CHAPTER 15

Adult Hormone Therapy in Transgender Patients

Melany Castillo, Roy E. Weiss

Key Points

❖ The treatment and care of transgender individuals are now common practice in medicine, which requires medical personnel trained and experienced in the health needs of the transgender population.

❖ Hormone treatment should be administered to maximize the safest and most effective transition of desired sexual characteristics.

❖ Data on the effectiveness of cross-hormonal therapy protocols in the adult transgender population are limited and based on a few, nonrandomized studies.

❖ The significant consequences of male-to-female and female-to-male treatment affect cardiovascular disease, hormone-related cancers, and bone health.

❖ Perioperative management of patients may require brief cessation of hormone therapy.

❖ Reproductive function should be discussed with the patient and planned for appropriately.
The influence of the composition of the hormonal milieu and the timing of exposure on the establishment of gender identity are not fully understood. Most agree that there is a complex interaction between the genetic blueprint and hormonal regulation of genetic expression that influences psychological elements, resulting in self-perception of gender. Hormones, and specifically sex hormones (androgens and estrogens), can have a profound effect on the perception of one's gender. For example, intrauterine androgen exposure of XX females may predispose to gender identity disorders. In addition, XY males exposed to male-typical prenatal androgen have a high likelihood of declaring a male sexual identity, even when raised as female. However, inappropriate prenatal androgen exposure demonstrated unpredictable sexual identification. The prevalence of disorders of sex development is estimated at 0.1% to 2% of the global population, and of those, 8.5% to 20% present with gender dysphoria. Gender dysphoria is a psychiatric diagnosis, which should only be made after a careful endocrine evaluation and other disorders of sexual differentiation have been excluded.

Many syndromes affecting sexual development present at an early age, which prompt evaluation by the pediatrician. The clinical manifestations include clitoromegaly, penile agenesis, bilateral or unilateral cryptorchidism, posterior labial fusion, and hypospadias. Obtaining a thorough family history of maternal virilization during gestation, prenatal exposure to androgens, infertility, miscarriages, or consanguinity is important in understanding the etiologic factors for definable causes of gender dysphoria.

The initial assessment of any patient should include a thorough clinical history, physical examination, determination of sex chromosomes, pelvic/abdominal ultrasonography, measurement of 17-hydroxyprogesterone, testosterone, gonadotropins, anti-Müllerian hormone, serum electrolytes, and urinalysis. According to the International Consensus Conference, disorders of sex development can be categorized as 46,XX or 46,XY or a mixed sex chromosome pattern (Table 15-1).

Hormonal Sex Reassignment

Initiation

As stated in the "World Professional Association for Transgender Health Standards of Care (WPATH SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People," transgender/transsexual patients need to fulfill eligibility and readiness criteria before proceeding with cross-sex hormone therapy. Patients undergoing sex reassignment therapy must understand the reversible and irreversible effects of cross-sex hormones. A comprehensive discussion of the patient's expectations should be done by the treating endocrinologist before the patient starts treatment.

The criteria suggested for transgender hormone therapy for transgender adults are as follows:

1. The treating physician should confirm that the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), or the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria for gender identity disorder or transsexualism are present.

2. The patient should have an understanding of what hormonal sex reassignment therapy can and cannot accomplish and the social benefits and risks.
3. There is an absence of psychiatric comorbidities that would interfere with the diagnostic workup or treatment.

4. Documented real-life experience should be undertaken for at least 3 months before the administration of hormones or a period of psychotherapy of a duration specified by the mental health professional after the initial evaluation (usually a minimum of 3 months).

After the eligibility criteria have been fulfilled, the readiness of the transgender patient for hormonal therapy should be evaluated. The WPATH SOC document three key elements:

1. The patient has had further consolidation of gender identity during the real-life experience or psychotherapy.
2. The patient has been evaluated for other mental health conditions (for example, sociopathy, substance abuse, psychosis, and suicidality).
3. Hormones are likely to be taken in a responsible manner.

As outlined by the 2009 Endocrine Society guidelines on endocrine treatment of transgender individuals, adverse mental health events can be prevented, if the transgender patient undergoing hormonal sex reassignment has a clear understanding of the mental and physical changes that will follow after hormonal therapy is initiated.

It is also essential for the caregiver to provide counseling with regard to the effects of cross-sex therapy on fertility and the available options to preserve fertility for the future. It has been our experience that patients, because of economic reasons or inaccessibility of proper endocrinologic consultation, frequently seek to obtain the hormones without physician supervision through various sources (for example, Internet purchasing). Although this is illegal in most locales, some patients find that this is the only way to obtain hormones. Unfortunately, the quality of the hormone preparations is questionable, and there is no monitoring of the patient for adverse events. We think that it is better for the patient to obtain the medications through a physician rather than without physician supervision, even if it means that not all the previous criteria are met.

**Hormone Therapy**

Transgender patients seek hormone therapy to achieve anatomic and psychological changes that will make them feel and appear more like members of their aspired-to-be gender. Using the same principle for hormone replacement therapy in the hypogonadal patient, the main objectives of hormonal therapy are to induce the development of secondary sex characteristics of the reassigned gender and to suppress the individual’s genetic sex characteristics by reducing and replacing endogenous hormones. Hormone treatment can be acceptably safe and provide improvement in the quality of life and mental well-being.

Areas that should be covered before the initiation of cross-sex hormone therapy by the treating endocrinologist are the risks and benefits of hormone therapy, the presence of comorbidities that can be exacerbated by hormonal treatment, and the relative contraindications to hormonal therapy (liver disease, diabetes, and metabolic syndrome). Smoking cessation is highly recommended to avoid an increased risk of cardiovascular disease and thromboembolism.
Table 15-1  Disorders of Sex Development

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiologic Factors</th>
<th>Suggested Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>46,XX</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Congenital Adrenal Hyperplasia</strong></td>
<td>Most common cause of female fetal virilization</td>
<td>Basal measurement of serum 17-hydroxyprogesterone, 11-deoxycortisol, DHEA, and 17-delta-5-hydroxypregnenolone Serum electrolytes ACTH stimulation test Genetic testing</td>
</tr>
<tr>
<td></td>
<td>Steroid biosynthetic is detected, leading to excessive or deficient production</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salt-wasting type causes hyponatremia with hyperkalemia and hypotension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk for adrenal crisis and its complications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21-alpha-hydroxylase (CYP21A2) deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11-beta-hydroxylase deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aldosterone synthase deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17-alpha-hydroxylase deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-beta-hydroxysteroid dehydrogenase deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipoid hyperplasia</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational Hyperandrogenism</strong></td>
<td>Exposure to maternal androgen or synthetic progestational agent</td>
<td>Pelvic ultrasound If a mass is identified, consider laparoscopic biopsy Maternal serum testosterone androstenedione Cell free fetal DNA to determine fetal sex; if male there is no concern for virilization</td>
</tr>
<tr>
<td></td>
<td>History of virilization of the mother during pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Luteoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Theca lutein cysts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placental aromatase deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exogenous progestin or androgen administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miscellaneous ovarian tumors cell tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sertoli-Leydig tumors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Krukenberg tumors (gastrointestinal cancer metastatic to ovaries)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polycystic ovary syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adrenal tumors</td>
<td></td>
</tr>
<tr>
<td><strong>Other Causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysgenetic testis or ovotestis; female or ambiguous; Mullerian structures can be present or not present</td>
<td>Pelvic ultrasound Peritonal karyotype FISH and SRY probe</td>
</tr>
<tr>
<td></td>
<td>SOX9 duplication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Müllerian structure abnormalities (Rokitansky-Mayer-Küster-Hauser syndrome)</td>
<td></td>
</tr>
<tr>
<td><strong>Ovotesticular Disorder of Sex Development</strong></td>
<td>Unusual condition characterized by histologically confirmed testicular and ovarian tissue; formerly known as true hermaphroditism</td>
<td>Pelvic ultrasound Peritonal karyotype FISH and SRY probe</td>
</tr>
<tr>
<td></td>
<td>SOX9 duplication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Müllerian structure abnormalities (Rokitansky-Mayer-Küster-Hauser syndrome)</td>
<td></td>
</tr>
</tbody>
</table>

ACTH, Adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; FISH, fluorescence in situ hybridization; SRY, sex-determining region Y protein.
### Disease | Etiologic Factors | Suggested Workup
--- | --- | ---
46,XY Uncommon Causes of Congenital Adrenal Hyperplasia | Star protein deficiency | Basal measurement of delta-5-pregnenolone after ACTH stimulation
| 3-beta-hydroxysteroid dehydrogenase deficiency | Basal measurement of ACTH (increase), corticosterone, 11-deoxy cortisol, and 18-hydroxy-deoxy cortisol | Cortisol, DHEA, androstenedione, testosterone, estradiol, 11-deoxy cortisol, and 17-alpha-hydroxy progesterone (reduced)
| 17-alpha-hydroxylase deficiency | 

**Swyer Syndrome or 46,XY Pure Gonadal Dysgenesis**

Phenotypically female with functional female genitalia and futile ovaries caused by lack of proper ovarian development; affected women do not undergo puberty given the lack of sex hormones

| SRY translocation (most common) | Pelvic ultrasound
| Mutations in NR5A, DHH, NR0B1, and DAX1 genes | Peripheral karyotype
| FISH and SRY probe |

**Testicular Regression Syndrome**

Female phenotype with atrophic Müllerian ducts

Irreparable damage to the testis at a critical stage in fetal development

Pelvic ultrasound

**Vanishing Testes Syndrome**

Phenotypically males with male genitalia, anorchia, and absent Müllerian ducts

Defeat of testicular function late in fetal life

Pelvic ultrasound
| Peripheral karyotype |
| FISH and SRY probe |

**Persistent Müllerian Duct Syndrome**

Phenotypically male with normal external genitalia, persistent Müllerian ducts, and variable cryptorchidism

Mutations in the AMH or AMHR2 gene

Pelvic ultrasound
| Serum levels of AMH |
| Sequence analysis of AMH or AMHR2 |

**Abnormal Androgen Synthesis/Androgen Insensitivity**

Phenotype of affected males usually consists of female-appearing external genitalia, blind vaginal pouch, and cryptorchidism

17-beta-hydroxysteroid dehydrogenase type 3 deficiency

5-alpha-reductase deficiency

LH receptor defects

Androgen insensitivity

AMHR2

Prenatal exposure to phenobarbital and phenytoin

ACTH, Adrenocorticotropic hormone; AMH, anti-Müllerian hormone; AMHR2, anti-Müllerian hormone receptor type 2; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; FISH, fluorescence in situ hybridization; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; SRY, sex-determining region Y protein; STAR, steroidogenic acute regulatory protein.
Most of the treatment recommendations are based on opinion and experience without large studies to support many of the recommendations. In an extensively researched consensus statement by committees and members of the Endocrine Society (United States), European Society of Endocrinology, European Society for Paediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society (United States), and the WPATH, the recommendations were based on "very low quality" or "low quality evidence" except in three instances. The need to confirm the diagnostic criteria of transsexualism, the medical conditions that can be exacerbated by cross-sex hormone therapy, and the effects on bone mineral density (BMD) were based on "moderate quality" evidence. Much of our knowledge regarding the use of cross-sex hormones is based on the supraphysiologic dosing of these hormones in same-sex individuals and extrapolated to the transgender community. This is obviously imperfect, and prospective studies are needed to make definitive recommendations.

### Female-to-Male Transgender Patients

The goal for female-to-male (FTM) transgender individuals is to induce virilization. To achieve this objective, there are different formulations and routes of administration of testosterone, including percutaneously administered gel, injectable intramuscular preparations, buccal tablets, and a nasal spray (Table 15-2). The main goal is to maintain a total serum testosterone level in the normal male range (350 to 1000 ng/dl).

There are several initiation protocols for androgen therapy, ranging from high doses of parenteral testosterone, with subsequent titration based on serum testosterone, or vice versa. Testosterone enanthate or cypionate can be delivered at doses of 100 to 200 mg every 2 weeks intramuscularly, or 1000 mg of testosterone undecanoate (not available in the United States) can be given every 12 weeks, with titration according to serum testosterone levels. After the desirable serum testosterone level is achieved, the patient can be switched to testosterone gel (25 to 50 mg/day).

Other protocols start with a lower dose of testosterone (for example, 100 mg of testosterone enanthate every 2 weeks) with subsequent adjustment. Therapy can also be initiated directly

### Table 15-2  Hormone Therapy Options for Female-to-Male Patients

<table>
<thead>
<tr>
<th>Hormone Therapy</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone enanthate or cypionate</td>
<td>100-200 mg IM every 2 wk or 50-100 mg IM weekly</td>
<td>Monitor levels midway between injections</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>1000 mg IM every 12 wk or 160-240 mg PO daily</td>
<td>Monitor levels midway between injections</td>
</tr>
<tr>
<td>Testosterone gel</td>
<td>2.5-10 mg daily</td>
<td>Higher incidence of breakthrough bleeding</td>
</tr>
<tr>
<td>Testosterone patch</td>
<td>2.5-7.5 mg daily</td>
<td>Patch can cause skin irritation</td>
</tr>
<tr>
<td>Testosterone nasal (Natesto)</td>
<td>5.5 mg per pump actuation; 1 pump actuation in each nostril TID</td>
<td>Monitor before next dose</td>
</tr>
</tbody>
</table>

Higher incidence of breakthrough bleeding

Patch can cause skin irritation

Monitor before next dose

Monitor levels midway between injections

Not available in the U.S.
with testosterone gel, although one caveat is that the virilization achieved with transdermal methods is slower, given the lower serum levels achieved with this route. On the other hand, the risk of having a supraphysiologic serum concentration of testosterone is less common with this approach, thus decreasing the theoretical risk of adverse reactions.

The physical changes induced by androgen therapy include male pattern hair growth, increased muscle mass, an increase in fat mass, clitoromegaly, increased libido, deepening of the voice, and cessation of menses. However, permanent cessation of menses may require high doses of testosterone, which is rarely achieved with testosterone gel. If breakthrough uterine bleeding continues, concomitant therapy with a progesterational agent may be needed, or endometrial ablation may be considered if hysterectomy is not desired. Recommended regimens include medroxyprogesterone acetate, 5 to 10 mg daily, or 17 alpha-ethinyl-3-desoxy-19-nortestosterone (Lynestrenol), 5 mg/day, which is not available in the United States. Other treatment options include depot medroxyprogesterone, 150 mg intramuscularly every 3 months, or a gonadotropin-releasing hormone (GnRH) agonist (for example, goserelin, 3.6 mg once every 4 weeks or 10.8 mg once every 12 weeks). The use of leuprolide and nafarelin has not been established for hormone reassignment therapy.

The estimated time for physical changes with testosterone therapy occurs in the first 3 to 6 months of treatment, although the maximum effect can take as long as 2 to 5 years for some patients8,11 (Table 15-3).

**Routine Follow-up: Recommended Clinical Practice**

The Endocrine Society recommends maintaining testosterone levels in the normal adult male range to prevent long-term side effects from therapy, such as erythrocytosis or transient elevation of liver enzymes. For this purpose, monitoring should be done every 3 months during the first years of therapy, and then once or twice a year thereafter8 (Table 15-4).
Monitoring of weight, blood pressure, and physical changes, and asking routine health questions regarding new risk factors focusing on cardiovascular risk and new medications should be done at each visit. In addition, periodic monitoring of CBC, renal function, liver enzymes, and lipid and glucose profiles is also recommended.

### Cardiovascular Risk

The metabolic effect of testosterone on the lipid profile is mainly on the increase of serum triglycerides and reduction of high-density lipoprotein levels with central fat redistribution for FTM patients. However, there is uncertainty regarding the degree of increase of cardiovascular risk with chronic testosterone use in FTM patients given the dearth of medical evidence in this matter. On the contrary, data from a meta-analysis of randomized clinical trials assessing the risks of adverse events associated with testosterone replacement in older men found no increased incidence of cardiovascular events in the treated group. Furthermore, data available from a university practice in The Netherlands with a median follow-up of 18½ years showed that for FTM transgender patients, total mortality and cause-specific mortality were not significantly different from those of the general population, and that for MTF transgender patients, the main increase in mortality was from non-hormone-related causes. Nevertheless, cardiovascular risk factors should be prevented and assessed according to available guidelines.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Frequency</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Baseline</td>
<td>Specifically assess family history of diabetes, osteopenia, smoking, and previous bone fractures</td>
</tr>
<tr>
<td>Physical examination (blood pressure, weight)</td>
<td>Baseline and every 2 to 3 mo in the first year and then yearly</td>
<td>Look for appropriate signs of masculinization and possible complications</td>
</tr>
<tr>
<td>Serum total testosterone</td>
<td>Every 2 to 3 mo until levels are between 350 and 1000 ng/dl</td>
<td>Adjust dose</td>
</tr>
<tr>
<td>Serum estradiol</td>
<td>Every 2 to 3 mo during first 6 mo or until cessation of menses</td>
<td>Usually serum estradiol &lt;50 pg/ml in first 3 mo</td>
</tr>
<tr>
<td>Liver function tests and CBC, lipid profile</td>
<td>Baseline; every 3 mo in the first year and then 1 to 2 times per year</td>
<td>Family history of diabetes should prompt A1c</td>
</tr>
<tr>
<td>BMD measurement</td>
<td>Baseline and at 60 yr of age Yearly</td>
<td>If risk factors are identified</td>
</tr>
<tr>
<td>Pap smear</td>
<td>Per American Cancer Society recommendations</td>
<td>If cervical tissue is present</td>
</tr>
<tr>
<td>Mammogram</td>
<td>Per American Cancer Society recommendations</td>
<td>If mastectomy is not performed</td>
</tr>
</tbody>
</table>
Based on the available evidence, there is no increased risk of developing venous thromboembolism during cross-sex hormone treatment in FTM transgender patients receiving androgen treatment.20

**Bone Health**

Sex steroid exposure has been found to influence bone metabolism.21-23 Prior studies in FTM transgender patients have shown that in the first 2 years of hormonal sex reassignment therapy, testosterone administration could prevent bone loss resulting from estrogen deficiency.24 Cortical bone is the most affected by androgen replacement therapy, showing higher BMD. During the first year of cross-sex hormonal therapy with testosterone, there is an increase in bone turnover markers.25

At the molecular level, testosterone can affect bone physiology in an indirect or direct fashion. The use of exogenous testosterone lowers the receptor activator of nuclear factor kappa B ligand (RANKL) levels but does not change osteoprotegerin levels, resulting in an increased osteoprotegerin/RANKL ratio, which may be beneficial to the bone by inhibiting osteoclastogenesis. Furthermore, aromatization of testosterone to estradiol affects the bone directly by increasing BMD.26 In addition, chronic testosterone exposure has an impact on body composition by increasing muscle and decreasing fat mass. Moreover, there is a direct effect on the adult skeleton,25 with larger bone and lower volumetric BMD at the radius and tibia, in FTM transgender patients when compared with age-matched females.

Overall, the available evidence shows preserved BMD in the transgender population. Thus an adequate level of serum testosterone (300 to 1000 ng/dl) must be maintained to preserve the beneficial effect of androgen therapy in the bones. For this purpose, luteinizing hormone can be used as a marker of adequate hormone dosing, of which the goal is to keep its level in the normal range. This recommendation is based on the inverse correlation between luteinizing hormone or follicle-stimulating hormone and BMD.27 Sufficient intake of vitamin D and calcium initiated and maintained as indicated in the standard guidelines for the general population is recommended.

**Cancer Screening**

The effects of lifelong administration of testosterone therapy on cancer remain to be determined; however, some evidence indicates that prolonged exposure to androgen can lead to increased endogenous estrogen levels mostly by partial aromatization of testosterone to estradiol, which triggers endometrial hyperplasia and possible estrogen receptor–positive breast cancer. However, a large cohort study of adverse events on a transgender population showed no increase in hormone-related cancers.28

**Ovarian Cancer**

The cases of ovarian cancer in FTM transgender patients have been reported.29,30 Immunohistochemical studies done in ovarian and endometrial tissue of FTM transgender patients receiving long-term treatment with testosterone therapy have shown an increase in androgen receptors, resembling those changes found in the ovarian tissue of patients with polycystic ovary syndrome,31 which may lead to androgen receptor–related ovarian
cancer. To prevent the risk of female reproductive tract diseases and cancer, the Endocrine Society recommends total hysterectomy and oophorectomy for FTM transgender patients receiving cross-sex hormone therapy. Although a seemingly prudent recommendation, this is based on very low evidence of support.8

Cervical Cancer
Currently there are no data regarding the prevalence of cervical cancer or cervical cancer screening among FTM transgender patients. Yet the American College of Obstetricians and Gynecologists recommends that an FTM transgender patient who has not undergone hysterectomy should follow the same screening guidelines as nontransgender females (American Society for Colposcopy and Cervical Pathology guidelines: www.ascp.org/guidelines).

In brief, the recommendations are as follows:
❖ Women younger than 21 years of age should not be screened, regardless of age at sexual initiation and other behavior-related risk factors.
❖ Women 21 to 29 years of age should have a Papanicolaou (Pap) test every 3 years.
❖ Women 30 to 65 years of age should have a Pap test and human papillomavirus test (co-testing) every 5 years (preferred); it is acceptable to have a Pap test alone every 3 years.

Breast Cancer
In one of largest studies in the transgender population, the estimated incidence of breast cancer in FTM transgender patients was significantly lower than in biologic women (5.9 per 100,000 person-years versus 15.4 per 100,000 person-years for biologic women).32 Today there are eight cases of breast cancer in the FTM transgender population published in the literature.32,33 These low incidence seems to be related to the high prevalence of mastectomy and testosterone therapy in the FTM transgender population. This estimation was based on a relatively small number of cases of breast cancer, and thus there should be cautious interpretation of these data.

The breast tissue of FTM transgender patients receiving long-term treatment with androgen therapy shows decreased glandular and increased fibrotic tissue. Based on the premise that exogenous testosterone is partially aromatized to estradiol and that the endogenous levels of estradiol do not decrease significantly in a treated FTM transgender patient, it is reasonable to link testosterone therapy with increased risk of breast cancer, especially in those patients who have not undergone total mastectomy. Conversely, breast cancer may develop in residual tissue after mastectomy. As a prevented intervention, a breast examination should be performed before initiation of cross-sex hormone therapy, with further assessment of family history for breast cancer. The Endocrine Society guidelines recommend following the same breast cancer screening guidelines for the general population.8,34

Male-to-Female Transgender Patients
Treatment Protocols
The hormone treatment needed to achieve phenotypic feminization of MTF transgender patients has two major components. The first is to decrease the virilization effect of endogenous testosterone with the use of antiandrogen agents, and the second is to promote feminization with estrogens. The main goal of using gestational agents (cyproterone acetate, not available in the United States), GnRH analogs (leuprolide, nafarelin, or histrelin), and
other medications that suppress androgen action is to obtain a reduction in serum testosterone levels similar to the ones found in adult women (less than 55 ng/dl).

GnRH agonists are mostly used in adolescent patients in Europe. Testosterone secretion is suppressed by inhibiting the release of gonadotropins; this mirrors the effects achieved by bilateral gonadectomy, which reduces testosterone to minimal levels. The downside of these medications is the high cost, and that it is not covered by health insurance in the United States. A second, much less expensive drug, spironolactone, which inhibits testosterone secretion and androgen effects by inhibiting its binding to the androgen receptor, can be used. In addition, it has some weak estrogenic activity (Table 15-5). After orchiectomy is performed, antiandrogen therapy is no longer recommended or needed. Estrogen is available in oral, transdermal, and parenteral formulations as conjugated estrogens, 17 beta-estradiol, and estrogen ester.

Testosterone production is diminished by estrogen treatment by suppressing gonadotropin output; however, it is more effective when used in addition to other antiandrogen treatments. In general, estrogen should be used in conjunction with antiandrogen agents, especially in patients who have not undergone orchiectomy, because otherwise the doses needed to suppress testosterone levels to the minimal range and to maximize feminization will be four to eight times greater than in a biologic woman, increasing the risk for adverse events, namely, thromboembolic events. The Endocrine Society guidelines recommend keeping serum estradiol at the mean level for premenopausal woman (less than 200 pg/ml) and testosterone level lower than 55 ng/dl. These levels should be measured every 3 months after cross-hormonal therapy has been initiated.

### Table 15-5 Hormone Therapy Options for Female-to-Male Patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral estradiol</td>
<td>2-8 mg/dl</td>
<td>Metabolized via the cytochrome P450 enzyme system; thus a potential drug-drug interaction can exist</td>
</tr>
<tr>
<td>Transdermal patch</td>
<td>0.1-0.4 mg twice weekly</td>
<td>Transdermal estradiol produces fewer changes in hemostatic variables</td>
</tr>
<tr>
<td>Parenteral estradiol</td>
<td>5-30 mg IM every 2 wk</td>
<td>Transdermal estradiol produces fewer changes in hemostatic variables</td>
</tr>
<tr>
<td><strong>Antiandrogen Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>20-60 mg PO daily</td>
<td>Progesterone affects lipid profile and BMD</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>100-200 mg PO daily</td>
<td>Use off-label</td>
</tr>
<tr>
<td>GnRH agonist (leuprolide)</td>
<td>3.75-7.5 mg IM monthly</td>
<td></td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>50-100 mg PO daily</td>
<td>Not available in the U.S.</td>
</tr>
<tr>
<td>Finasteride</td>
<td>1 mg PO daily</td>
<td></td>
</tr>
</tbody>
</table>
A serum estradiol level is a good marker to monitor cross-sex hormone therapy in MTF patients who receive estradiol or its ester in the transdermal, oral, or parenteral form. The exceptions to the rule are conjugated or synthetic estrogens (ethinyl estradiol), whose levels are not detectable by a blood test. Ethinyl estradiol should be avoided, given the association with significant increased risk of venous thromboembolic disease and death from cardiovascular events.35

A treatment protocol used in the United States includes spironolactone, 100 to 200 mg/day, plus transdermal 17 beta-estradiol, 100 to 400 μg twice a week, or in oral form in a dose of 2 to 6 mg/day. In Europe cyproterone acetate, 100 mg/day, plus oral 17 beta-estradiol valerate, 2 to 4 mg daily, is the most common cross-sex hormone therapy used.

Physical Changes

The feminization effect of estrogen and antiandrogen therapy includes decreased facial and body hair, redistribution of fat mass, decreased oiliness of the skin, decreased libido, cessation of morning erections, and breast tissue growth. Physical changes start in about 3 to 6 months but can take up to 2 to 3 years to have its full effect8,12,36,37 (Table 15-6).

Breast development is one of the most important feminization features desired by MTF transgender patients. The increase in breast size usually begins within 2 to 3 months after the start of cross-sex hormone treatment and progresses over 2 years with the development of an A cup, which corresponds to Tanner stages 2 and 3 in most MTF transgender
patients. This may explain the high percentage (60% to 70%) of MTF subjects pursuing surgical augmentation. The available evidence suggests no association between the type or dosage of estrogen therapy, including a protocol with progestational properties, on final breast size.\textsuperscript{37} At the initiation of hormone therapy, it is essential that MTF transgender patients have realistic expectations regarding the physical changes that will follow cross-sex hormone therapies, especially on breast development. Testicular and prostate gland atrophy will occur over a long period (about 3 years) on hormonal sex reassignment therapy.

**Table 15-7  Monitoring Male-to-Female Transgender Patients Receiving Hormone Therapy**

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Frequency</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Baseline</td>
<td>Specifically assess family history of diabetes, osteopenia, smoking, previous bone fractures, and breast, colon, and prostate cancer</td>
</tr>
<tr>
<td>Physical examination (blood pressure, weight, genital examination)</td>
<td>Baseline and every 2-3 mo in the first year, then yearly</td>
<td>Look for appropriate signs of feminization and possible complications</td>
</tr>
<tr>
<td>Serum total testosterone</td>
<td>Baseline and every 2-3 mo until levels are &lt;55 ng/dl</td>
<td>Within normal female range</td>
</tr>
<tr>
<td>Serum estradiol</td>
<td>Baseline and every 2-3 mo during first 6 mo and then every 6 mo</td>
<td>Adjust dose of estrogen preparation so that serum levels are not greater than 100-200 pg/ml</td>
</tr>
<tr>
<td>Serum electrolytes</td>
<td>Every 2-3 mo in first year and then 1 to 2 times per year</td>
<td>Only if taking spironolactone</td>
</tr>
<tr>
<td>BMD measurement</td>
<td>Baseline and at 60 yr of age</td>
<td>If risk factors identified</td>
</tr>
<tr>
<td>Serum prolactin</td>
<td>Baseline; yearly during transition period, then biannually thereafter</td>
<td>To monitor lactotroph hyperplasia</td>
</tr>
<tr>
<td>Routine cancer screening</td>
<td>Per American Cancer Society recommendations</td>
<td>Colon, breast, and prostate</td>
</tr>
</tbody>
</table>

Routine Follow-up: Recommended Clinical Practice

The Endocrine Society guidelines recommend maintaining estradiol and testosterone levels in the mean values found in premenopausal woman (less than 200 pg/ml of estradiol and less than 55 ng/dl of testosterone), avoiding supraphysiologic doses and levels of estradiol to prevent increased risk of liver dysfunction, the development of hypertension, and of critical importance, thromboembolic events. For this purpose, monitoring should be done every 3 months during the first years of therapy and then once or twice a year thereafter (Table 15-7).

As in FTM transgender patients, weight, blood pressure, physical changes, routine health questions, new risk factors focusing on cardiovascular risk, and new medications should be assessed during routine visits, including periodic monitoring of CBC, renal function, liver enzymes, lipids, glucose, and electrolytes, especially in patients receiving spironolactone. In
addition, patients receiving estrogens, gonadotropin suppression, or antiandrogen therapy should have a prolactin level check before and during cross-hormone therapy, given the stimulatory effect of estrogen on pituitary lactotrophs. However, the risk of an estrogen-induced prolactinoma in MTF transgender patients seems low based on available evidence. If elevation of prolactin develops, estrogen therapy can be reduced or discontinued.

**Cardiovascular Risk**

Cross-hormonal therapy is well tolerated and has been associated with few side effects. However, the MTF transgender population has more cardiovascular pathology than FTM transgender subjects receiving androgen therapy. Despite favorable changes seen in the lipid profile of MTF transgender patients taking estrogen and antiandrogen therapy, such as an increase in high-density lipoprotein cholesterol and a decrease in low-density lipoprotein cholesterol levels, there is no reduction of cardiovascular events in this particular population. Moreover, there is an increase in triglycerides, blood pressure, subcutaneous fat, and visceral fat, which are features of metabolic syndrome.

There is a strong association between the use of ethinyl estradiol and cardiovascular events. In an MTF transgender population between the ages of 40 and 65 years, a threefold increase in cardiovascular mortality was found in those patients who had taken ethinyl estradiol or oral contraceptives compared with those who used another type of estrogens; the adverse effect was confirmed only for patients actively taking ethinyl estradiol. However, during the past 40 years, there has been a decrease in the prevalence and incidence of thromboembolic disease, probably because of the use of transdermal estradiol and other forms of estrogen preparation (transdermal patches or gel, oral estradiol, or conjugated equine estrogens). Therefore preexisting cardiovascular risks should be taken into consideration when deciding on the type and route of administration for estrogens and antiandrogenic therapy, with special emphasis on avoiding the use of ethinyl estradiol.

**Bone Health**

Available evidence suggests that estrogens are a major regulator of bone turnover in both men and women and that serum estradiol levels in elderly men have a positive correlation with BMD.

In the MTF transgender population, the use of estrogen therapy decreased bone turnover markers and preserved and increased BMD at the level of the femoral neck and lumbar spine after 12 and 24 months of continued use of cross-sex hormone therapy. However, the effect was no longer observed after a longer follow-up period (32 to 63 months).

During treatment with antiandrogen therapy, MTF transgender patients experience a state of hypogonadism, which constitutes a substantial risk factor for bone loss. However, the concomitant use of estrogen seems to be able to maintain bone mass in the male skeleton in the absence of testosterone. Therefore, to preserve the beneficial effect of estrogen, cross-hormonal therapy should be continued, even after gender affirmation surgery. As outlined by the Endocrine Society, BMD measurements should be taken if there are risk factors for...
osteoporosis (for example, previous fractures, family history, glucocorticoid use, and prolonged hypogonadism) at 60 years of age in patients with a low risk for osteoporosis or in those who are noncompliant with hormone therapy.

**Cancer Screening**

The incidence of hormone-related cancers is not higher in the MTF transgender population in short- and medium-term follow-up studies. Yet the duration of exposure to cross-sex hormones may influence susceptibility to certain cancers, although there are insufficient data.

**Breast Cancer**

In a biologic man, the incidence of breast cancer is approximately 1 in 100,000. The peak incidence occurs at 68 to 71 years of age, representing a much older population when compared with the peak age of breast cancer in women. The epidemiology of breast cancer in the MTF transgender population resembles the pattern seen in men, with only 11 cases reported in the literature, and in those, 3 were likely not related to estrogen use.

Studies such as the Women’s Health Initiative have suggested that estrogen therapy does not increase the risk of breast cancer in the short-term. However, one concern regarding long-term estrogen treatment is the induction of carcinomas of estrogen-sensitive tissues, such as the breast.

The usefulness of screening mammography is still to be determined. The Endocrine Society recommends that MTF transgender individuals who have increased risk factors for breast cancer follow the screening guidelines as recommended for biologic women.

**Prostate Cancer**

The incidence of prostate cancer in transgender patients is rare, with only six cases reported in the literature. Commonly, prostate cancer expresses androgen receptors; however, after testosterone depletion, as in the case of MTF transgender patients, androgen receptor levels are increased, which may suggest a greater sensitivity to androgens.

The long-term effects of estrogen in the prostate are unknown. Estrogen therapy does not induce hypertrophy or premalignant changes in the prostate, and castration early in life protects against prostate cancer. The same principle could be applied to MTF transgender individuals who undergo antiandrogen therapy or orchiectomy at a young age.

MTF gender reassignment surgery generally does not include prostatectomy, and therefore the risks and benefits of prostate cancer screening should be discussed with MTF transgender patients, as is done in biologic men, especially for those with risk factors for prostate cancer and in those who started cross-hormone therapy later in life. After the patient agrees to screening, rectal or transvaginal (neovaginal) examination of the prostate should be performed. The use of prostate-specific antigen levels as a screening tool is not straightforward, given that it could be falsely low in the presence of prolonged exposure to estrogen. In the MTF population, 1 ng/ml should be used as the upper limit of normal and not 4 ng/ml as is used in biologic men. However, the rate of increase in prostate-specific antigen is a significant predictor of malignancy in both XY men and MTF transgender individuals.
Special Topics in Hormone Replacement Therapy

Hormone Therapy Before Sex Reassignment Surgery

Surgical sex reassignment is viewed as the final step to provide relief from the dichotomy between the body habitus and gender identity, and thus a careful preoperative evaluation of the transgender patient should be done in line with available guidelines. Preoperative management should take into consideration that MTF patients receiving estrogen treatment can be predisposed to venous thrombosis, leading to serious complications, such as pulmonary embolism, chronic venous insufficiency with edema, or chronic leg ulcers. In addition, this treatment also carries a risk of serious bleeding. Fortunately, there are no reports of venous thrombosis in FTM patients receiving testosterone treatment. Without any data or evidence to the contrary, it is recommended that cross-sex hormonal therapy should be discontinued 2 weeks before sex reassignment surgery or other elective surgery.

Hormonal Therapy After Sex Reassignment Surgery

Hormonal therapy should be restarted after sex reassignment surgery to guarantee a patient’s general well-being and to prevent the consequences of sex steroid deficiency, such as osteoporosis, although in MTF transgender patients, the dose of antiandrogen agent can be reduced by more than half or even discontinued after oophorectomy. After surgery the risk of venous thromboembolism decreases slowly over 2 weeks. In the absence of data, it seems prudent to recommend that hormonal treatment should be delayed 3 to 4 weeks after surgery, or at least until full mobilization has been achieved.

Aging Transgender Population and Hormonal Sex Reassignment Therapy

Information regarding the management of hormones in the aging transgender population is very limited. A recent publication by Gooren and Lips addressed several important questions, such as the age at which cross-sex hormone therapy should be discontinued and whether transgender persons older than 50 to 60 years of age should be accepted for cross-sex hormone treatment. Rather than providing a cutoff age, a summary of goals was concluded based on the available evidence of the hormonal effects on the transgender and cisgender population: (1) The dose of hormonal therapy should be adjusted in the aging transgender population to maintain the sex characteristics of the new sex, and (2) blood levels of sex hormones should be kept within the normal range to preserve BMD in both sexes. With aging there is a known increased risk for malignancies and cardiovascular mortality, and thus there should be a discussion of the risks with the transgender individual who has decided to continue lifelong cross-sex hormone therapy.

Although there may be an increase in the side effects of cross-sex hormone therapy in elderly patients, there is no strong evidence to suggest that it is harmful. Many transgender individuals are unwilling to surrender the sexual characteristics of the new sex achieved with hormone therapy, even after aging.

Reproduction in the Transgender Population

The WPATH SOC and the clinical practice guidelines of the Endocrine Society state that transgender individuals should be encouraged to consider their fertility options before
starting cross-sex hormone treatment. Therefore transgender patients should be referred to a reproductive specialist, with whom a detailed exploration of the available options is discussed, preferably before initiation of hormone therapy.

Cross-sex hormone therapy has some irreversible actions on the reproductive male apparatus, with a direct effect on spermatogenesis and sperm motility and density, leading to hypospermatogenesis, azoospermia, and atrophy of the testes. Cryopreservation of sperm or preservation of testicular tissue are alternatives to preserved fertility in MTF transgender patients, although it should be done before initiation of feminization hormones. Preserved gametes can be used for insemination of a female partner, in vitro fertilization, or intracytoplasmatic sperm injections. In 2014 the first live birth after uterus transplantation in a biologic woman was reported, which opens the window for possible use of this technology in the MFT population. However, it seems impossible for MTF transgender patients to become pregnant.

For the FTM population, the possibilities of pregnancy are wider, because testosterone therapy does not deplete primordial follicles or affect its capacity for development. Also, because some FTM transgender patients retain the ovaries and uterus, this makes pregnancy more feasible. However, androgen therapy can affect reproductive capacity, as seen in patients with hyperandrogenism, such as in polycystic ovary syndrome. There are several reports of FTM transgender individuals who have had successful pregnancies after temporary discontinuation of androgen therapy. Currently there are no available published guidelines.

Conclusion

The main goal of hormone therapy in the transgender population is to provide a safe and effective hormonal regimen that will result in the development of the physical characteristics of the desired gender. The caregiver should maintain hormone levels close to the physiological range and minimize the potential long-term risk of these regimens. Unfortunately, more work is needed in prospective studies to evaluate these hormone therapies and their long-term effects. Careful monitoring by the endocrinologist within a multidisciplinary team approach will provide the best outcome for the patient.

References
