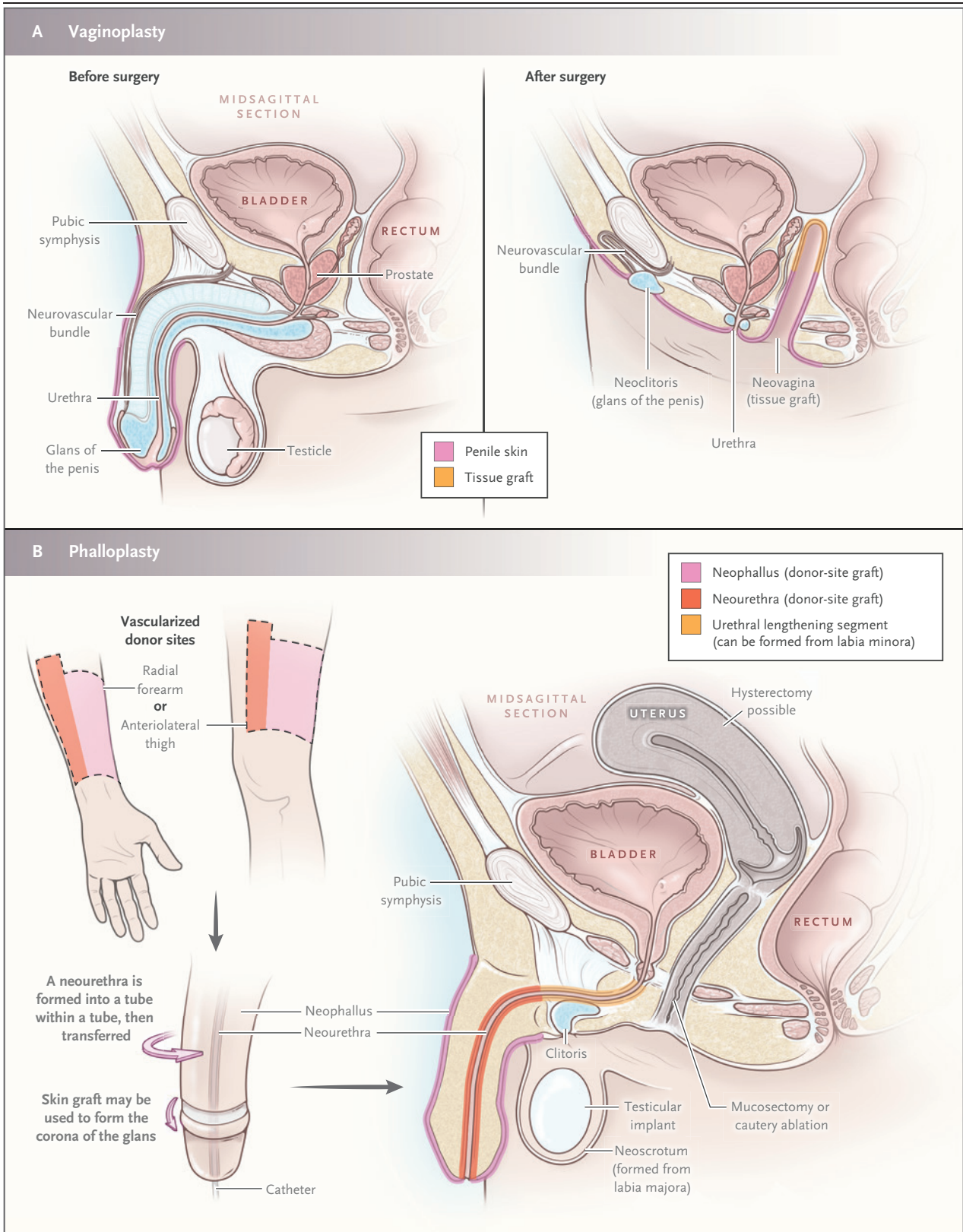


Figure 1 (facing page). Typical Approaches to Genital Reconstruction Surgery for Transgender Persons.

Common techniques used in complete genital reconstruction in transgender women include orchiectomy, penectomy, and vaginoplasty; emphasis is placed on the preservation of sexual and urinary function and on cosmesis. Panel A shows the most common technique, penile inversion vaginoplasty. In this procedure, the penile skin is used to line the vagina, and the glans is used to form the clitoris. The neurovascular bundle is preserved. Panel B shows a common approach used for phalloplasty in transgender men. In this procedure, tissue is taken from elsewhere on the body to create a phallus; the forearm and thigh are common donor sites. A neourethra may be created, although current urethral lengthening techniques are often associated with stricture risk. Vaginectomy is possible with techniques that include mucosectomy and cauterization.

esters are increasingly administered subcutaneously rather than intramuscularly because therapeutic levels can be achieved with greater patient comfort.³⁹ The use of skin patches may be limited by associated pruritic reactions. Long-acting testosterone (testosterone undecanoate) is available, but concerns about related risks of pulmonary oil microembolism and anaphylaxis have prompted the requirement of a Risk Evaluation and Mitigation Strategy for use in the United States. Buccal testosterone patches are also available but are difficult to use. Data are lacking to suggest relative superiority of specific testosterone treatment options. Target levels are more easily achieved with parenteral therapy. Transdermal therapy may achieve more uniform levels.

Androgens stimulate erythropoiesis. Exogenous androgens may be associated with polycythemia, particularly in persons with other risk factors for an elevated hematocrit, such as sleep apnea. The hematocrit should be monitored and, if elevated, possible alternative explanations investigated. Androgen doses can be decreased as long as there are no untoward consequences of dose reduction, such as a resumption of menses. Data from cross-sectional and cohort studies have shown no consistent pattern of changes in lipid levels or increases in the risk of cardiovascular disease among transgender men receiving treatment with androgens.^{29,30} Although guidelines note concern regarding increased risks of breast or endometrial cancer in association with androgen therapy and suggest that practitioners consider hysterectomy in transmasculine patients to avoid the risk of endometrial cancer,²⁵ there are no data that support the existence of such risks.^{29,40}

MONITORING OF TRANSFEMINE AND TRANSMASCULINE THERAPIES

The Endocrine Society guidelines suggest monitoring hormone levels in transgender patients with each adjustment in hormone dose (approximately every 3 months during the first year). Once target levels are achieved, they should be monitored once or twice a year or whenever the dose is changed. Clinicians should also ask patients about social interactions with family, friends, and coworkers to help in determining the need for mental health support.

Transgender-specific data regarding the monitoring of preventive health measures are lacking. Clinicians should follow strategies for cisgender persons. Transgender patients should undergo bone mineral density testing if they have had prolonged periods of hypogonadism or if they have other risk factors for osteoporotic fractures that would warrant such investigation in the general population.^{41,42} Similarly, routine cancer screening should be performed on the tissues and organs present in accordance with the guidelines established for the general population.²⁵

FERTILITY

Transgender-specific hormone therapy may reduce fertility. Genital reconstruction surgery that includes the removal of gonads can destroy reproductive potential entirely. Before they start any treatment, patients should be encouraged to consider fertility preservation.⁴³ Transgender women may consider cryopreservation of sperm⁴⁴ and transgender men cryopreservation of oocytes or embryos. Preservation of embryos is a more established procedure,^{43,44} but the costs of cryopreservation of both oocytes and embryos are high. Egg harvest has been performed in transgender men who have intact ovaries while they continue testosterone treatment (Lekovich J, Mount Sinai Health System: personal communication). Management is more complicated with transgender children, who may be uncertain regarding their future interest in fertility and may not have developed gametes that are suitable for storage.

MEDICAL TREATMENT OF TRANSGENDER YOUTH

Although detailed discussion of transgender youth is beyond the scope of this review, the following recommendations should be considered. Children who present for evaluation of transgender identity should be assessed for co-

Table 3. Surgical Options for Transgender Patients.

Category	Additional Description	Comments
Transfeminine patients		
Facial feminization ⁴⁷	Examples include brow lift, rhinoplasty, cheek implantation, lip augmentation, mandible contouring, and tracheal shave	Matching appearance with anatomy visible in public can be a higher priority (including for safety) than physical changes appreciated only by patient and intimate contacts. Surgical procedures can be the same as those for cisgender women, which may mean improved access to surgery. Because the procedures are considered to be cosmetic for cisgender women, insurance may not cover them.
Breast augmentation ⁴⁸		Matching appearance with anatomy visible in public can be a higher priority than physical changes appreciated only by the patient and intimate contacts. Surgical procedures can be the same as those for cisgender women, which may mean improved access. Because the procedures are considered to be cosmetic for cisgender women, insurance may not cover them.
Genital reconstruction surgical procedures ⁴⁹	Orchiectomy, penectomy, and vaginoplasty (construction of a vagina, clitoris, and labia, often using penile skin for vaginal lining)	Vaginoplasty surgical techniques have been established, but the surgeries are complex and are available only at select centers.
Transmasculine patients		
Chest reconstruction ⁴⁸	Bilateral mastectomy and reconstruction of masculine chest	Chest reconstruction surgery is the most common transmasculine surgical procedure ⁴⁸ ; in a report from one center, 93% of transgender men receiving hormones sought this procedure. ⁴⁶ Surgical procedures can be extensions of techniques used in cisgender men with gynecomastia, which may improve access.
Hysterectomy and oophorectomy		Surgical procedures are not transgender-specific and are therefore the most widely available for transgender persons.
Metoidioplasty ⁵⁰	Release of ligaments surrounding the clitoris to create a microphallus of several centimeters in length	This specialized surgery is limited to select centers. Sensation preservation with good sexual function is the goal. The procedure is associated with a risk of urethral stricture if paired with urethral lengthening.
Phalloplasty ⁵⁰	Creation of a neophallus using tissue from elsewhere on body (often forearm)	Genital reconstruction is the least common surgery performed because of its high morbidity as compared with other procedures. ⁵⁰ This highly specialized surgery is performed only at select centers. Scars at the donor site may be disfiguring. The neophallus may have sensation (in part through preservation of clitoral tissue) but not erectile function. A prosthesis can be placed for vaginal penetration. Techniques to extend the urethra through a neophallus are often associated with urethral strictures; additional surgery may be needed.

existing mood disorders; the risk of suicide is higher in these children than in their cisgender peers.⁴⁵ The timing for social transition (gender presentation in public) should be discussed. No medical intervention is indicated before puberty because levels of estrogen and testosterone are not appreciable until that time. At Tanner stage 2 (the start of puberty), reversible puberty blockers, such as GnRH agonists, may be used. Under the care of a multidisciplinary team, youth with well-established gender identity that is incongruent with their sex recorded at birth may begin hormone therapy. Adolescents presenting after puberty may be treated with sex

steroid hormones, with doses adjusted to adult levels.

TRANSGENDER-SPECIFIC SURGICAL OPTIONS

Among medically treated transgender persons, surveys suggest that approximately half seek transgender-specific surgical procedures, although survey data are limited by the possibility of selection bias.^{27,46} Plans may shift over time, so providers should revisit options with transgender patients periodically. Although hormone therapy is not a necessary prerequisite for surgery, for those patients receiving hormone therapy, guidelines from both WPATH and the Endo-

crine Society recommend the deferral of surgical procedures other than transmasculine chest surgery until transgender persons have completed at least 1 year of hormone treatment.^{23,25} Surgical options are reviewed in Figure 1 and Table 3.

AREAS OF UNCERTAINTY

The long-term consequences of hormone therapy in transgender persons and the best strategy for surveillance remain unclear. Studies that compare the effects of different medical regimens and strategies for monitoring patients are lacking. For example, the measurement of estradiol alone in transgender women does not reflect levels of other estrogens that may be present (e.g., estrone produced by the liver after oral ingestion of estradiol). Some persons choose lower hormone doses (e.g., because they identify as nonbinary); it is unknown whether lower doses are associated with bone loss.

GUIDELINES

Both the Endocrine Society and WPATH provide guidelines for the medical care of transgender persons.^{23,25} The current recommendations are generally consistent with these guidelines, with some distinctions. Whereas the Endocrine Society's revised guideline no longer mandates that providers of mental health determine gender identity in adults, the guideline still expresses preference for participation by these providers when making that assessment; absent further data, we express no such preference for adults unless there is evidence of mental health issues. The Endocrine Society guideline also recommends monitoring prolactin levels in transgender women and considering hysterectomy in transgender men as prophylaxis for cancer. We

refer to new data that suggest these procedures may not be necessary.^{27,37,42}

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette is a transgender man who is interested in hormone therapy. After establishing that gender identity has been persistent and that the patient is competent to make medical decisions, the provider should review the patient's expectations regarding hormone therapy as well as his interest in fertility and in surgery. Screening by the clinician or a mental health consultant is warranted for mental health conditions that may confound the assessment of gender identity or complicate management of care. We would then review with the patient the expected benefits and potential risks of hormone therapy along with a timeline of when changes may be expected. We typically begin with weekly subcutaneous self-administration of 50 mg of a testosterone ester after the patient has received training in the clinic. The usual goals for dose adjustment include ending menses while keeping the testosterone level in the normal range, maintaining the hematocrit below 50%, and treating acne, if indicated. In addition, if the patient expresses interest, specific surgical procedures and their challenges should be discussed. Surgery for the removal of reproductive organs should take place only after the patient has considered the implications for fertility.

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