Chapter 8
Endocrine Care of Transgender Adults

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Endocrine Care of the Transgender Patient

Introduction

Since the mid-twentieth century, transgender individuals have become increasingly visible. Strong advocacy group efforts and increasing government support have improved access to medical care for people with gender dysphoria. Physicians should be aware of the unique conditions and challenges affecting this population. Healthcare professional organizations such as the American Medical Association (AMA), the Endocrine Society, and the World Professional Association for Transgender Health have concluded that hormonal and surgical treatment of gender dysphoria is medically necessary to prevent long-term morbidity. Furthermore, physicians caring for transgender persons must have sufficient experience to recognize gender dysphoria as a spectrum of conditions, and should be adept in tailoring therapy to the individual patient. Many, but not all, gender dysphoric individuals presenting for care will ultimately seek endocrine therapy for the modulation of endogenous hormone production and exogenous hormone supplementation, to improve their quality of life.

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General Considerations

The goals of hormone therapy in individuals suffering from gender dysphoria are determined by many factors including age, capacity to consent to treatment, pre-existing health conditions, risk factors for future disease, access to care, and the patient's desired outcomes with regards to gender transition. While some individuals with gender dysphoria desire to live as the opposite gender, others prefer to live as neither gender and seek suppression of all evidence of a sexual or gender representation.

Hormonal therapy for individuals with gender dysphoria is but one of many treatments available, and must be considered in the context of contemporaneous psychological care and possible surgical interventions. In addition, the developmental stage at which the patient presents for evaluation and treatment (i.e., prepubertal, during puberty, or in adulthood having completed puberty) will necessarily affect the goals and possible outcomes of hormone treatment. A discussion of the care of transgender children and adolescents is presented elsewhere in this volume.

Hormonal treatment for patients with gender dysphoria must begin with an assessment of the individual's expectations and goals of care. Prior to initiating hormonal therapy, patients should be counseled regarding realistic expectations of masculinization/feminization, and the time course over which potential changes may occur. The initial discussion should include a thorough medical history that may elucidate potential risks to hormonal treatment. A family history of gynecologic and breast cancers, cardiovascular disease, diabetes, hypertension, and hyperlipidemia should be noted if present. Patients who previously have not been in the care of a mental health provider should be assessed for psychological stability, as psychiatric disease has been reported in over 56% of patients seeking gender-affirming hormone treatment [1]. Providers should inform individuals of the particular benefits, limitations, and risks of treatment, specific to the individual's age, previous experience with hormones, and concurrent physical or mental health concerns. Additionally, a detailed psychiatric, social, and sexual history are warranted as certain behaviors such as cigarette smoking, excessive alcohol consumption, and high-risk sexual activity may increase the inherent risks of hormone treatment. A physical exam should be performed including measurements of height, weight, and blood pressure. Breast, rectal, and genital exams may provoke anxiety and severe discomfort in patients with gender dysphoria, and should be approached delicately and with explicit consent. Laboratory evaluation should include a complete blood count, electrolytes, kidney, liver, and thyroid function tests, lipid profile measurements, fasting glucose and HbA1C, β-HCG (for native females), and baseline levels of testosterone, estradiol, FSH, LH, and prolactin. Where appropriate, screening for cervical cancer, breast cancer, and prostate cancer may be warranted. Additionally, a careful risk assessment for the development of estrogen- and androgen-sensitive cancers should be conducted prior to initiating therapy. For patients interested in testosterone therapy, an evaluation for sleep apnea may be indicated [2].

Obtaining informed consent for hormone therapy is important to ensure that patients understand the psychological and physical risks and benefits of hormone therapy. Adverse effects of hormonal treatment, such as infertility, may be irreversible with prolonged treatment, and these should be discussed openly and frankly when developing a treatment plan. It has been suggested that patients should have demonstrated an understanding of the psychosocial implications of gender transition by completing a social transition to their affirmed gender, however more recent guidelines recognize the difficulty of making a social transition in the absence of a biochemical and physical transition.

Developing a Treatment Plan

The overall framework of endocrine care for gender dysphoria consists of treatments aimed at suppressing the natal gender characteristics and treatments aimed at affirming the desired gender. Feminization and masculinization refer to the physical changes that allow transgender individuals to feel comfortable in society in their affirmed gender. Hormonal regimens will vary based on the age, treatment status, and desired outcomes of the individual. Access to care and availability of treatment modalities varies greatly geographically.

Puberty

The onset of puberty is of particular significance in the lives of children with gender dysphoria. For many children who have not socially transitioned away from their natal gender, the physical transitions occurring in puberty serve to reverse much of their initial discomfort. By contrast, a marked increase in gender dysphoria at the onset of puberty is highly suggestive that the condition will not remit [3–5]. It is because of this dichotomous reaction to pubertal changes that hormonal therapy is not recommended in children who have not yet achieved Tanner stage 2 of puberty. At this stage, current guidelines [5] recommend initiating hormonal treatment to halt the progression of puberty rather than the initiation of cross-sex hormones. Suppression of puberty increases the interval during which gender dysphoria may resolve, while allowing the individual to remain less identified with the bothersome gender as peers develop secondary sexual characteristics. Furthermore, suppression of puberty prevents development of potentially irreversible secondary sexual characteristics such as changes in voice and bone structure, allowing the body some capacity to develop physical characteristics of either sex once this suppression is lifted. A discussion of pubertal suppression can be found in the chapter on pediatric management of transgender individuals elsewhere in this volume.

For transgendered patients managed with puberty suppression, adult care begins with puberty induction. Induction of female puberty in this scenario requires

administration of increasing doses of estrogen to mimic the gradual rise in levels seen in the progression of puberty in natal females. In the setting of delayed onset of male puberty followed by induction of female puberty, endogenous androgen production is typically minimal due to continuous suppression of LH and FSH and rarely requires additional suppression or antiandrogen treatment. GnRH analogs used for puberty suppression should be continued until adult premenopausal estrogen levels have been achieved, at which time attempts to wean GnRH can be made. Antiandrogen medications can be used to mitigate the effects of endogenous hormone production [3, 4, 6, 7].

Induction of male puberty is achieved with increasing doses of subcutaneous or intramuscular injections of testosterone esters beginning at 12.5 mg/m^2/week and increasing every 6 months until a serum testosterone level in the normal adult range has been reached. Suppression of endogenous hormones is no longer required once adult testosterone levels have been achieved, sufficient virilization has occurred, or the patient undergoes gonadectomy. However, continued use of GnRH analogs along with testosterone may allow for a reduction in the testosterone dose required to maintain adult levels [3, 6].

In patients who began puberty suppression at a later developmental stage, induction of cross-gender puberty should be allowed to progress more rapidly, with higher starting doses of gender-affirming hormones. Throughout the period of puberty induction, patients should be monitored with quarterly measurements of height, weight, blood pressure, and Tanner stage. Hemoglobin/hematocrit, serum levels of lipids and testosterone for transgender males, and levels of prolactin and estradiol for transgender females should be assessed every 6 months prior to dose adjustments of hormonal therapy. In addition, all patients undergoing puberty induction should undergo bone age monitoring along with vitamin D level measurements annually as well as yearly bone mineral density testing with DEXA until early adulthood.

Hormone Therapy for the Transgender Female

The treatment of individuals with gender dysphoria presenting in postpubertal adulthood relies more heavily on the suppression of natal characteristics and often requires intensified hormonal treatment compared with that of persons presenting before or during puberty. Gender-affirming hormonal treatments have been developed and influenced by the regimens used for hypogonadism.

The treatment of transgender females relies on suppressing native androgen production as well as supplementation of female hormones [8, 9]. There is significant global variability in the treatment regimens due to cost and availability of medication. Both natural estrogens including estrone, estradiol, and 17β-estradiol, and synthetic estrogens (estradiol valerate, estradiol benzoate, and ethinylestradiol) are available in a variety of forms and combinations (Table 8.1). The oral estrogens most commonly used include micronized estradiol (2–4 mg/day), estradiol valerate (2–4 mg/day), ethinylestradiol (20 μg/day), and conjugated estrogens

Table 8.1 Feminizing hormones

Name	Route	Dose	Comments
Micronized estradiol	Oral	2–4 mg/day	Inexpensive
Estradiol valerate	Oral	2–4 mg/day	
Ethinylestradiol	Oral	20 μg/day	Not recommended, high DVT risk Not detectable in serum assays
Conjugated estrogens	Oral	1.25–2.5 mg/day	
17β-estradiol	Transdermal	100–200 μg/day	Lowest DVT risk, higher cost
Estradiol cypionate	IM	3 mg/month	Long latency period
Estradiol valerate	IM	5–20 mg/2 weeks	
Estradiol undecylate	IM	100 mg/month	

(1.25–2.5 mg/day). A transdermal patch of 17β estradiol (100–200 μg/day) is the estrogen of choice to reduce the risk of thromboembolic disease [8, 10] and may be preferred due to the lack of associated changes in lipid profile or markers of coagulation (discussed in more detail below). However, the use of transdermal delivery is limited by a higher cost relative to oral preparations. Intramuscular depots [estradiol cypionate (3 mg/month), estradiol valerate (5–20 mg/2 weeks), estradiol undecylate (Progynon, 100 mg/month)] have been used, but these agents have a longer latency period before the development of noticeable physical changes, often leading to self-discontinuation or dose escalation by patients [11, 12]. In addition, a number of estradiol/progestin combination tablets are available, typically used as oral contraceptives.

The initial dose of estrogen should be increased gradually until achieving sufficient feminization without exceeding the normal native female premenopausal range (typically 100–200 pg/mL). This is usually achieved with an oral preparation of 2.0–6.0 mg/day; a transdermal patch of 0.025–0.2 mg/day or parenteral injections of 2–10 mg/week. It should be noted that conjugated and synthetic estrogens such as ethinylestradiol are not detectable in the serum by conventional assays [13] and are no longer recommended [2, 14–24]. Serum target levels may change as the patient ages to account for reduced drug clearance as well as the natural decline in endogenous estrogen production that occurs in natal females at menopause. Older transgender females may continue to require high-dose estrogen supplementation to maintain a female body habitus and continued suppression of androgen production after the typical age of menopause.

Estrogen supplementation into the normal premenopausal female range can suppress testosterone production into the low-normal range, but is usually insufficient to achieve a reduction of levels into the normal female range [9, 13, 24–31] (ideally <50 ng/dL). Treatments aimed at further reducing testosterone levels include progesterone supplementation (more common in Europe), androgen receptor antagonists (more common in the US), GnRH agonists (primarily in the UK) and 5α-reductase inhibitors (Table 8.2) [2, 8, 10, 13, 32, 33]. Orchiectomy may be necessary to achieve optimal reductions in testosterone levels and male pattern secondary sex characteristics.

Table 8.2 Antiandrogens

Type	Route	Dose	Comments
GnRH analogs			
Goserelin	SubQ	3.8 mg/ 4 weeks	Most commonly used in the UK High cost Tolerated well Variations in geographic availability of agents
Leuprolide	IM	3.75 mg/ 4 weeks	
Buserelin	SubQ/ intranasal	200–1200 μg/ day	
Triptorelin	IM	3.75 mg/ 4 weeks	
Histrelin	SubQ depot	50 μg/day	
Progesterone			
Cyproterone acetate	Oral	25–100 mg/ day	Preferred agent in Europe. Cyproterone acetate not available in the USA
Medroxyprogesterone	Oral	10 mg/day	
Androgen receptor blocker			
Spironolactone	Oral	100–400 mg/day	Preferred in the US, low cost Risk of hepatotoxicity
Flutamide	Oral	250–500 mg/day	
Bicalutamide	Oral	25–50 mg/ day	
Enzalutamide	Oral	160 mg/day	
5α-reductase inhibitors			
Finasteride	Oral	5 mg/day	May be beneficial following gonadectomy
Dutasteride	Oral	0.5 mg/day	

GnRH agonists create continuous stimulation of the GnRH receptor, thus interrupting the normal pulsatile rhythm responsible for the secretion of LH and FSH. Lack of pituitary stimulation leads to downstream inhibition of testosterone and dihydrotestosterone secretion from the testes and estradiol and estrone from ovaries. Small studies have reported successful gonadotropin suppression using goserelin acetate (3.8 mg subcutaneous injection every 4 weeks) [34] and leuprolide [35] (3.75 mg intramuscular injection every month), in combination with estrogen. There are few published reports [36] describing the use of additional GnRH analogs in the treatment of transgender adults, however many studies have shown a dramatic suppression of gonadotropins with buserelin [37, 38]. Triptorelin has been successfully used in the treatment of transgender adolescents [12]. Long-term androgen suppression for up to 2 years can be achieved with histrelin (50 μg/day) subcutaneous implants, and is a suggested option for patients who desire but are unable to undergo gonadectomy [15].

Supplementation with progesterone or its derivatives can reduce serum testosterone levels by 70–80% in native males [39]. Certain progestins such as cyproterone acetate (25–100 mg/day) and medroxyprogesterone (10 mg/day) possess additional testosterone receptor antagonist activity [40] making them attractive drugs for androgen suppression in transgender females. Studies suggest that cyproterone acetate is more effective than medroxyprogesterone in reducing testosterone levels into the female range [10, 25, 35, 41] which may be attributed to additional antigonadotropic effects [10]. The use of additional progesterone to promote breast growth is controversial [42–44]. There is some evidence that breast development, mood, and sexual desire are increased with progesterone supplementation [43]. Adverse effects including liver toxicity and severe depression have been reported in association with cyproterone acetate [10, 45]. In addition, long-term use of cyproterone acetate may increase the risk of meningiomas [10, 46–48].

Additional treatment modalities aimed at reducing the effects of testosterone include androgen receptor blockers and 5α-reductase inhibitors (due to the reduced conversion of testosterone to the more potent dihydrotestosterone). Spironolactone, a potassium-sparing diuretic used in the treatment of hypertension and congestive heart failure, is a steroid compound with androgen receptor blocking activity when administered at higher doses (100–400 mg/day). Additional antiandrogenic effects are mediated via inhibition of the 17α-hydroxylase enzyme leading to decreased testosterone synthesis and secretion, as well as by modest estrogen receptor agonist activity [49, 50]. Some studies suggest spironolactone may inhibit breast development via activation of the estrogen receptor leading to early breast bud fusion, though this remains controversial [44] as gynecomastia is a well-described adverse effect of spironolactone [51].

Non-steroidal selective androgen receptor antagonists, developed as a treatment for androgen-sensitive prostate cancer, are occasionally used in transgender females who do not achieve their desired results or do not tolerate alternative drugs [52]. There are isolated reports of successful outcomes with flutamide (Eulexin), though reportedly not as effective as cyproterone acetate in reducing testosterone levels [12]. Both flutamide and bicalutamide (Casodex), in conjunction with oral contraceptive pills, have shown significant improvements in hirsutism in natal females with polycystic ovarian syndrome (PCOS) [53–57]. The use of these agents as antiandrogens in transgender patients has been limited by concerns of hepatotoxicity. However, at low doses, these agents have shown to be both well tolerated and effective when used for the treatment of hirsutism [57].

The putative mechanism of 5α-reductase inhibitors (finasteride 5 mg/day PO, dutasteride 0.5 mg/day PO) should lead to a reduction and regression of male secondary sex characteristics through inhibition of conversion of testosterone to dihydrotestosterone. Evidence exists for the role of these agents in improving scalp hair loss, reducing body hair growth and sebaceous gland secretions, and improving skin consistency in transgender females [6]. However, blocking of dihydrotestosterone synthesis leads to an increased concentration of testosterone availability to specific receptors, limiting the efficacy of this class of medications in reducing

testosterone levels [2, 14, 15]. In addition, this class of drugs has been linked to worsening depression [10, 58], and liver toxicity [14]. Dutasteride (0.5 mg) is more effective than finasteride in blocking the type 1 isozyme, which is present in the pilosebaceous gland and may lead to larger reductions in scalp hair loss and body hair growth. Unlike other antiandrogen medications, 5α-reductase inhibitors may continue to be useful after gonadectomy for management of hair loss [59]. For older transgender females, antiandrogens may become the primary component of treatment as estrogen requirements are reduced in parallel to the decline in estrogen levels in natal females that occurs with menopause [60].

The effects of estrogen along with antiandrogen medications are typically observed beginning 3 months into treatment. The most desired effects of gender-affirming hormones for transgender females are the development of female secondary sex characteristics including: enlarged breasts, decreased facial and body hair, development of female pattern weight distribution and body habitus, and softening of the skin. Clinically significant estrogen levels will also lead to a reduction in spontaneous and sexually stimulated erections, reduced ejaculatory volume and sperm concentrations, and changes in sweat and odor patterns. Longer hormone exposure is necessary for significant decreases in testicular and prostate size. The maximal effect of hormone therapy on secondary sex characteristics typically occurs 2 years after starting treatment [61]. The degree and rate of these changes are hard to predict and are dependent on the type of medication, the dose, and route of administration. Many transgender females are dissatisfied with breast growth achieved through hormonal therapy, and opt for surgical augmentation [10, 19]. One multicenter study reported modest breast development, occurring primarily within the first 6 months of treatment. No clinical or laboratory parameters were found to predict breast development [62].

Failure to achieve testosterone suppression with standard antiandrogen regimens despite maximal therapy and medication adherence should prompt evaluation for endogenous testosterone production from a tumor, or undisclosed exogenous testosterone use to maintain sexual function during the transition. In transgender females wishing to retain erectile function, sildenafil or tadalafil can be used as supportive measures.

Transgender females should be informed of the risks of estrogen treatment and evaluated for preexisting conditions that may pose an increased risk. The most well-known adverse effect of estrogen therapy is the development of thromboembolic disease. There is an increasing risk of this complication with advancing age, active cigarette smoking, and concurrent use of progestins. Providers should encourage all patients on estrogen therapy to stop smoking. Transdermal and parental administration of estrogen is associated with a decreased risk of thromboembolic disease as compared to oral administration, attributed to reduced first-pass hepatic metabolism [10, 63]. In addition, synthetic estrogens appear to confer an increased risk of thromboembolism as compared to natural estrogens [10, 64]. The mechanism for this effect remains unknown.

Additional adverse effects of estrogen use in transgender females include liver dysfunction, gallstones, hypertriglyceridemia, and weight gain. The role of estrogen

in the development of cardiovascular disease remains controversial. One study of 161 transgender females showed no increased incidence of cardiovascular mortality [65]. Alterations in lipid metabolism include decreased LDL and increased triglycerides [10, 66–70]. The effects of estrogen on HDL levels are unclear, with studies reporting both increases [50, 71] decreases [24, 72], and no change [70]. The effect of estrogen on HDL may be partially related to route of administration, with transdermal estradiol more likely to increase HDL [67, 69]. Increased insulin resistance and the development of type 2 diabetes has also been reported during estrogen treatment [42]. Elevated prolactin levels are nearly universal, though mild, in transgender females. There are reported cases of prolactinomas in this population that may result from enhanced growth of pituitary lactotrophs under the influence of increased estrogen levels [11, 24, 73–75]. In these cases, prolactinomas may resolve when the dose of estrogen or progesterone is reduced. The evaluation of elevated prolactin with MRI of the pituitary is controversial in the absence of visual or other symptoms as asymptomatic prolactinomas do not require treatment in this population [76]. Furthermore, the prolactin raising effects of psychotropic medications may be enhanced by estrogen administration.

Gender-affirming hormone treatment in transgender females has been reported to reduce blood pressure [42], however, this effect is likely due to a reduction in testosterone levels leading to reduced hematocrit rather than increased estrogen concentrations. This finding is supported by reports that administration of ethinylestradiol in combination with cyproterone acetate lead to increased blood pressure and arterial stiffness [24, 42, 71, 77] and that use of oral contraceptives in cis-gender females can lead to hypertension that resolves on discontinuation [78].

Sexual function is greatly affected by exogenous hormones. High estrogen levels can lead to reduced libido, as well as reduced spontaneous and sexually stimulated erections. High levels of hypoactive sexual desire disorder are reported in transgender females, with one study reporting that over 75% of individuals never or rarely experience spontaneous or responsive sexual desire [79].

Hormone Therapy for the Transgender Male

Gender-affirming treatment for the transgender male consists primarily of exogenous testosterone administration. While testosterone is available in oral (outside of the USA), buccal, topical, transdermal preparations and as subcutaneous implants, intramuscular injections are most often prescribed as they are available at relatively low cost (Table 8.3). There are no standardized protocols for the initiation of testosterone therapy, but expert opinions recommend a low initial dose with gradual increases, as is typically done in treating patients with hypogonadism. Intramuscular injections of short-acting testosterone esters such as testosterone cypionate (Depo-testosterone) (200 mg), decanoate (Sustanon) (250 mg) or enanthate (Delatestryl) (250 mg) administered every 2–4 weeks are among the most commonly prescribed. However, these agents do not mimic circadian release of the

Table 8.3 Masculinizing hormones

Name	Route	Dose	Comments
Testosterone cypionate	IM	200 mg/ 4 weeks	Short-acting preparations do not mimic circadian release
Testosterone decanoate	IM	250 mg/ 4 weeks	
Testosterone enanthate	IM	250 mg/ 4 weeks	
Testosterone undecenoate	IM	1000 mg/ 12 weeks	Must be administered in physician's office in the US. High cost
Androderm, Testoderm	Transdermal patch	5 mg/day	Skin irritation at patch site may occur
Androgel, Testim	Transdermal gel	5 g/day	Risk of transfer to intimate partner
Striant	Lozenge	30 mg/12 h	
Crystalline testosterone (Testopel)	SubQ depot	600 mg/4–6 months	
Testosterone undecanoate (Andriol)	Oral	80–160 mg/day	Multiple daily doses required

hormone. Supraphysiologic levels of testosterone (with associated adverse effects) occur at the time of injection, with hypogonadal symptoms occurring in the days leading up to the next injection. Some centers include two doses of intramuscular progesterone (500 mg) 3–4 days after each testosterone injection [11]. A newer preparation, testosterone undecanoate (Nebido), is now available for injection every 12 weeks to achieve more consistent levels, although at considerably higher cost. Transdermal patches (Androderm, Testoderm) and gels (AndroGel, Testim) can be used daily (5 mg/patch or 5 g of gel) for more consistent testosterone levels, however these delivery methods can be complicated by skin irritation at the patch site and transfer of hormone from the gel to an intimate partner. Bioidentical testosterone lozenges (Striant) (30 mg every 12 h) can provide consistent levels, but have been associated with gum irritation, changes in taste, and headaches [80]. Subcutaneous implants of crystalline testosterone (Testopel) (600 mg/4–6 months) can maintain stable and physiologic testosterone levels without the need for daily dosing. Finally, oral testosterone undecanoate (Andriol) is now available in doses of 80–160 mg/day, but requires multiple daily doses and has a short history of clinical use. It should be noted that non-injectable forms of testosterone are inferior to injectable forms in suppressing menstruation for reasons that remain unknown.

Testosterone is essential for the development of male secondary sex characteristics. Androgen receptors are located throughout the body, leading to a multitude of physical and psychiatric changes in association with testosterone therapy. Gender-affirming treatment in transgender males aims to promote a deepened voice,

clitoral enlargement, increased facial and body hair, cessation of menses, atrophy of breast tissue, decreased body fat, and an increase in muscle mass and strength. The expected onset of these changes ranges from 1 to 12 months after starting therapy, with maximal effects achieved as late as 5 years after initiation. The first manifestations of virilization include changes in body hair and skin, and cessation of menses. Clitoromegaly and voice deepening typically occur within 6 months of starting therapy. Clitoral growth may be associated with pain prior to significant elongation, and is reported to peak 6 months following initiation of testosterone [13, 72, 81]. Alopecia may occur in those genetically predisposed after prolonged testosterone use. Providers should avoid increasing the dose of testosterone to hasten masculinization, as this may lead to increased conversion to estrogen. Reduced doses of testosterone should be considered following oophorectomy [80].

In some patients, the side effects of testosterone treatment limit the dose, leading to incomplete menstrual suppression. As in transgender females, GnRH agonists are highly effective in suppressing endogenous ovarian hormone production, leading to amenorrhea [2, 82]. Menstruation can also be suppressed by continuous progesterone therapy administered systemically or locally (for example, with an intrauterine device in individuals with an intact uterus). Ovarian production of estrogen is decreased in the presence of continuous progesterone due to negative feedback at the level of the pituitary inhibiting secretion of FSH and LH. In transgender males, androgenic progesterones have the added advantage of reducing sex hormone binding globulin concentrations leading to a relative increase in available testosterone [82, 83].

Available preparations include oral norethindrone (Micronor, Camila, Deblitane, Heather, Jencycla, Jolivette, Sharobel) as a 0.35 mg tablet which should be taken at the same time daily. Norethindrone acetate (Aygestin), medroxyprogesterone acetate (Provera), Lynestrenol (Orgametril) and micronized progesterone (Prometrium) are alternative daily oral preparations. Medroxyprogesterone acetate depots are available as intramuscular gluteal or deltoid injection (Depo-Provera) or subcutaneous (Depo-SubQ) injections administered every 12–14 weeks obviate the need for daily dosing. Long-term progesterone therapy is available for up to 3 years as intradermal etonogestrel (Implanon) or up to 5 years as an intrauterine device with levonorgestrel (Mirena, Liletta). Breakthrough bleeding may occur for 3 months following placement [8]. If menses are not suppressed with hormone treatment, endometrial ablation may be required. Contraception should be continued in all transgender females, who have not undergone gonadectomy as testosterone monotherapy may be insufficient to prevent ovulation and is contraindicated in pregnancy.

Very little is known regarding the utility of antiestrogen medications in transgender males. Aromatase inhibitors such as anastrozole or letrozole have been used off-label as adjunctive therapies to suppress menstruation in transgender men by preventing the conversion of testosterone to estrogen. Aromatase inhibitors have been shown to safely and effectively increase testosterone levels in hypogonadal natal males [84, 85], however, there are no published reports of their use in transgender males. Reduced estrogen concentrations in transgender males is

theorized to reduce vaginal bleeding and pelvic pain. Menopausal side effects attributed to aromatase inhibitors in natal women are attenuated or absent in transgender men with concurrent use of testosterone. These agents may be of particular benefit in obese patients as aromatase is naturally expressed in adipose tissue. Anecdotal evidence supports a role for selective estrogen receptor blockers such as raloxifene to reduce uterine bleeding in transgender men on testosterone treatment with unsuppressed menses [59].

While testosterone treatment is generally well tolerated, adverse effects can occur and may lead to significantly increased risk of life-threatening disease. A rise in hemoglobin and hematocrit concentrations is nearly universal with testosterone administration. While the development of overt polycythemia (hematocrit >50) is a common finding in natal men using exogenous testosterone, the rise in hematocrit in transgender females is typically less pronounced. The degree to which polycythemia increases the risk of deep venous thrombosis (DVT) in transgender males is unclear because of the lack of evidence to suggest that testosterone treatment increases the incidence of DVT [20, 86, 87]. Untreated severe obstructive sleep apnea is a relative contraindication to testosterone treatment as this may further increase the risk of polycythemia and deep venous thrombosis [88]. In addition, testosterone may exacerbate underlying sleep apnea by increasing weight and muscle mass. The mechanism by which testosterone increases erythropoiesis remains unknown and appears to be unrelated to increased erythropoietin [89, 90]. Polycythemia occurs most often with intramuscular preparations of testosterone [91].

A causal relationship between testosterone use and cardiovascular disease remains controversial [20, 80, 92–94]. Testosterone use is associated with worsening of numerous cardiac risk factors including: hypertension, weight gain, salt retention, increased LDL and triglyceride levels, reduced HDL levels [42, 93, 95], and reduced homocysteine levels [14, 96, 97]. A controlled study of transgender males reported an increased incidence of cardiovascular mortality [98], however, this finding was not confirmed in small studies of transgender males compared to the general population [94]. Two studies examined the effects of hormone therapy in patients with preexisting risk factors such as hyperlipidemia and hypertension. In one study, no patients experienced cardiovascular events over an average of 10 years of treatment [20]. A second study of 138 subjects reported no significant increase in cardiovascular events over an average of 7.4 years of therapy compared to the general population [99]. However, the use of testosterone in patients with a history of unstable coronary artery disease is not recommended [80, 100].

Studies are equivocal with respect to the effects of testosterone on increasing insulin resistance in transgender males [94, 99]. Multiple studies have reported a lowering of fasting glucose in transgender males [24, 42, 71, 101]. Others have reported no change in fasting glucose or insulin activity as measured by the homeostatic model assessment-insulin resistance [71, 72, 102–104]. A case-control study [105] found an increased incidence in type 2 diabetes in transgender men using testosterone, despite maintenance of a stable body weight.

The increase in muscle mass associated with testosterone use can lead to an increase in measured creatinine levels and glomerular filtration rate [42, 72, 106, 107]. The significance of these changes with respect to renal function is unclear: In murine models, testosterone has both protective and damaging effects [108, 109]. No long-term studies have reported significant effects on kidney function in transgender patients.

An increased risk of uterine and ovarian cancer in association with testosterone use in transgender males remains controversial [80, 82, 93, 110–113]. This may be related to the development of polycystic ovaries in patients on testosterone therapy [112–114] as testosterone may increase ovarian volumes and induce stromal hyperplasia [13]. However, more recent studies suggest that the de novo development of polycystic ovaries in transgender males is different from the a priori presence of polycystic ovaries in natal females with PCOS [6, 110]. A baseline higher incidence of PCOS in transgender males as compared with cis-gender females has been reported warranting closer follow-up in this group. PCOS is an independent risk factor for cardiac disease, type 2 diabetes mellitus, as well as ovarian and endometrial malignancies, which may confound the observed association between these outcomes and testosterone use. Endometrial atrophy occurs in a subset of patients in response to testosterone [112]. An increased risk of endometrial cancer may be due to the effects of testosterone conversion to estrogen without opposing progesterone.

The risk of breast cancer remains present in transgender males. Although testosterone leads to a reduction in breast glandular tissue accompanied by an increase in fibrous connective tissue [115, 116], as with endometrial cancer, aromatization to estradiol may promote malignancy. Multiple cases of breast cancer have been reported in transgender males, including following mastectomy [117–121], however testosterone therapy has been shown to reduce the risk of breast cancer [117]. The risk of breast cancer in transgender males is higher in post-oophorectomy and menopausal patients [111].

Additional less severe adverse effects of testosterone therapy include the development of cystic acne, baldness (male pattern), and unwanted body hair. Cystic acne will often improve with topical or oral retinoic acid treatment. Finasteride and topical minoxidil can be considered to improve male pattern baldness. Insufficient evidence exists regarding the effects of testosterone on exacerbating underlying psychiatric conditions. Some individuals may experience a bothersome increase in libido, which can be managed with low-dose SSRIs [122, 123]. This effect is exacerbated by painful intercourse resulting from thinning of the vaginal epithelia [13, 124].

Screenings and Follow-Up

Transgender females and transgender males should be closely followed by a multidisciplinary team of physicians during and following their transition.

Following the initiation of hormone treatments, patients should undergo quarterly physical exams including measurements of weight and blood pressure, to document any physical changes related to gender transition. Additionally, smoking cessation counseling and screening for depression should be provided at each visit. Serum levels of testosterone, estradiol, progesterone, LH, FSH, prolactin, lipids, fasting glucose, liver enzymes, and creatinine should also be monitored at these visits until appropriate stable levels have been achieved. In patients using periodic intramuscular testosterone injections, a trough level should be collected. Testosterone levels in transgender males should be maintained in the normal male range of 300–1000 ng/dL [80] and in transgender females should be suppressed into the normal female range of <50 ng/dL. Ideal estrogen levels in transgender females are in the normal premenopausal range for native females (100–200 pg/mL), taking into account that this goal may change as the patient ages. Sex hormone binding globulin (SHBG) levels are expected to increase in transgender females, and decrease in transgender males [72]. It should be noted that normal values for metabolic and hormonal parameters have not been established for transgender individuals, and care should be taken in interpreting parameters with sex-specific reference ranges [125].

Establishing objective targets to evaluate a dosing regimen can be challenging given that appropriate hormone levels are unknown for transgendered individuals, and that clinical/phenotypic response is related to genetics as well as the age at which treatment was started. Titration should be guided by patients' goals, in the setting of measured hormone levels and safety considerations. For transgender females, one approach is to begin both estrogen and antiandrogen medications at low doses, escalate in parallel until appropriate estrogen serum levels have been achieved, and then increase the dose of antiandrogen to achieve improved feminization and further androgen suppression if needed.

Once a consistent dosing regimen has been established, the frequency of monitoring can be decreased to 6 months for 1 year, and annually thereafter. Annual visits should also include a thorough assessment of ongoing cardiovascular risk and sexual health. Recommendations for breast cancer screenings are the same for both transgender and cis-gender females, as well as transgender males who have undergone a mastectomy. In patients with an intact uterus, cervical cancer screenings should continue as per recommended guidelines for natal females. Endometrial ultrasound is recommended every 2 years or if unexpected bleeding occurs following cessation of menses. Periodic hepatic ultrasound can be considered in patients taking oral testosterones to screen for hepatic tumors [80]. An individualized approach to prostate cancer screening is recommended for transgender females.

The need for osteoporosis screening is equivocal in transgender patients as both estrogen and testosterone have profound effects on bone metabolism. While some centers recommend annual bone densitometry [11], there is little evidence to support this. Estradiol will stimulate endosteal bone apposition. Testosterone stimulates radial bone expansion and has anabolic effects on the periosteum, as well as downstream effects related to its conversion to estradiol [126]. Increased cortical

bone size, cortical thickness, and bone mineral density have been reported in transgender males [127–130]. It has been reported that transgender females have high rates of osteoporosis which may pre-date the initiation of hormone therapy [131, 132] possibly due to poor nutritional status and low levels of physical activity [65]. Despite this, the incidence of fragility fractures in transgender females is low [133]. Serum levels of estradiol are better predictors of bone mineral density than testosterone levels [134, 135]. In evaluating transgender patients who underwent transition following puberty, birth gender should be used when estimating osteoporosis risk. In patients who have not undergone gonadectomy, osteoporosis screening may not be necessary. Bone mineral density should be assessed every 2 years in patients without ovaries [80]. Testosterone therapy may benefit transgender females by a direct stimulatory effect of testosterone on bone in addition to the effects of estrogen [130].

Special attention to deep venous thrombosis prophylaxis is necessary for patients undergoing surgical procedures while on hormone therapy. While no clear evidence exists for discontinuation of treatment, some experts recommend cessation of hormone therapy for up to 4 weeks prior to elective procedures [27] and reintroduction of estrogen therapy when the patient is fully ambulatory [32]. A recent retrospective study of over 900 patients [136] on testosterone treatment demonstrated no increased risk of postoperative in-hospital mortality, myocardial infarction, stroke, or major thromboembolism.

Conclusions

The use of cross-sex hormones in the treatment of gender dysphoria is an evolving field. More studies are needed to better elucidate the optimal regimens for feminization and masculinization while reducing the rate of adverse effects. Increasing global awareness and acceptance of transgender medicine should help this field to make significant strides in the coming years.

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