Transgender women: Evaluation and management

Authors: Vin Tangpricha, MD, PhD, Joshua D Safer, MD, FACP
Section Editors: Peter J Snyder, MD, Alvin M Matsumoto, MD
Deputy Editor: Kathryn A Martin, MD

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INTRODUCTION

The terms transgender and gender incongruence describe a situation where an individual's gender identity differs from external sexual anatomy at birth. Health care providers should be familiar with commonly used terms (table 1). Gender identity-affirming care, for those who desire, can include hormone therapy and affirming surgeries, as well as other procedures such as hair removal or speech therapy [1].

This topic will use the term transgender in the broadest sense to include any person with incongruence between gender identity and external sexual anatomy at birth. The evaluation and management of transgender women are discussed here. The evaluation and management of transgender men, the primary care of the transgender adult, and gender diversity in children and adolescents are reviewed separately. (See "Transgender men: Evaluation and management" and "Primary care of transgender individuals" and "Gender development and clinical presentation of gender diversity in children and adolescents" and "Management of transgender and gender-diverse children and adolescents".)

STANDARDS OF CARE

Several large medical professional organizations have issued guidelines to assist providers in the care of transgender individuals (the World Professional Association for Transgender Health [WPATH] [1], the Center of Excellence for Transgender Health [2], the Endocrine Society [3], and the American College of Obstetricians and Gynecologists [ACOG] [4]).

The Endocrine Society has released updated guidelines for the treatment of gender dysphoria/gender incongruence [3]. The new guidelines replace the term "transsexual" with "gender dysphoria" or "gender incongruence" and specify detailed professional qualifications for clinicians who diagnose, assess, or treat individuals with gender dysphoria/gender incongruence. Specifically, they now suggest that decisions regarding social transition for prepubertal youth be made in conjunction with a mental health or similarly experienced professional. They continue to recommend the management and monitoring of transgender adolescents and adults by a multidisciplinary team, as well as counseling patients about the time course of hormone-induced physical changes and options for fertility preservation. We agree with the updated guidelines.

EPIDEMIOLOGY

Prevalence — Reports suggest that 0.3 to 0.6 percent of the adult population is transgender [5-7]. The prevalence of transgender individuals depends upon the definition used to classify a person as transgender. For example, in studies that include only individuals who had undergone hormone therapy, gender-affirming surgery, or had diagnostic codes documenting transgender, the reported prevalence of transgender was 7 to 9 per 100,000 people [8]. However, studies that include transgender status based upon self-report indicate a prevalence of transgender of approximately 871 per 100,000 people [8]. One study estimated that there are approximately 25 million transgender individuals worldwide [9].

PATHOPHYSIOLOGY

Although the mechanisms remain unclear, there is evidence for a biologic basis of gender identity [10].

Evidence for a biologic basis for gender identity primarily includes:

- Data on gender identity in intersex individuals (also known as disorders of sex development [DSD]).
- Data from twins showing greater transgender concordance among identical twins relative to fraternal twins [11].
- Neuroanatomical differences associated with gender identity [12].
- There has also been suspicion that for some predisposed individuals, gender identity may be influenced by prenatal androgen exposure [13].

Because sample sizes of most studies on this subject are small, further research is required to assign specific biologic mechanisms for gender identity [10].

INITIAL PRESENTATION

Most transgender individuals present in adulthood or late adolescence. While some transgender individuals present to mental health providers for diagnosis, it is now common for many transgender individuals to see primary care providers for initial guidance. Some transgender individuals will present directly to endocrinologists for hormone prescriptions. Typically, transgender adults report gender incongruence throughout their lives, starting well before puberty.

Although many transgender adults will be straightforward in their presentation, others will have the diagnosis confounded by mental health concerns. Therefore, the diagnosis of gender dysphoria or gender incongruence should be made by qualified medical providers who are both facile with the diagnostic criteria [14] and have the necessary experience assessing the mental health issues, such as mood disorders, that might confound the diagnosis.

Parallel to the greater exposure in public media, greater societal acceptance, and greater access to care, transgender individuals now tend to present at a younger age than in the past [15].

Psychiatric conditions — Some transgender individuals have coexisting psychiatric conditions [16]. If these are present, they may improve with cross-sex hormonal therapy [17-19]. Indeed, transgender individuals who present at younger ages have fewer mental health concerns [15].

If mental health concerns are identified, they should be stable prior to advancing therapy.

OVERVIEW OF APPROACH

Initial assessment — Although many transgender adults will be straightforward in their presentation, others will have the diagnosis confounded by mental health concerns. Therefore, the diagnosis of gender dysphoria or gender incongruence should be made by qualified medical providers who are familiar with the diagnostic criteria [3,14] and have the necessary experience assessing the mental health concerns that might confound the diagnosis.

Typically, transgender adults report gender incongruence throughout their lives, starting well before puberty. The evaluation and management of transgender men and gender identity development and gender diversity in children and adolescents are reviewed separately. (See "Transgender men: Evaluation and management" and "Gender development and clinical

presentation of gender diversity in children and adolescents" and "Management of transgender and gender-diverse children and adolescents".)

Counseling before treatment — Before initiating transgender hormonal or surgical treatment, the clinician should counsel the patient about the following:

- **Diagnosis** – The initial diagnosis of gender dysphoria/gender incongruence should be made by qualified medical providers with expertise in the diagnostic criteria. In addition, the diagnosis should be validated by qualified medical providers with the necessary knowledge of the mental health concerns that might confound the diagnosis.

- **Care team** – Optimally, a transgender patient seeking medical treatment should have access to providers with expertise in transgender-appropriate primary care, transgender hormone therapy, and mental health support for transgender persons.

- **Expectations** – Transgender hormone therapy and surgery are usually undertaken with the goal of making the external appearance more congruent with gender identity. Unrealistic expectations that subjects may have about other benefits of hormonal and surgical treatment must be addressed.

  Contacts with other transgender individuals who are already undergoing treatment may be helpful in shaping an individual's expectations of what can be achieved and what problems, personally and socially, may arise during transgender medical treatment. A supportive network of family and friends is often important.

  Physical changes may be more or less apparent in certain individuals, relating to other underlying biology. Some physical changes may be quickly apparent, while others manifest over months and years. The rapidity and degree of physical changes may be difficult to predict and may not relate to the dose of hormones. Transgender individuals should be prepared for regular monitoring of changes and the assimilation of those changes into daily living.

- **Risks and benefits of treatment** – The patient should be aware of the risks and benefits of hormonal or surgical therapy [20,21]. The patient should be able to understand and articulate the additional risks of these therapies and should be competent to consent to therapy.

- **Future fertility** – Transgender individuals who undergo gender identity-affirming therapy may lose reproductive potential. Thus, before starting any treatment, patients should be encouraged to consider fertility issues [14]. (See 'Fertility considerations' below.)

Individualized approach — The approach to patient care should be individualized. Such individualization becomes even more nuanced when dealing with individuals who describe themselves as being nonbinary, eg, having both masculine and feminine identity attributes. While hypogonadism carries risk to bone health and should be addressed, both male and female hormone patterns, along with the entire continuum in between, can be safe. Similarly, surgical requirements may vary significantly among patients [22]. For example, for transgender men, chest reconstruction surgery (breast reduction) is often the highest priority, with only a minority of patients choosing other surgeries. For transgender women, facial feminization procedures, breast augmentation, and genital reconstruction surgeries may all be of interest, depending on the individual.

Hormone therapy goals — The usual aim of transgender hormone therapy is to induce physical changes to match gender identity [23]. The treatment goal is to maintain hormone levels in the normal physiological range for the target gender.

Historically, some transgender individuals self-medicated with hormones for a variety of reasons, including fear of rejection by health care providers, delays in initiation of hormone therapy, and the cost of undergoing treatment. Therefore, there should be careful assessment for self-medication, both past and current [24].

Criteria for starting treatments — Criteria for starting hormone therapy include [14]:

- Persistent, well-documented gender dysphoria/gender incongruence
- Capacity to make a well-informed decision
- Relevant medical or mental health issues are well controlled

The criteria for initiating **genital** surgical treatment include the **same criteria for hormone therapy**, but an **additional criterion** is added due to their increased invasiveness [1]:

- **One year of continuous hormone therapy and living in the desired gender role** is expected, unless it has been determined the hormone therapy is not medically indicated. This criterion is **not** required for surgeries like chest reconstruction or other nongenital surgeries.

  Additional details for surgical procedures are available in the World Professional Association for Transgender Health (WPATH) Standards of Care [1].

EVALUATION AND DIAGNOSIS

Diagnostic criteria — The current criteria for gender incongruence include:

- Persistent incongruence between gender identity and external sexual anatomy at birth
- The absence of a confounding mental disorder or other abnormality

The diagnosis of gender incongruence must be made before considering transgender hormone and surgical therapy [3]. Such diagnosis should include screening for confounding mental health concerns.

In addition, it is essential to identify any medical and/or psychiatric diagnoses that may require treatment before considering hormone therapy [3,14].

Presently, most cases of transgender identity are diagnosed in adulthood, but increasingly, children and adolescents with gender dysphoria present for diagnosis and treatment.

The clinical presentation of gender diversity in children is reviewed separately. (See "Gender development and clinical presentation of gender diversity in children and adolescents", section on 'Clinical presentation'.)

Gender dysphoria — Patients also may be diagnosed with gender dysphoria, which is defined as the discomfort arising in some individuals from the incongruence between their gender identities and their external sexual anatomy at birth.

The diagnosis of gender dysphoria is generally done by a mental health professional; however, other health care professionals who have the appropriate experience and training can also diagnose gender dysphoria. Mental health providers typically use the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) to make a diagnosis [25]. Core components of the DSM-5 diagnosis of gender dysphoria include longstanding discomfort with the incongruence between gender identity and external sexual anatomy at birth along with interference with social, school, or other areas of function [25].

HORMONAL THERAPY

Transgender women (male-to-female, MTF) — Priorities for many transgender women include elimination of facial hair growth, induction of breast formation, and a more female fat/muscle distribution. To accomplish this, a reduction of the biological effects of androgens to normal female levels is required.

Administration of estrogens alone will suppress gonadotropin output and, therefore, androgen production, but dual therapy with one compound that suppresses androgen secretion or action and a second compound that supplies estrogen is more effective. In addition, dual therapy may permit the use of lower doses of estrogen (see 'Adverse events' below). We suggest either

antiandrogen therapy (spironolactone or cyproterone acetate [CPA]) or gonadotropin-releasing hormone (GnRH) agonist therapy, combined with estrogen therapy (transdermal or oral 17-beta-estradiol). We suggest against the use of ethinyl estradiol because of an increased risk of venous thromboembolism (VTE).

Suppression of androgen secretion or action — Several agents are available to inhibit androgen secretion or action. Both spironolactone (in the United States) and CPA (in Europe) are popular as first-line therapy given their effectiveness and low cost. Both are also widely used in women, primarily for the treatment of hirsutism (table 2). (See "Management of hirsutism in premenopausal women", section on 'Antiandrogens'.)

GnRH agonists are the ideal approach given their ability to suppress the hypothalamic-pituitary-gonadal axis and, therefore, testosterone secretion. However, they are typically second-line therapy because of their high cost.

Antiandrogens — Spironolactone, a mineralocorticoid receptor antagonist, is the most widely used drug in the United States for transgender women. It is a competitive inhibitor of the androgen receptor as well as an inhibitor of testicular steroidogenesis, although the mechanism of the latter is not worked out [26,27]. The recommended dose of spironolactone is 100 to 300 mg/day (table 2) [28].

CPA is both a progestin (which suppresses gonadotropins) and an androgen receptor antagonist that is available in most countries but not the United States. When used as an antiandrogen for transgender women the dose of CPA can range from 25 to 100 mg/day [3].

Progestins — While progestins such as medroxyprogesterone acetate (MPA) are sometimes used as a strategy to suppress gonadotropins and, therefore, testosterone secretion, we do not suggest them as part of standard hormonal care for transgender women. MPA has been associated with excess cardiovascular and breast cancer risk in older postmenopausal women taking conjugated estrogen.

There are reports that progestins interfere with optimal estrogen-induced breast development when inducing puberty in girls. However, some clinicians claim improved breast development with progestins despite absence of evidence for that [29].

After any genital surgery that includes orchiectomy, antiandrogens are no longer needed to suppress testosterone secretion [30].

GnRH agonists — Long-acting gonadotropin-releasing hormone (GnRH) agonists, used parenterally, inhibit gonadotropin secretion and, as a result, suppress testicular testosterone production with few adverse events [31]. However, as noted, the cost of long-acting GnRH

agonists, along with the more difficult administration, make them a second-tier therapy in most centers.

Other — Finasteride inhibits 5-alpha-reductase 2 activity and, therefore, partially inhibits conversion of testosterone to the more potent dihydrotestosterone (DHT). It has been used in the management of benign prostatic hyperplasia, prostate cancer, hair loss in men and women, and, occasionally, for hirsutism in women. There are no available data for its use in transgender individuals, where it would be predicted to have little utility if the testosterone levels are down and there is no substrate to generate DHT. (See "Treatment of androgenetic alopecia in men", section on 'Finasteride' and "Medical treatment of benign prostatic hyperplasia" and "Management of hirsutism in premenopausal women", section on 'Antiandrogens'.)

We suggest against the use of nonsteroidal antiandrogens such as flutamide and nilutamide. They increase gonadotropin secretion, causing increased secretion of testosterone and estradiol (only the latter would be desirable). But more importantly, flutamide has been associated with hepatotoxicity. (See "Management of hirsutism in premenopausal women", section on 'Antiandrogens'.)

Many transgender women require electrolysis, laser hair removal [32], or both because terminal hair on the face continues to grow even without the continued androgen stimulation [14]. (See "Removal of unwanted hair", section on 'Electrolysis' and "Removal of unwanted hair", section on 'Laser and intense pulsed light' and "Management of hirsutism in premenopausal women", section on 'Role of direct hair removal methods'.)

Estrogen — The usual approach includes estrogen therapy to help suppress endogenous androgen secretion and to replace it with estrogen. There is a wide range of estrogens from which to choose (table 2). However, 17-beta-estradiol is the most commonly prescribed. Transdermal estrogen has been associated with a lower risk of VTE and stroke than oral estrogens in postmenopausal women. However, oral formulations, which are considerably less expensive than transdermals, are typically used in transgender women as they tend to be at low risk for VTE.

Transgender women with testis intact will require relatively high doses of estrogens to suppress testosterone into the female range, even with an adjunct antiandrogen agent.

Typical regimens include:

- Transdermally, 50 to 200 mcg/24 hours once or twice a week.
- Orally, 2 to 4 mg/day, occasionally as high as 10 mg.

- In Europe, oral 17-beta-estradiol valerate 2 to 4 mg per day is also used.
- Parenteral estrogens (estradiol valerate or cypionate) are sometimes used if target serum estradiol (E2) levels cannot be achieved with oral or transdermal preparations (table 2).

Conjugated estrogen levels are not measured with commercial E2 assays, and therefore, estradiol preparations may be preferred in order to monitor them more clearly.

We suggest against the use of oral ethinyl estradiol, a potent and inexpensive estrogen used in oral contraceptives. It was used in doses of 50 to 100 mcg/day in transgender women in the past, but it was associated with an excess risk of venous thrombosis, particularly in subjects over 40 years [26,33-35]. It has also been associated with an increased risk of cardiovascular death [36]. (See 'Adverse events' below.)

Several relative contraindications for estrogen require additional evaluation and treatment prior to the initiation of hormones, including a history of breast cancer, VTE, cardiovascular disease, cerebrovascular disease, and severe liver dysfunction. Hyperprolactinemia should be treated before starting estradiol therapy. (See 'Adverse events' below.)

Clinical outcomes — Although a goal of therapy is to reduce the hormonally induced male secondary sex characteristics, complete elimination is not possible. In transgender women, effects of androgens on the skeleton, such as greater height, size and shape of hands, feet, jaws, and pelvis, and voice (laryngeal prominence), cannot be reversed.

However, there are many changes that do occur (table 3). The initial changes (over the first three to six months) include a possible decrease in sexual desire along with decreased rates of growth of facial and body hair. There will also be some initial growth of breast tissue, a decrease in oiliness of the skin, and early redistribution of fat mass [3].

The main clinical outcomes include (table 3):

- **Sexual hair** – Adult male beard growth is very resistant to inhibition by combined hormonal intervention and, especially in individuals with European ancestry, additional measures such as laser hair removal or electrolysis to eliminate facial hair are usually necessary.
- **Breast development** – Breast formation starts almost immediately after initiation of estrogen administration and decreased androgen levels; breast development is typically maximal at two years [26,37-39]. Some transgender women may report nipple tenderness and discomfort during the period of breast growth. Androgens have an inhibitory effect on breast formation, and therefore, estrogens will be most effective in a milieu devoid of androgen action.

- **Skin** – Androgen deprivation leads to a decreased activity of the sebaceous glands and may result in dry skin or brittle nails [40].
- **Body composition** – Following androgen deprivation, there is an increase in subcutaneous fat and a decrease in lean body mass [41]. Body weight usually increases.
- **Testes** – Atrophy of the testes (if not surgically removed) occurs over many years. Lacking gonadotropic stimulation, the testes become atrophic and may occasionally enter the inguinal canal, which may cause discomfort.
- **Prostate** – Atrophy of the prostate also occurs over many years.
- **Voice** – Antiandrogens and estrogens have no effect on the properties of the voice, so transgender women may choose to consult a specialized phoniatric center for speech therapy. Pitch and resonance are the usual focus of therapy because the combination of these two voice characteristics are thought to account for the majority of how a speaker's gender is perceived [42]. Speech therapy may lead to more feminine speech [43]. Laryngeal surgery is reported by some to change the pitch of the voice but reduces its range.
- **Sexual function** – Feminizing hormone therapy may reduce sexual desire, reduce erectile function, and decrease ejaculation among transgender women [44]. Some transgender women choose to reduce hormone doses to balance the degree of feminization with the level of sexual function, while others report no need for dose adjustments. Following genital surgery, sexual function (sexual desire, arousal, pain with sex, and orgasm) is variable for transgender women and depends on preoperative sexual function, the type of surgery performed, and hormonal status [45].

Monitoring — Clinical monitoring of transgender women on hormone therapy should occur approximately every three months during the first year with each hormone regimen adjustment. After the first year, monitoring should be once or twice yearly (table 4 and table 5). In addition to clinical assessment that the patient is comfortable with the regimen, monitoring should include the following:

- Serum total testosterone concentrations to determine when the patient is at goal (eg, the normal female range for testosterone).
- For patients using spironolactone as the antiandrogen agent, serum potassium concentrations should be monitored following the paradigm for the use of any potassium-sparing diuretic (ie, keeping the potassium in the normal range). Concomitant use of other potassium-sparing diuretics may accentuate the risk for hyperkalemia.

- E2 concentrations should be monitored to avoid supraphysiologic levels (eg, maintain levels <200 pg/mL [734 pmol/L]) (table 4). One author of this topic uses a higher cutoff of <300 pg/mL (1101 pmol/L).

  In addition, some advocate the monitoring of other estrogen-sensitive labs including triglycerides and serum prolactin. (See 'Adverse events' below.)

- All individuals with breast tissue require monitoring for breast cancer. In the absence of transgender-specific data, standard breast screening guidelines developed for women should be followed (table 5). (See "Primary care of transgender individuals", section on 'Breast cancer'.)

- All individuals with prostate tissue require monitoring for prostate carcinoma. In the absence of transgender-specific data, standard prostate screening guidelines developed for men should be followed [3], even though prostate cancer might be rare in transgender women who have undergone genital surgery that includes gonadectomy (table 5). (See "Primary care of transgender individuals", section on 'Prostate cancer'.)

- Bone mineral density (BMD) testing is often performed in transgender individuals at risk for osteoporosis and fractures (for example, if estrogen therapy is discontinued) (table 4). However, as long as estrogen is being administered, bone density should be preserved. In individuals at low risk, the Endocrine Society guidelines suggest screening for osteoporosis beginning at age 60 years (and in those who are not compliant with hormone therapy). Others suggest routine screening starting at age 65 years [2]. (See "Overview of dual-energy x-ray absorptiometry" and "Primary care of transgender individuals", section on 'Osteoporosis'.)

Long-term maintenance therapy — After gender-affirming genital surgery that includes orchiectomy, antiandrogen therapy may be discontinued.

Continuous estrogen therapy is also required to avoid symptoms of sex hormone deficiency and to prevent bone loss and osteoporosis [46-48]. The appropriate doses of estrogen are described above and in the table (table 2). (See 'Estrogen' above.)

Adverse events

Cardiovascular

- **VTE** – Several studies have demonstrated an increased risk of VTE in transgender individuals receiving cross-hormone therapy, particularly transgender women on estrogen.

In a retrospective study of over 1000 transgender individuals in the Netherlands, the incidence of venous thromboembolic complications was 2 to 6 percent in transgender women treated with oral ethinyl estradiol [33,35]. This rate was approximately 20-fold higher than that of the control male population. In a follow-up study of the same cohort, no increased risk was seen in users of estrogen preparations other than ethinyl estradiol [36]. Based upon these observations, current guidelines recommend against the use of ethinyl estradiol [3].

However, VTE has been observed with other estrogen formulations as well. In a study of 214 transgender women receiving oral estradiol, transdermal estradiol, or estradiol gel, 11 individuals experienced a venous thrombosis or pulmonary embolism (5.1 percent) [49]. No events were seen in the control groups of cisgender men or women. Other risk factors for venous thrombosis in those who had a VTE included immobilization after surgery, smoking, or a hypercoagulable disorder.

In an electronic medical record-based cohort study that included 2842 transgender women matched to approximately 48,000 cisgender men and 48,000 cisgender women, the transgender women had a higher incidence of VTE than both control groups (hazard ratios for both approximately 2) [50]. Most transgender women were receiving oral estradiol; the average maximum daily dose was 4 mg (range 1 to 10 mg) and was the same for those who did or did not have a VTE.

The difference seemed more pronounced with increased follow-up, with two- and eight-year absolute risk differences of 4.1 and 16.7 per 1000 persons relative to cisgender men and 3.4 and 13.7 per 1000 persons relative to cisgender women. This pattern is different from that seen in postmenopausal women taking hormone therapy, where VTE risk is highest in the first year of use and then declines. This suggests that long-term monitoring is important in this population. (See "Menopausal hormone therapy and cardiovascular risk", section on 'Venous thromboembolism'.)

Although data on VTE risk in transgender women on hormone therapy undergoing surgery are not available, we suggest stopping estrogen therapy two to four weeks before major surgery with immobilization. Once subjects are fully mobilized again, estrogen therapy may be resumed, typically within four weeks [51].

The incidence of thrombophilias appears to be the same in the transgender population as the general population. Therefore, routine pretreatment screening for thrombophilias is not suggested. When thrombophilias are detected, it has been suggested that treatment with anticoagulants be administered if estrogen therapy is to be continued [21].

- **Cardiovascular disease** – Although the considerable sex difference in the prevalence of cardiovascular disease between men and women might lead one to expect concern with transgender hormonal treatment, the actual risk remains to be established [38]. Older studies that suggested increased cardiovascular events in transgender women were confounded by use of ethinyl estradiol [36,49,51]. In the large cohort study described above, the incidence of ischemic stroke and myocardial infarction in transgender women was similar to control men. However, it appeared that ischemic stroke risk was higher in transgender women who started their estrogen during follow-up, particularly after six years of therapy. However, this analysis was limited due to the small number of patients [50].

  Until further data are available, risk factors for cardiovascular disease should be reviewed in transgender individuals treated with hormones [28]. Patients at risk for cardiovascular disease should be made aware that the impact of hormone treatment on risk is not known. (See "Primary care of transgender individuals", section on 'Cardiovascular disease' and "Overview of established risk factors for cardiovascular disease".)

Other

- **Triglycerides** – Oral estrogens should be avoided in patients with familial hypertriglyceridemia as they may cause significant elevations in triglycerides. There is a small incidence reported of elevated triglycerides with estrogen. Very high levels of triglycerides (>2000 mg/dL [22.59 mmol/L]) would place patients at risk for acute pancreatitis. We therefore suggest measuring lipids before initiating hormone therapy. A meta-analysis of 16 studies concluded that cross-sex hormone therapies increase serum triglycerides [48].

  We suggest obtaining a fasting lipid panel prior to initiating hormone therapy as patients with familial hypertriglyceridemia could be at risk for severe hypertriglyceridemia (and possible acute pancreatitis) with oral estrogen therapy.

- **Mortality** – The increased mortality rates in transgender women observed in early reports may be related to morbidity due to failure to treat rather than from the treatment itself. For example, in a report of 966 MTF and 365 female-to-male (FTM) transgender persons, the mortality rate was 51 percent higher in the transgender woman population, mainly due to drug abuse, human immunodeficiency virus (HIV), cardiovascular disease, and suicide [36]. Users of oral ethinyl estradiol had a threefold excess risk of cardiovascular death.

  Current estimates of mortality rates in one study of transgender persons (both transgender women and transgender men) was approximately 9.3 percent over a 10-year follow-up

period. The causes of death were similar to those in the United States population over the same study period with the exception of suicide, which was higher in the transgender persons [52]. (See 'Estrogen' above.)

- **Hyperprolactinemia/prolactinoma** – Reports that transgender women treated with estrogen develop hyperprolactinemia are confounded by the no-longer-used ethinyl estradiol 100 mcg/day as well as the progestin CPA, which is not used in the United States. Limited data suggest that both estrogen and CPA may be associated with hyperprolactinemia in transgender women [53].

  Prolactinomas have been reported only occasionally [33]. However, these patients were on both estrogen and CPA. Some expert groups suggest routine measurements of serum prolactin in transgender women receiving estrogen [28].

  Like for any patient, pituitary magnetic resonance imaging (MRI) is indicated in patients with hyperprolactinemia whose prolactin levels do not normalize with reduction of the estrogen or CPA dose [28]. (See "Clinical manifestations and evaluation of hyperprolactinemia", section on 'Laboratory/imaging tests'.)

- **Cancer** – Guidelines for breast cancer screening in transgender women are reviewed separately but, in general, mammography screening is discussed with transgender women ≥50 years with additional risk factors for breast cancer (table 5). (See "Primary care of transgender individuals", section on 'Screening/preventive care'.)

  Cases of prostate cancer among transgender women have been reported [54]. Even transgender women who have had genital surgery will be at some risk because the prostate must be left in place. Therefore, some monitoring may be required following the framework for nontransgender men (table 5).

Fertility considerations — Transgender individuals who take cross-sex hormone therapy may limit fertility potential unless hormones are stopped. Individuals who undergo gender confirmation surgery lose their reproductive potential altogether. Thus, before starting any treatment, patients should be encouraged to consider fertility issues [55,56].

Transgender women may consider sperm cryopreservation (ideally before initiating hormone therapy) [57]. (See "Effects of cytotoxic agents on gonadal function in adult men".)

GENDER CONFIRMATION SURGERY

Gender confirmation surgery (also referred to as gender-affirming surgery) is often the last (and most considered) step in the treatment process. Individuals can and do live successfully in their preferred gender role without genital surgery. The steps that are required before initiating surgical treatment are reviewed above. (See 'Hormone therapy goals' above and 'Counseling before treatment' above.)

Prior to surgery, the clinician should continue to counsel the patient to acknowledge the limitations of what gender confirmation surgery can achieve. In addition, the patient should continue to work closely with the supporting medical and mental health providers as appropriate.

There are three categories of gender confirmation surgery for transgender women:

- Facial feminization surgeries are sometimes performed to create more feminine features.
- Some individuals choose to have breast augmentation, but there is no consensus on the optimal timing of the procedure. While some experts have suggested delaying until after two years of hormone therapy [28], there is evidence that up to 80 percent of individuals achieve Tanner 3 breasts after only 12 months of treatment [58,59]. (See 'Clinical outcomes' above.)
- Finally, for some transgender women, genital reconstruction surgery may be desired. Aspects of genital surgery include a bilateral orchiectomy performed to remove the main source of endogenous testosterone. In addition to gonadectomy, other procedures can include penectomy and vaginoplasty (typically with surgical construction of a vagina, clitoris, and labia, usually using the penile skin for vaginal lining and scrotal skin for the labia) [28,60].

  Vaginal dilators should be used on a regular basis postoperatively to maintain the vaginal length if sexual intercourse is the goal. Some transgender women may be lesbians, and engaging in receptive vaginal intercourse may not be a goal.

A detailed review of male to female transgender surgery is found separately. (See "Transgender surgery: Male to female".)

Outcomes — Little attention has been given to this subject, and research has been based on self-reports. As expected, there is a correlation between sexual function and the quality of the neovagina [61]. While not all postoperative transgender persons are orgasmic, many more report sexual satisfaction [17,45,62].

A hormonal factor to consider may be the androgen depletion for transgender women. It may be that women need a small amount of androgen to have normal sexual desire, although this is not proven. Given the irreversibility of gender confirmation surgery and, to a lesser degree, of cross-sex hormone administration, it would be desirable to have insight into factors that predict success or failure. Although regrets are rare, they do occur. Regrets are seen more often in those with difficulty in transitioning their appearance or limited social skills [17,63]. (See 'Hormone therapy goals' above.)

PSYCHOSOCIAL OUTCOMES OF TREATMENT

Transgender treatment that includes hormonal therapy results in significant improvement in quality-of-life and psychosocial outcomes, as illustrated in a meta-analysis of 28 studies that enrolled 1833 transgender individuals (1093 transgender women, 801 transgender men) who underwent transgender treatment that included hormones [17]. Very low-quality evidence from the pooled analysis suggested improvements in gender dysphoria symptoms, psychological functioning, sexual function, and overall quality of life.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Transgender health".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Being transgender (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Transgender is an umbrella term that is used to describe individuals with gender diversity; it includes individuals whose gender identity is different from their sex recorded at birth. Such individuals may define themselves as transmasculine, transfeminine, or nonbinary (the last term meaning they have gender identity attributes that are both male and female). (See 'Introduction' above.)

- Transgender individuals should have their gender incongruence diagnosed by medical professionals with appropriate experience. It is necessary to ascertain that there is persistent gender incongruence and that the person is able to understand the risks and benefits of intervention. (See 'Initial assessment' above.)

- Before initiating transgender hormonal or surgical treatment, the clinician should counsel the patient about risks and benefits of the hormonal or surgical therapy, including impact on fertility, as well as realistic expectations about outcomes. (See 'Counseling before treatment' above.)

- For transgender women (male-to-female [MTF]), we suggest either antiandrogen therapy (spironolactone or cyproterone acetate [CPA]) or gonadotropin-releasing hormone (GnRH) agonist therapy (**Grade 2C**), combined with estrogen therapy (transdermal or oral 17-beta-estradiol) (table 2) (**Grade 2B**). We suggest against the use of ethinyl estradiol because of an increased risk of venous thromboembolism (VTE) (**Grade 2B**). (See 'Transgender women (male-to-female, MTF)' above.)

- For transgender women, the most important risk associated with estrogen therapy is VTE. (See 'Cardiovascular' above.)

- Transgender women treated with estrogen should follow the same screening guidelines for breast cancer as for nontransgender women (table 5). (See 'Monitoring' above.)

- We agree with the Endocrine Society guidelines that transgender individuals should follow the screening guidelines for all tissues present, independent of expressed gender. For example, prostate cancer screening should be done in individuals with a prostate (table 5). (See 'Monitoring' above.)

- We suggest that transgender women receiving hormone therapy be monitored to avoid supraphysiologic serum estradiol (E2) concentrations (eg, maintain E2 levels <200 pg/mL

[734 pmol/L]) and to verify that serum testosterone levels reach the normal physiologic female range (table 4). Serum potassium should be checked in those taking a potassium-spironolactone, and some experts suggest monitoring serum prolactin and triglycerides because of exogenous estrogen administration. (See 'Monitoring' above.)

- Gender confirmation (or affirmation) surgeries can be considered after living one year in the desired gender role and after one year of continuous hormone therapy (unless there a medical contraindication to hormone therapy). This criteria applies to genital surgeries but **not** to other procedures such as chest reconstruction. Details of surgery are described above. (See 'Gender confirmation surgery' above.)

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Topic 7456 Version 20.0

GRAPHICS

Terms used to describe various aspects of gender and sexuality*

Gender identity	An individual's innate sense of feeling male, female, neither, or some combination of both.
Natal or birth-assigned/birth-designated sex	Typically assigned/designated according to external genitalia or chromosomes.
Gender expression	How gender is presented to the outside world (eg, feminine, masculine, androgynous); gender expression does not necessarily correlate with birth-designated sex or gender identity.
Gender diversity	Variation from the cultural norm in gender identity, expression, or gender role behavior (eg, in choices of toys, playmates); "gender diversity" acknowledges the spectrum of gender identities and replaces "gender nonconformity," which has negative and exclusionary connotations.
"Transgender" ("trans" as an abbreviation)	Umbrella term that is used to describe individuals with gender diversity; it includes individuals whose gender identity is different from their birth-designated sex and/or whose gender expression does not fall within stereotypical definitions of masculinity and femininity; "transgender" is used as an adjective ("transgender people"), not a noun ("transgenders").
Gender dysphoria or incongruence	Distress or discomfort that may occur when gender identity and birth-designated sex are not completely congruent.
Transsexual	Older, clinical term that has fallen out of favor; historically, it was used to refer to transgender people who sought medical or surgical interventions for gender affirmation.
Sexual orientation	An individual's pattern of physical and emotional arousal (including fantasies, activities, and behaviors) and the gender(s) of persons to whom an individual is physically or sexually attracted (gay/lesbian, straight, bisexual); sexual orientation is an entirely different construct than gender identity, but is often confused with it; the sexual orientation of transgender people is based upon their identified gender (eg, a transgender man who is attracted to other men might identify as a gay man; a transgender woman who is attracted to other women might identify as a lesbian).
Sexual behaviors	Specific behaviors involving sexual activities that are useful for screening and risk assessment; many youth reject traditional labeling (homosexual, heterosexual, bisexual) but still have same-sex partners.
Transgender man/transman/transmasculine person	Person with a masculine gender identity who was designated a female sex at birth.
Transgender woman/transwoman/transfeminine person	Person with a feminine gender identity who was designated a male sex at birth.
Nonbinary gender identity	Person of any birth-designated sex who has a gender identity that is neither masculine nor feminine, is some combination of the two, or is fluid. Other terms that may be used for nonbinary gender identity include genderqueer, gender creative, gender independent, bigender, noncisgender, agender, two-spirit, third sex, and gender blender.

* These are cultural and descriptive terms, not diagnostic terms, which are specific to medical and pathology-based paradigms.

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Graphic 86993 Version 12.0

Hormone regimens for adult transgender persons

	Dose range	Comment
Transfeminine regimens (MTF transgender persons)*		
Estrogen¶		
Oral: estradiol (17-beta-estradiol valerate)	2 to 4 mg/day	Some providers report giving higher doses.
Transdermal: estradiol patch	0.025 to 0.2 mg per 24 hours, changed once or twice weekly, depending on specific preparation type	Lower risk of thromboembolism compared with oral estrogen options.
Parenteral		
Estradiol valerate	5 to 30 mg IM every two weeks	Prolonged time to onset of effect and steady state, greater risk of accumulation and overdose.
Estradiol cypionate	2 to 10 mg IM every week	
Antiandrogens*		
Spironolactone	100 to 300 mg/day oral	Monitor blood pressure and electrolytes.
Cyproterone acetate$^{\Delta}$	25 to 50 mg/day oral	
GnRH agonists		
Leuprolide	3.75 to 7.5 mg IM depot monthly OR 11.25 mg IM depot every 3 months	Inhibits gonadotropin secretion.
Goserelin	3.6 mg SQ implant monthly	Expensive.
Transmasculine regimens (FTM transgender persons)		
Testosterone$^{\Diamond}$		
Parenteral		
Testosterone enanthate or cypionate	50 to 100 mg IM or SQ every week OR 100 to 200 mg IM every two weeks	Weekly injections produce less peak-trough variation in effect (eg, mood); injection site reaction may occur.
Testosterone undecanoate$^{\Delta\S}$	1000 mg IM every 10 to 12 weeks	Produces stable physiologic testosterone levels over 10 to 13 weeks.
Transdermal		
Testosterone gel 1% and 1.6%	2.5 to 10 grams of gel per day (equivalent to 25 to 100 mg/day testosterone)	Less variation in serum testosterone levels than injectable preparations; gel formulations can result in interpersonal transfer if contact occurs before fully dried (rare).
Testosterone patch	2.5 to 7.5 mg/day transdermal	Transdermal patch may produce lower serum testosterone levels and more skin irritation compared with gels.

Suggestions shown in table are based upon case descriptions and experience. Regimen and dose must be carefully individualized based upon patient age, goals of therapy, whether pre- or postgonadectomy, and comorbid medical conditions and risks. Refer to UpToDate topics on transgender men and transgender females.

MTF: male-to-female; IM: intramuscular; GnRH: gonadotropin-releasing hormone; SQ: subcutaneous; FTM: female-to-male.
* Dose of estrogen should be adjusted according to serum 17-beta-estradiol levels (ie, 100 to 200 pg/mL) and effect. Lower doses of estradiol are generally sufficient for feminization goals when combined with an antiandrogen, GnRH agonist, or after gonadectomy. Antiandrogen therapy is discontinued after gonadectomy.
¶ Synthetic estrogens (eg, ethinyl estradiol) are not recommended, due to elevated risk of thromboembolic disease, cardiovascular

mortality, and inability to regulate dose by measurement of serum levels.
Δ Not available in the United States. Available widely elsewhere.
◊ Doses of testosterone should be adjusted according to serum testosterone levels (ie, normal male range 320 to 1000 ng/dL) and effect. Time to onset of effect of parenteral preparations may be less than with transdermal preparations. Supplemental agents such as depot medroxyprogesterone 150 mg every 3 months or oral medroxyprogesterone 5 to 10 mg/day or oral lynestrenol 5 to 10 mg/day (not available in the United States) have been used as an add-on option when starting testosterone therapy to induce cessation of menses.
§ 1000 mg initially, followed by an injection at 6 weeks, then at 12-week intervals.

Data from:

1. *Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society* clinical practice guideline. J Clin Endocrinol Metab 2017; 102:1.*

Graphic 69460 Version 8.0

Feminizing effects in male-to-female transgender persons

Effect	Onset	Maximum
Redistribution of body fat	3 to 6 months	2 to 3 years
Decrease in muscle mass and strength	3 to 6 months	1 to 2 years
Softening of skin/decreased oiliness	3 to 6 months	Unknown
Decreased sexual desire	1 to 3 months	3 to 6 months
Decreased spontaneous erections	1 to 3 months	3 to 6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3 to 6 months	2 to 3 years
Decreased testicular volume	3 to 6 months	2 to 3 years
Decreased sperm production	Unknown	>3 years
Decreased terminal hair growth	6 to 12 months	>3 years*
Scalp hair	Variable	—¶
Voice changes	None	—Δ

* Complete removal of male sexual hair requires electrolysis or laser treatment or both.
¶ Familial scalp hair loss may occur if estrogens are stopped.
Δ Treatment by speech pathologists for voice training is most effective.

Graphic 54189 Version 11.0

Monitoring of transgender persons on gender-affirming hormone therapy: Transgender females

1. Evaluate patient every three months in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every three months.
a. Serum testosterone levels should be <50 ng/dL.
b. Serum estradiol should not exceed the peak physiologic range: 100 to 200 pg/mL.
3. For individuals on spironolactone, serum electrolytes (particularly potassium) should be monitored every three months in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline[1]. In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower-level recommendations.

BMD: bone mineral density.

Reference:

1. *Giltay EJ, Hoogeveen EK, Elbers JM, et al. Effects of sex steroids on plasma total homocysteine levels: a study in transsexual males and females. J Clin Endocrinol Metab 1998; 83:550.*

Graphic 67967 Version 12.0

Specific issues in screening for transwomen and transmen with past or current hormone use

	Transwomen (MTF)	Transmen (FTM)
Breast cancer	Discuss screening in patients >50 years with additional risk factors for breast cancer*	Intact breasts: Routine screening as for natal females
		Postmastectomy: Yearly chest wall and axillary exams ¶
Cervical cancer	Vaginoplasty: No screening	Cervix intact: Routine screening as for natal females
		No cervix: No screening
Prostate cancer	Routine screening as for natal males	N/A
Cardiovascular disease	Screen for risk factors	Screen for risk factors
Diabetes mellitus	On estrogen: Increased risk	Routine screening Δ
Hyperlipidemia	On estrogen: Annual lipid screening	On testosterone: Annual lipid screening
Osteoporosis	Testes intact: Routine screening as for natal males	Screen all patients >65 years Screen patients age 50 to 65 if off hormones for >5 years
	Postorchiectomy: Screen all patients >65 years Screen patients age 50 to 65 years if off hormones for >5 years	

* Estrogen/progestin therapy for >5 years, family history, body mass index (BMI) >35.

¶ While there is no evidence to support clinical breast examinations in this population, we perform yearly chest wall and axillary exams and use this as an opportunity to examine scar tissue, examine any changes, and educate the patient about the small but possible risk of breast cancer.

Δ Transmen with polycystic ovary syndrome (PCOS) should be screened for diabetes as for natal females with PCOS. Refer to the UpToDate material on further evaluation after diagnosis of PCOS in adults.

Graphic 102596 Version 2.0

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