

Gender Affirming Hormone Therapy for Transgender Females

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Abstract: The provision of hormone therapy, both estrogens and antiandrogens, to adult transgender females is well within the scope of practice of the obstetrician gynecologist. The goal is to induce feminizing changes and suppress previously developed masculinization. Estrogens in sufficient doses will usually achieve both goals with augmentation by antiandrogens. The primary short-term risk of estrogens is thrombosis, but long-term risk in transgender females is unclear. Optimal care requires pretreatment education and assessment, individualized dosing, ongoing routine monitoring, and standard breast and prostate cancer screening.

Key words: transgender females, gender affirming, estrogen, antiandrogens, androgen blockers, hormone therapy

Introduction

Gender affirming hormone therapy for transgender females is well within the scope of practice for the general obstetrician gynecologist with some modest expansion of the knowledge base required to prescribe reproductive hormones and manage reproductive concerns. As the

demand for gender affirming hormone therapy increases and the necessity of appropriate monitoring of this lifelong regimen both expand the requirement for knowledgeable health care providers to provide such care, it is imperative that primary care providers, including obstetrician gynecologists, become comfortable with and incorporate such care into their practices. This section will discuss the evaluation, initiation, and long-term management of such therapy in an attempt to serve as a guide to assist women's health care providers to expand their practices to incorporate the care of adult transwomen. Of note, the assessment, particularly familial and psychosocial, of children expressing gender nonconformity and the management of adolescents maintaining gender dysphoria are beyond the scope of this discussion.

Goals

The goals of gender affirming hormone therapy are fundamentally simple in adult transwomen but frustratingly limited in execution.¹ Adult transgender females have undergone a full pubertal development to

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an adult body incongruent with their identity, so the physical goals are twofold and simultaneous: First, to regress as much of adult male sexual development as can be accomplished while, second, inducing as much of adult female sexual development as possible, both without incurring unacceptable long-term risk. The ultimate result is a combination of hormonally induced changes superimposed on that individual's genetic capacity for development such as breast size and body contour.

Long-term safety of a lifelong medication is an equally important goal, mandating that appropriate risk assessment and risk reduction are of paramount importance. However, it is critical to recognize that many, if not most, transgender women do not consider gender affirming hormone therapy as elective, but as a necessity for achieving a body in concert with their identity. This occasional conflict between "necessary" therapy and risk can be a management challenge that may require input from an appropriate health care team (Table 1).

Estrogens

BIOLOGY

Estrogens can be considered as any molecules that can bind to either or both of the two human estrogen receptors, ER α and ER β , and induce a response.² Classically, endogenous human estrogens are 18 carbon steroids with varying binding affinities and potencies produced primarily by the ovaries and placenta that have widespread effects. There are many natural and man-made

compounds, both steroidal and nonsteroidal, that have the capacity to bind to estrogen receptors and function both as agonists and/or antagonists, frequently in different tissues at the same time. These are known as selective estrogen receptor modulators, or SERMs, of which human natural estrogens are a specific subset.

Estrogens as a class are hydrophobic steroids that do not readily cross the gut and did not go into solution in blood, therefore require carrier proteins to transport them from their source to target tissues. This is of particular importance in deciding both which estrogens to prescribe and the route of administration. In general, 17 β estradiol will cross mucous membranes and skin more readily than across gut mucosa so absorption is more efficient across such interfaces than through the gastrointestinal tract and prescribed doses can be lower. Estrogens can be conjugated to other molecules to improve absorption across the gut, and to lengthen the half-life as in depot estrogen intramuscular injections. Once estrogens reach target cells, they readily cross the cell membrane, bind to the cytoplasmic estrogen receptors and are translocated to the nucleus to induce multiple effects.

Estrogen receptors are found in most tissues in humans such that estrogens have widespread effects on multiple systems. With the onset of puberty and the undulating increase in estrogen secretion by the ovaries, skeletal growth is accelerated, particularly in long bones, subcutaneous fat increases, particularly in the hips and thighs, and mammary ducts begin to grow leading to breast development. The Mullerian system matures with the eventual onset of endometrial proliferation and bleeding. The hypothalamic-pituitary-ovarian axis matures with the evolution of cyclic follicular growth and ovulation requiring both positive and negative feedback by estrogens on the central nervous system. Pubertal changes require 3 to 5 years before stabilization

TABLE 1. *Goals of Hormone Therapy in Transwomen*

Induce female secondary changes
Suppress male secondary changes as much as possible
Optimize safety

and are accompanied by significant maturation and psychosocial development.

Long-term estrogen exposure appears to be associated with the location and amount of both subcutaneous and visceral fat, as well as slowing of intra-arterial plaque formation. Estrogens can maintain neuronal dendritic density but studies are conflicting regarding long-term maintenance of cognitive function. Estrogens slow bone turnover with an associated reduced risk of osteoporosis and fractures.

OPTIONS

There are multiple therapeutic options for estrogen administration. There is a large and varied body of knowledge regarding the use of exogenous estrogens, both in the treatment of menopausal symptoms³ and in combined hormonal contraceptives.⁴ Both of these uses are familiar to the generalist obstetrician gynecologist, so the extension of that familiarity into gender affirming hormone therapy is quite manageable. In general, estrogen treatment for transwoman has tended to more closely align with menopausal hormone therapy, with some notable differences in dosing.

TYPES

The types of estrogens utilized for gender affirming hormone therapy in the United States tend to fall into 2 broad categories: The naturally occurring human estrogens and nonhuman derived estrogens.² The naturally occurring human estrogens include 17 β estradiol (E2), estrone (E1), and estriol (E3). Nonhuman derived estrogens include conjugated equine estrogens derived from pregnant mare's urine and esterified estrogens derived from plant sources.

The human estrogens 17 β estradiol and estrone occur in a natural bidirectional equilibrium and are produced primarily in ovaries and from peripheral conversion from androgens in fat and muscle.² Both can bind to both estrogen

receptors, but E2 is much more potent than E1 and, therefore, much more commonly used in gender affirming therapy. Estriol is primarily produced during pregnancy and is very much less potent than estradiol, so is not typically used in Transwomen. Estradiol can be conjugated to increase its oral availability and half-life, most commonly to ethinyl estradiol as is used in most combined hormonal contraceptives and some menopausal therapies.

Conjugated equine estrogens (CEE) include estrone as well as a number of estrogens produced by horses but not humans, effectively a mixture of selective estrogen receptor modulators.² There is extensive clinical experience with CEE in treating menopausal symptoms and in other hypoestrogenic states. The largest clinical trial of estrogen therapy, the Women's Health Initiative (WHI), utilized CEE either alone in women without a uterus or in combination with medroxyprogesterone acetate in women with a uterus.^{5,6} Much of the current thinking regarding the short and long-term risks of estrogen use originated or has been extrapolated from the WHI. Esterified estrogens (EE) are a plant derived oral generic alternative to CEE containing primarily estrone and equilin.

ROUTES

17 β estradiol can be administered to humans through multiple routes including oral, across buccal, vaginal, or rectal mucous membranes, transdermally, transnasally, or through intramuscular or subcutaneous injections. This versatility has contributed to its primary use for gender affirming hormone therapy in addition to its potency. Oral E2 must be micronized to improve its absorption across the GI tract, and occasionally may not be absorbed well because of problems with breakdown of incipients in some patients. Micronized E2 can also be administered across mucous membranes, most commonly sublingually,

with markedly improved absorption such that doses can usually be cut in half. The same tablets formulated for oral administration can be used sublingually and are generally quite well tolerated.

Transdermal estradiol has been well studied in patch form,⁷ with multiple dosing options available. However, most transwomen require substantially higher doses than those the patches formulated for menopausal therapy provide and require the use of several patches simultaneously to achieve appropriate serum levels. Transdermal estradiol also comes in spray, cream, lotion and gel forms, and can be readily compounded.

DOSES

The dose of estrogen utilized in gender affirming hormone therapy is determined by the dual role required to induce the desired physical changes as well as to suppress the endogenous secretion of androgens.⁸⁻¹⁰ In general, doses are substantially higher than those sufficient to treat menopausal symptoms, depending greatly on the estrogen used and the route of administration. Oral micronized E2 frequently is administered in doses of 6 to 10 mg daily to fully suppress T to the normal female range and to optimize breast ductal development. Sublingual E2 may require doses of 2 to 4 mg daily to achieve the same results, whereas transdermal E2 patch therapy can require the use of up to four 0.1 mg patches used simultaneously (Table 2).

RISKS

The risks of gender affirming hormone therapy are largely extrapolated from extensive clinical trial and clinical data of the risks of combined hormonal contraception and menopausal hormone therapy.³⁻⁶ As such, there are obvious limitations to such extrapolations in that the doses, associated hormones and duration of therapy in transwomen are usually quite different. Moreover, specific

TABLE 2. *Available Estrogens and Routes of Administration*

Estrogen	Route of Administration	Doses
17 β Estradiol	Oral	2-10 mg daily
	Sublingual	1-5 mg daily
	Transdermal patch	0.1-0.4 mg daily
	Transdermal gel, cream, lotion, or spray	Unknown
Conjugated equine estrogens	Oral	1.25-7.5 mg daily
	Intravenous, topical cream	Unknown
Esterified estrogens	Oral	1.25-7.5 mg daily
Estradiol valerate, estradiol cypionate	Intramuscular, subcutaneous	2-10 mg weekly

data in transwomen are quite limited. In addition, transwomen requesting gender affirming hormone therapy may not consider it an elective option but rather a medical necessity to achieve the physical status with which they identify. Therefore, it is imperative that providers supply the best estimate of both short and long-term risks of estrogen use to transwomen with the honest admission of limited data and a sincere attempt to find ways to administer estrogen even in transwomen with significant risk factors.

SHORT TERM

The most concerning immediate risk of estrogen therapy is the well-documented increase in venous thromboembolic events (VTE) with associated increases in heart attacks, strokes, and pulmonary emboli as well as cardiovascular mortality.^{3,5-7} The WHI estrogen-progestin trial reported an overall doubling of the risk of all venous thrombotic events, although the increase in

actual events was only 0.18%, whereas the estrogen only trial noted a 33% increase in such events with an actual increase in incidence of 0.07%.

The thromboembolic risks of estrogen may be primarily related to the route of administration. Orally administered E2 and CEE induce a “first pass” effect in the liver with an increase in prothrombotic factors.² Nonoral administration, primarily through transdermal patches, has been shown to not increase VTEs compared with a control population in the Million Women’s Study.⁷ Other forms of nonoral administration are less well studied, including sublingual and injectable, but presumably would be closer to transdermal or transvaginal administration in risk than oral preparations.

Studies of VTE risk in transwomen taking estrogen are limited. A recent electronic medical record review of 2842 transwomen at 3 Kaiser Permanente sites noted a 4.1-fold and 3.4-fold increased risk of VTE compared to cisgender men and cisgender women, respectively, at 2 years of therapy that increased to 16.7 and 13.7 fold increased risk at 8 years.¹¹ Ischemic stroke showed similar results, but acute myocardial infarction did not. The majority of transwomen took oral estradiol.

A significant increase in VTEs was noted in a cohort taking ethinyl estradiol (EE) with a decrease in risk when the EE was discontinued.¹² A large, multinational review reported a VTE rate of <1%.¹³ Other short-term risks are much less common than VTE but include hypertriglyceridemia,¹⁴ induction of prolactinoma growth,¹⁵ hypertension,¹⁶ and cholelithiasis.¹⁷

LONG TERM

Long-term risks of estrogen therapy in transwoman are frustratingly undocumented, in large part because no true long-term studies have been published. In a study describing cumulative experience over 32 years in 2236 transwomen and

876 transmen,¹⁰ no increase in mortality, including cardiovascular mortality, was noted. Few hormone-related cancers were observed, but a significant increase in VTE risk with oral ethinyl estradiol prompted discontinuation of that formulation with no subsequent observed increased risk with other estrogen preparations.

Perhaps the most concerning suspected long-term risk is an increase in breast cancer in transwomen. No data currently exist regarding such risk. The WHI noted a demonstrable increased risk in breast cancer incidence in postmenopausal women following 5½ years use of CEE with medroxyprogesterone acetate, but an overall decrease in the incidence of breast cancer in women taking CEE alone.¹⁸ These effects were independent of body mass index, and the estrogen only affect may be greater in Black women.

BY TYPE

The type of estrogen used for affirming hormone therapy seems to be a significant variable in VTE risk. Several studies suggest that CEE, more traditionally used in the United States, are more thrombogenic than 17 β estradiol, more traditionally used in Europe. Whether this has been a major contributor to the overall popularity of E2 for affirming hormone therapy is unclear.

BY DOSE

The risks of gender affirming estrogen therapy in transwomen by dose have been very under studied. Studies of dose effect in menopausal women are conflicting but suggest modest, if any, differences.⁷ However, the doses typically used in transwomen are substantially higher and may confer additional, albeit unquantified and unsubstantiated, risks.

BY ROUTE

Route of administration is a major determinant of VTE risk with estrogen therapy. Several studies have demonstrated no increased thromboembolic risk

**TABLE 3. *Risks of Estrogen Therapy
in Transwomen***

Risk of Adverse Outcome	Level of Risk	Level of Certainty
Venous thromboembolic disease	High	High
Hypertriglyceridemia	Moderate	Moderate
Cholelithiasis	Moderate	Moderate
Coronary artery disease	Moderate	Modest
Cerebrovascular disease	Moderate	Modest
Macroprolactinoma	Low	Modest
Breast cancer	Uncertain	Low
Prostate cancer	Uncertain	Low

with transdermal patches⁷ or transvaginal¹⁹ therapy when compared with oral therapy or no therapy. Vaginal estrogen also showed no increase in stroke, invasive breast cancer, or colorectal cancer, and a decrease in the risks of CHD, fracture, and all-cause mortality.¹⁹ Data for sublingual, intramuscular or subcutaneous, or other topical routes of administration are lacking, but extrapolation of risk assessment from existing transdermal or transvaginal administration suggest lower risk than oral therapy (Table 3).

Antiandrogens/Androgen Suppressors

Most regimens for gender affirming hormone therapy in transwoman include at least one secondary medication to directly suppress androgen production and/or to counteract the effects of circulating androgens, most particularly testosterone (T). Suppression of terminal hair growth in hair follicles containing androgen receptors, especially in sexually dimorphic areas such as the chin, cheeks, sternum, upper abdomen, and upper back, requires reduction of serum testosterone levels to the normal female range as very modest increases above that range can induce growth.² Doses of estrogen sufficient to induce feminization may be inadequate for full androgen suppression, and may

require an antiandrogen to achieve a satisfactory clinical outcome.

Antiandrogens can be classified into those that suppress androgen production, those that suppress conversion of testosterone to its potent metabolite, dihydrotestosterone (DHT), and those that prevent signaling through the androgen receptor. Although clinical information regarding their relative efficacy and side effects varies significantly, often practical considerations such as cost and route of administration dictate the choice of antiandrogen in any specific regimen.

SPIRONOLACTONE

Spironolactone is the most widely prescribed and studied of the antiandrogens utilized in gender affirming hormone therapy.^{1,20} Unique among the antiandrogens, it is in the class of potassium sparing diuretics through its antimineralocorticoid action. However, it cross-reacts with many other steroid hormone receptors such that it functions as a predominant antagonist of the androgen receptor, a selective estrogen receptor modulator of the estrogen receptors, a weak agonist of the progesterone receptor, and an antagonist of the glucocorticoid receptor. It also directly inhibits the production of androgens and is a modest inhibitor of 5 α reductase (5 α R), the enzyme that converts T to DHT.

Initially marketed in 1959, spironolactone is primarily used for hypertension, heart failure, and to treat hirsutism in addition to gender affirming hormone therapy. Because of its potassium sparing effects by decreasing sodium reabsorption in the collecting ducts of the kidney, it can cause hyperkalemia and is contraindicated in patients with renal or hepatic disease, or cardiovascular disease susceptible to arrhythmias. Hyperkalemia can be a significant concern in older transwomen, but young patients with normal renal function infrequently note any adverse effects.

Doses up to 200 mg daily, in divided doses, are typically necessary to achieve effective antiandrogenic results. Higher doses are occasionally required to achieve full T suppression but are more likely to induce electrolyte abnormalities or light headedness. Lower doses may be utilized in older patients, or doses can be titrated up dependent on tolerance. Generic spironolactone is readily available and generally inexpensive, contributing to its widespread use by transwomen who frequently have had significant financial constraints.

5 α Reductase Inhibitors

The 5 α reductase inhibitors (5ARIs) finasteride and dutasteride suppress the conversion of circulating testosterone to dihydrotestosterone (DHT), a reaction that occurs in the target tissues, primarily hair follicles and external genitalia.²¹ DHT is about 10-fold more potent in androgenic activity than testosterone at the androgen receptor and the primary inducer of terminal hair growth and sebum production in hair follicles. The primary indicators for this class of medications are androgenic alopecia, benign prostatic hypertrophy, and prostate cancer adjuvant therapy. Most of the reported side effects with 5ARIs, including gynecomastia and erectile dysfunction, are welcome changes in transwoman and not considered a concern.

Finasteride can be administered orally in doses of 1 mg daily as for androgenic alopecia or 5 mg daily as for benign prostatic hyperplasia. Efficacy by dose has not been well studied. Dutasteride is less well studied, but oral doses of 0.5 mg daily have been effective for androgenic alopecia. A “postfinasteride syndrome” has been described to occur in about 1% of men completing a course of finasteride, reporting loss of libido, erectile dysfunction, depression, suicidal ideation, anxiety, panic attacks, Peyronie’s disease, penile shrinkage,

gynecomastia, muscle atrophy, cognitive impairment, insomnia, severely dry skin, and tinnitus. The origin of these symptoms is uncertain but the duration may be prolonged, prompting some transwomen to avoid the use of finasteride.

ANDROGEN RECEPTOR BLOCKERS

Androgen receptor blockers bind directly to the androgen receptor and either competitively inhibit binding by testosterone or DHT, or irreversibly bind and induce variable antagonist/agonist effects. The prototype drug in this class is flutamide, a competitive inhibitor of the androgen receptor infrequently used clinically today due to complications including liver failure and death. Bicalutamide is a safer, longer acting alternative with a more favorable safety profile, although a small percentage of users will show elevated liver enzymes and rare cases of liver failure have been reported. Bicalutamide is approved for use in prostate cancer at an oral dose of 50 mg daily, but has been used in the treatment of hirsutism, polycystic ovary syndrome, precocious puberty, persistent erections, and in sex offenders. Studies in transwomen are quite limited, but bicalutamide appears to be effective and induces an actual increase in serum estradiol levels, a welcome adjunct effect in transwomen (Table 4).

GNRH AGONISTS/ANTAGONISTS

Gonadotropin-releasing hormone agonists or antagonists (GnRHa) are potent analogs of GnRH that either down regulate GnRH receptors in pituitary gonadotrophs (agonists) or competitively block those receptors (antagonists). They are utilized to shut down pituitary stimulation of gonadal steroid production and secretion, specifically in the testes in transwomen. While very effective in achieving gonadal suppression, their administration is limited to nonoral forms. Routes of administration include daily subcutaneous injections, daily

TABLE 4. *Available Antiandrogens/
Androgen Suppressors
and Routes of Administration*

Antiandrogen	Route of Administration	Doses
Spironolactone	Oral	100-200 mg daily
Finasteride	Oral	1-5 mg daily
Dutasteride	Oral	0.5 mg daily
Bicalutamide	Oral	50 mg daily

nasal spray, long acting depot injections, and long acting implants. They are clinically utilized in the treatment of hormone dependent cancers including prostate and breast, endometriosis, uterine fibroids, precocious puberty, and infertility.

In early pubescent transgender children, GnRH agonists are standard therapy to block the progression of puberty and allow for time to determine further psychosocial and medical therapy. They can be utilized in transgender adults if adequate androgen suppression cannot be achieved by other means, but they are quite expensive and limited by the route of administration. In general, they are generally used only as a last resort to achieve satisfactory gonadal suppression in transwomen who cannot tolerate an antiandrogen such as spironolactone or do not achieve adequate suppression with an appropriate dose of estrogen.

GnRH antagonists provide prompt, competitive inhibition of the GnRH receptor, but are generally short acting and not utilized for gender affirming hormone therapy. Primarily given as daily subcutaneous injections, they have been used for infertility therapy and to treat prostate cancer (Table 5).

Progestins

There a wide variety of progestins available for clinical use, including the parent progesterone in oral micronized or injectable form, as well as medroxyprogesterone

TABLE 5. *Available Gonadotropin-releasing
Hormone Agonists (GnRHa) and
Routes of Administration*

GnRHa	Route of Administration	Doses
Leuprolide	Intramuscular/ subcutaneous	3.75 mg monthly or 11.25 mg every 3 mo
Nafarelin	Nasal spray	2 puffs/daily 2 times a day
Goserelin	Subcutaneous implant	3.6 mg monthly/ 10.8 mg every 3 mo
Triptorelin	Intramuscular	3.75 mg monthly/ 11.25 mg every 3 mo/22.5 mg every 6 mo
Buserelin	Nasal spray	2 puffs 3 times a day
Histrelin	Subcutaneous implant	50 mg yearly

acetate (MPA) and the multiple progestins utilized in combined hormonal contraceptives. The indications for progestins as a component of gender affirming hormone therapy are 2-fold, and somewhat controversial. The first is as a single agent contraceptive in transwomen engaging in penetrative sexual intercourse with cisgender men, whereas the second is an adjunct to enhance optimal breast development.

Progestins for contraceptive use include the depot form of MPA typically given as an intramuscular injection every 3 months at a dose of 150 mg. Although providing good contraception, this has been associated with weight gain and mood disorders. An etonogestrel implanted rod can be placed with an effective duration of 3 years and the potential for modest weight gain. Intrauterine devices containing levonorgestrel are effective for upwards of 5 years with little systemic exposure and few side effects but require placement and removal with a risk of uterine perforation and expulsion. Progesterone alone is not a proven contraceptive.

The use of progesterone, or progestins, to enhance breast development is controversial and not based on any reliable evidence. Although there are many anecdotal reports of breast growth with the addition of such agents to estrogen therapy in transwomen, no objective clinical trials are available to provide guidance on choice of medication, dose, duration, or response rate. Extrapolation from the experience in inducing breast growth in adolescent girls with absent or delayed pubertal development suggests that simultaneous initial administration of progestins with estrogen may result in abnormal and limited growth due to the simultaneous induction of ductal proliferation and terminal lobular differentiation. It is therefore recommended to initiate breast growth with estrogen alone until stability is reached with a consideration for trial of progesterone/progestin at that time. The risks of long-term progesterone/progestin therapy are unknown in transwomen.

Physical Changes

The physical changes attainable with gender affirming hormone therapy in transwomen are limited by the irreversible in utero and pubertal development induced by testosterone, specifically phallic growth, scrotal development and descent of the testes, lengthening of the vocal cords, and bone and cartilage growth including a supraorbital ridge and prominent nasal and thyroid cartilage enlargement. The various types of gender affirming surgery for transwomen have been developed to variably deal with these changes. However, very significant and clearly visible alterations in appearance are a primary goal of hormone therapy and will occur to varying degrees in essentially all women who choose to initiate treatment.

ESTROGEN INDUCED

The most prominent physical effects of estrogen therapy in transwomen are

2-fold: The induction of breast development from the rudimentary ducts in the back of the nipples of all humans, and the alteration in body composition both by increasing the volume and changing the location of fat mass. Both sets of changes can occur at variable rates and to varying degrees in individual transwomen, a source of considerable frustration for many. Depending on the regimen chosen, the rate of change tends to be most rapid in the first 6 to 12 months of therapy with slowing thereafter. In general, most transwomen will notice no further hormonally induced changes in either by 2 years of use.

Breast growth is initially induced by estrogen through estrogen receptors in the rudimentary ducts located behind the nipple complex to begin to lengthen and branch extensively. These ducts are organized in lobes, and then lobules, with terminal end buds at the tips of the growing ducts. Their growth is accompanied by increases in the surrounding stroma and fat pad. Exposure to progesterone in later puberty when women become ovulatory induces some final ductal growth and initial lobulo-alveolar development in preparation for full gland differentiation during pregnancy with exposure to pregnancy induced hormones.

The ultimate size and shape of induced breasts in transwomen is not accurately predictable and is determined primarily by genetic capacity for growth. It is not clear if breasts initially exposed to a testosterone induced puberty have a different capacity for development than prepubertal breasts with no such exposure. Although family history of breast characteristics may provide a transwoman with some clue as to her capacity for growth, such predictions may be frustratingly misleading for many. It remains unclear whether supplemental progesterone/progestins augment ultimate breast growth in transwomen, although there are many anecdotal

testimonials claiming such a response. In view of the known course of development in normal puberty, and a description of abnormal breast growth with the early addition of progestins, it seems prudent to hold off on adding progesterone/progestin therapy until initial estrogen-induced ductal growth is complete.

Body composition changes with estrogen therapy include both an increase in total fat mass as well as a redistribution of the location of both new and existing fat. Specifically, subcutaneous fat deposition increases significantly in the hips and thighs with the variable reduction from the waist. In addition, general deposition of subcutaneous fat throughout the body, particularly in the face, often occurs, frequently with the perception of bony change through increases in the overlying fat layer. Overall weight changes do not tend to occur, primarily because of decreases in lean mass due to decreases in muscle mass.

Many, if not most, transwomen on gender affirming hormone therapy will also report subtle changes in emotionality not typically associated with significant changes in overall mood. These changes tend to be described as more intense responses to emotional situations or “feelings closer to the surface and more accessible.” Most transwomen who report such changes respond very favorably to them.

ANDROGEN SUPPRESSION

Suppression of endogenous androgen secretion and supplemental blockade of the effects of residual androgens results in a constellation of changes of quite variable onset and duration. These include the reduction or loss of spontaneous erections, the slower loss of muscle mass coincident with the estrogen-induced increase in fat mass, and the very slow decrease in androgen-induced terminal hair growth. Gonadal size and consistency may also change over the course of 6 to 12 months.

Depending on the regimen chosen, the occurrence of spontaneous erections may

relatively rapidly decrease as endogenous testosterone levels fall below the normal male range where erectile dysfunction becomes a common symptom. Erections can typically still be induced, and the achievement of orgasm is still generally maintained albeit the characteristics typically are different. Often this is achieved with initial spironolactone dosing even with relatively modest initial estrogen doses. Other antiandrogens, notably finasteride, are frequently less effective at suppressing erectile function.

Changes in muscle mass may be quite subtle as they also depend on ongoing physical activity and underlying familial tendencies. In general, they tend to compensate for the increases in fat mass induced by estrogen such that overall weight changes are more behaviorally driven than hormone induced. Excessive muscle loss with perceived generalized weakness is not a concern with gender affirming hormone therapy.

Changes in terminal hair growth require suppression of endogenous testosterone levels to the normal female range, 10-fold lower than the normal male range. At those levels, newly developing hair shafts from new dermal papilla are not induced to increase their diameter or pigmentation such that they become unpigmented, thin vellous hair characteristic of ciswomen. The newly growing, thin, unpigmented shaft pushes the old, thick, pigmented shaft out of the follicle and remains in place throughout the next 3 to 5-year growth cycle. But, since the hair cycle is a continuous, unsynchronized turnover of all hair follicles in a 3 to 5-year cycle, it takes that period of time for all previously developed terminal hair to be replaced. Similarly, existing androgen-induced loss of crown hair should cease with full androgen suppression, but regrowth of lost hair will take a comparable 3 to 5-year time frame and is unpredictable in extent.

Transwomen can accelerate the turnover process by modalities that remove

existing terminal hairs, such as laser therapy, as long as they maintain a suppressed testosterone level to prevent regrowth of terminal hair and induce the expected regrowth to be vellous hair. Electrolysis can actually destroy dermal papilla such that no hair regrowth occurs from that follicle. Modalities that do not cause actual loss of terminal hair, such as shaving, will not accelerate the overall perception of decreased terminal hair.

Decrease in sperm production is induced as soon as T production declines, but clearance of sperm in an ejaculate will depend both on that decrease and on the number of ejaculations necessary to expel all sperm stored in the epididymis and vas deferens. Complete azoospermia may not be achieved, but severe oligo-spermia is standard, so fertility capacity is markedly reduced. Since erectile function is also constrained such that penetrative sex is usually not achievable, the risk of pregnancy in a transwoman sexually active with a fertile ciswoman is very low. However, cross-sex hormone therapy in transwomen has not been specifically studied as a contraceptive, so efficacy is inferred only (Table 6).

Starting Therapy

CONSENT

There are 2 models of care provision in prescribing gender affirming hormone therapy in common use today in United States. The first is set forth in the standards of care by the World Professional Association for Transgender Health (WPATH) requiring a letter of referral from a mental health professional experienced in working with transpeople attesting to the appropriateness of initiating medical therapy. The second is the informed consent model whereby patients are counseled regarding the risks, benefits, and expected results of medical therapy, sign an appropriate consent form

TABLE 6. *Effects of Gender Affirming Hormone Therapy in Transwomen*

Effect	Onset	Completion
Decreased spontaneous erections	Rapid 1-3 mo	Persistent
Decreased sexual desire	1-3 mo	Persistent
Breast growth	Intermediate 2-6 mo	1-2 y
Body fat redistribution	3-6 mo	1-2 y
Muscle mass loss	3-6 mo	1-2 y
Softer, less oily skin	3-6 mo	1-2 y
Decreased testicular volume	3-6 mo	2-3 y
Decreased sperm production	Uncertain	Persistent
Decreased terminal hair growth	Slow 3-12 mo	3-5 y
Cessation of scalp hair loss	3-12 mo	Persistent
Recovery of scalp hair loss	Quite variable	Variable

and begin therapy. They each have their proponents and critics.

The WPATH model has been in place since 1979 and is designed to assure as much as possible that patients are in good mental health, fully understand the physical and social implications of medical therapy and have access to psychological support as they undergo their physical transition. It is frequently required by health insurance plans which cover medical therapy. It requires mental health professionals familiar with gender non-conforming clients and trained in both the assessment and recommendation for medical therapy. However, it is frequently considered a significant impediment to accessing medical therapy, both for cost and time reasons.

The informed consent model relies on the education and judgment of the prescribing provider to fully inform patients and assess them for any medical or

psychosocial concerns that might put them at increased risk. This places the primary burden of responsibility of screening patients for significant mental health concerns on the medical professional but can significantly hasten the initiation of therapy and obviate the expense of seeing a mental health professional. However, some mental health providers have raised concern that significant mental health issues may not be unearthed prior to the initiation of therapy with possible untoward outcomes. In general, this model requires a signed consent form for the provision of medical services to document that fully informed consent has been obtained.

PRETREATMENT ASSESSMENT

Before initiating therapy, a full history and appropriate physical examination should be performed. Patients with significant medical conditions should have clearance from their respective health care providers clearing them for estrogen and antiandrogen therapy. If there are any relative contraindications to either form of therapy, consultation with that provider is in order to determine if a safe regimen can be identified, keeping in mind that transwomen do not usually consider medical therapy an elective decision.

Pretreatment testing generally includes assessment of serum electrolytes, lipids, and baseline hormone levels, particularly E2 and T. Some practitioners also measure the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Older patients may also require further assessment with an electrocardiogram or other assessment of cardiopulmonary function.

Any age-appropriate screening tests should also be recommended, and age-appropriate immunizations discussed. Transwoman 18 to 26 years of age should be counseled regarding immunization against human papilloma virus. Pretreatment mammograms are not indicated as the risk of finding a malignancy is

exceptionally small and the mechanical difficulties in obtaining a study are quite significant (Table 7).

CHOICE OF ESTROGEN

Traditionally, oral micronized E2 has been the most common estrogen prescribed for its ready availability, ease of use, and relative low cost. Similarly, oral CEE can be chosen but does not have a generic equivalent and may be more expensive. Increasingly, sublingual micronized E2 is being prescribed at doses about half of the oral route. Transdermal E2 patches are recommended for transwomen with specific risk factors for venous thromboembolic events. There are fewer data regarding other forms of nonoral estrogen therapy.

Some estrogen regimens recommend a gradual increase in estrogen dosing to better mimic a normal, if shortened, pubertal progression. However, it is not clear if the

TABLE 7. *Pretreatment Assessment of Transwomen*

Concern	Assessment	Provider
Mental health (WPATH model)	Counseling	Mental health professional
Mental health (informed consent model)	Office assessment	Prescriber
Thromboembolic risk	History	Prescriber
Other medical conditions	History and physical examination	Prescriber
Renal function (for spironolactone)	Metabolic profile	Prescriber
Hepatic function (for antiandrogens)	Metabolic profile	Prescriber
Dyslipidemia	Lipid profile	Prescriber
Baseline endocrine function	Serum estradiol, testosterone (FSH, LH)	Prescriber
Identified medical risks	Referral	Consultant

final outcome is different other than rate of growth if an estimated full dose is initiated immediately. A common oral starting dose is 2 mg E2 daily with an anticipated 2 mg increase in 2 to 3 months and increases every 2 to 3 months until optimal doses are achieved. A comparable starting dose of CEE would be 2.5 mg orally daily. Transdermal estradiol patches can be started at a daily dose of either 0.05 or 0.1 mg estradiol with patches being changed either weekly or twice a week, depending on brand. Similar to oral therapy, additional patches applied simultaneously of an equal size can be placed every 2 to 3 months until satisfactory results are obtained.

Most transwomen achieve appropriate T suppression at oral E2 doses of 6 to 8 mg daily, or 3 to 4 mg of sublingual E2 daily. Transdermal patches may require three to four 0.1 mg patches simultaneously to achieve such suppression.

CHOICE OF ANTIANDROGEN

Spironolactone is the major antiandrogen begun simultaneously with initiation of estrogen. Transwomen with normal renal function and no history of undiagnosed syncopal episodes usually do well at a full initial starting dose of 100 mg twice a day orally. Divided doses are recommended due to the relatively short half-life, but daily dosing can be utilized in patients who have difficulty in remembering to

take all doses. Higher doses do not generally add significantly more antiandrogen activity. If patients do exhibit signs of hypovolemia or electrolyte disturbances, particularly hyperkalemia, spironolactone should be stopped and electrolytes checked. Usually such patients can restart the medication at a lower dose of 50 mg twice a day orally and do well.

Finasteride is available for patients with a history of renal concerns or syncope episodes and is generally well tolerated. The 1 mg daily oral dose is approved for the prevention of crown hair loss, whereas the 5 mg oral dose is approved as an adjuvant therapy for prostate cancer. Finasteride can be started at the lower dose and increased if the antiandrogen effect is insufficient, but it is unclear if either dose demonstrates superior results. Postfinasteride syndrome has been described as noted above. Dutasteride is a longer acting 5 α reductase inhibitor with comparable results in limited studies with no reported post use syndrome to date (Table 8).

Monitoring Therapy

Patients receiving gender affirming hormone therapy should be given the warning signs of venous thrombotic events including sudden chest pain, sudden shortness of breath, hemoptysis or persistent calf pain,

TABLE 8. Initial Gender Affirming Hormone Regimens In Transwomen

Medication	Initial Dose	Route	Maintenance Dose
	Antiandrogen		
Spironolactone	100 mg twice a day	Oral	100 mg twice a day
Finasteride	1 mg a day	Oral	1-5 mg a day
Dutasteride	0.5 mg a day	Oral	0.5 mg a day
	Estrogen		
Micronized 17 β estradiol	2-4 mg a day	Oral	6-8 mg a day
Micronized 17 β estradiol	1-2 mg a day	Sublingual	2-4 mg a day
17 β estradiol patch	0.1 mg weekly	Transdermal patch	2-4 patches weekly
Estradiol valerate	10-20 mg biweekly	Intramuscular	20-40 mg biweekly
Estradiol cypionate	2 mg biweekly	Intramuscular	5 mg biweekly
	Progestin		
Micronized progesterone	100 mg nightly	Oral	200 mg nightly

and queried about such symptoms at each return visit.

Most gender affirming hormone therapy regimens recommend a follow-up visit at 3 months after initiating therapy, then every 3 to 6 months for the first year of therapy with semiannual to annual visits thereafter. After 2 years of therapy, annual visits are generally sufficient in that most physical changes other than terminal hair loss are stabilized yet the risk of VTE events remains variably elevated. Prescriptions also require annual updating, and recommendations for good primary care, either with the prescribing practitioner or with a primary care provider, are essential. This includes appropriate cancer screening including prostate and breast.

Initial monitoring of response to therapy with electrolyte and lipid status assessment is appropriate at the first follow-up visit but checking E2 and T levels at that time almost universally indicates a need for a higher estrogen dose. It is equally appropriate to screen electrolytes and lipids at the initial follow-up visit, increase the estrogen dose, and begin screening hormone levels at the next follow-up visit when a sufficient dose of estrogen may have been achieved and no further increases are required.

Most transwoman will require 6 to 8 mg of oral micronized estradiol in divided doses to adequately suppress testosterone to the normal female range of less than 50 ng/mL, generally achieving E2 serum levels of 100 to 200 pg/mL. If testosterone is not adequately suppressed, a dose as high as 10 mg daily can be tried, but frequently an unsuppressed testosterone suggests poor oral absorption and indicates an alternate route of administration. It is appropriate to switch to sublingual E2 at half the comparable dose or to transdermal E2 patches. Physical response to therapy is another modality of monitoring, with an anticipation of progressive breast growth and development

and body composition changes as clear evidence of hormone effect.

Once testosterone has been suppressed to the normal female range, and estradiol levels are in the mid normal range for reproductive age ciswomen, repeat studies are generally recommended at each follow-up visit. Some practitioners also measure gonadotropins to verify that they are suppressed to the low/low normal range for reproductive age women. As long as the sex steroid levels and serum electrolytes remain stable, a comparable regimen can be maintained for quite some time.

Long-term Care and Screening

Duration of gender affirming hormone therapy is generally considered to be for life, or until the risks clearly outweigh the benefits and patients agree to discontinue therapy. Currently, there is no indication for modifying the estrogen dose at the average age of menopause of 51 years of age in ciswomen. Similarly, there is no known upper age limit at which point gender affirming hormone therapies must be discontinued. As with any chronic, lifelong therapy, cost effective but appropriate screening is essential and can generally be accomplished with annual measurements of serum E2, T, and electrolytes if the patient is on spironolactone. It is not clear if a lower dose of estrogen is sufficient in older transwomen, but terminal hair will be induced to regrow if a lower dose of estrogen is insufficient to adequately suppress testosterone.

Breast cancer screening should be initiated consistent with current guidelines for ciswomen. It is unclear at what time after initiation of therapy that mammograms should be initiated in women who have reached the recommended age of screening. In the absence of evidence-based recommendations for screening initiation, many practitioners will begin screening 5 years post initiation in age-appropriate women with follow-up screening per the guidelines.

Transwomen on hormone therapy still need age-appropriate prostate cancer screening according to current guidelines. It is not yet clear if the risk of prostate cancer, or the progression of prostate cancer, is altered by gender affirming hormone therapy, so routine recommended surveillance in anyone with an existing prostate seems most prudent.

There is no evidence that gender confirming hormone therapy alters bone biology such that transwomen have any increased risk of bone loss, subsequent osteoporosis and resulting fractures. Therefore, bone density screening should follow age-appropriate clinical guidelines for comparably aged ciswomen (Table 9).

Special Situations

TRANSWOMEN WITH INCREASED THROMBOTIC RISK

The most vexing clinical circumstance in prescribing gender affirming hormone therapy to transwomen is in the patient with a history of nonattributable (fracture, surgery, etc.) thromboses or a known thrombophilia. As noted previously, transgender patients generally do not consider therapy as “elective,” but rather as an essential component in achieving the physical status that matches their innate identity. Thus, it is incumbent on the prescribing provider to fully explore all options for receiving such therapy in the safest possible manner, in part to assure appropriate follow-up and monitoring. Transwomen who cannot access prescribed therapy have many other avenues available to obtain the medications they desire and may embark on an extended course of self-therapy with unnecessary risk and without prophylactic anticoagulation. Many such women are very amenable to weighing risks and benefits and deciding to accept known risks in return for very desired physical changes.

It is also important that practitioners feel as comfortable as possible with the

TABLE 9. Monitoring Gender Affirming Hormone Regimens in Transwomen

Visit	Assessment	Timing
Initial follow-up	Serum estradiol, testosterone, metabolic profile, lipid panel	3 mo
First year of therapy	Serum estradiol, testosterone, metabolic profile	Every 3 mo
Second year of therapy	Serum estradiol, testosterone, metabolic profile	Every 6 mo
Maintenance	Serum estradiol, testosterone, metabolic profile; lipid panel per guidelines	Yearly
Breast cancer screening	Mammogram	Begin at 5 y of therapy, then per guidelines
Prostate cancer screening	Per current guidelines	Per current guidelines

therapy they provide. For transwomen with known or suspected increased thrombotic risk, a referral to a hematologist or other provider with similar expertise before prescribing estrogen is very appropriate, both to assess actual risk and to provide recommendations regarding risk reduction strategies. The initiation of antithrombotic therapy before the initiation of estrogen with close follow-up by the same provider frequently allows transwomen with thrombotic risk to most safely initiate therapy. Close contact between providers is also ideal for long-term monitoring.

The choice of estrogen therapy is another strategy to reduce thrombotic risk. Orally administered estrogens confer the highest risk of thrombotic events, so nonoral administration is the optimal choice. Transdermal estradiol patches are well studied in postmenopausal general populations and

less thrombogenic than orally administered estrogens,⁷ although data are lacking in a transgender population. Other nonoral routes of administration, such as intramuscular, subcutaneous, sublingual, or other forms of topical administration are less well studied, particularly in transgender populations, but are inferred to have reduced thrombotic risk by extrapolation from transdermal patches. A common limiting factor to nonoral therapy is cost, prompting many patients to request sublingual use of micronized estradiol tablets with the associated requirement for dosage adjustment.

TRANSWOMAN WITH INCREASED RISK FOR ESTROGEN DEPENDENT CANCERS

Gender affirming hormone therapy in transwomen with a known or suspected increased risk for estrogen dependent cancers, specifically breast cancer, presents a difficult management decision and deserves optimal counseling before initiating any therapy. Referral for appropriate cancer risk assessment to provide full information regarding cancer risk, with or without estrogen therapy, is essential to both allow the patient to make the most informed decision and to institute risk reduction strategies in conjunction with estrogen therapy. Once again, transwomen are frequently quite willing to initiate therapy regardless of risk in their desire for physical changes, so an optimal monitoring plan for early cancer detection is most appropriate.

Type of estrogen, dose or route of administration are not known modifiers of cancer risk in general or in transwomen with a known increased risk. The effect of exogenous estrogen on prostate cancer risk is unknown.

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