Endocrine Treatment of Transsexual Male-to-Female Persons

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10.1 Background

In line with the emerging conceptualization of gender nonconformity [1] and the new view that proposes that passing for the opposite gender should not be assumed as the final goal for all nonconforming individuals [2, 3], hormonal treatment of gender dysphoric (GD) individuals should be individualized based on patient desires and outcomes [4]. In fact, therapy needs to be designed to address the specific needs of the patient who may not wish to live fully as an individual of the opposite gender [5]. Therefore, individuals with GD could benefit from flexibility in treatment, depending on their final goals with regard to aligning identity with body [5]. This is particularly the case when male-to-female (MtF) hormonal treatment is considered. In fact, different pharmaceutical options are available [4], and current guidelines [6] do not address the preferential order in which therapies should be chosen. In addition, it should be considered that follow-up data on the long-term side effects of cross-sex hormonal treatment (CHT) are still limited [7–10], and no randomized controlled trials are available. Therefore, ideal formulations and dosages of CHT are unknown to date. Current protocols for CHT are similar to those of hypogonadal individuals and aim at hormone values in the normal physiological range [6, 10]. Sustained supraphysiological levels of estrogen increase the risk for serious adverse reactions, such as thrombosis, whereas subphysiological levels may induce the effects known from hypogonadal states [10]. Moreover, patients' clinical characteristics and response should guide specialists in drugs and dose selection [4].

Endocrine treatment of gender dysphoric adults has two major goals: (1) to reduce the secondary sex characteristics of the natal sex and (2) to induce those of the desired gender [6] – as much as the client wishes [5].

In order to achieve these aims, it is needed to decrease endogenous hormone levels (androgens) and replace them with those of the reassigned sex [6]. Administration of estrogens alone will suppress gonadotropin secretion (and, consequently, androgen production). However, dual therapy, with both antiandrogens and estrogens drugs, is more effective to further reduce androgens and, consequently, to boost the feminizing effects of estrogens [4, 6].

10.2 Recommendations Before Starting Treatment

Before prescribing CHT, the treating endocrinologist needs to confirm that client fulfills diagnostic criteria for GD [11] and the eligibility and readiness criteria for hormonal transition (see Table 10.1) [1, 6].

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Table 10.1 Criteria for cross-sex hormone treatment as reported in Standards of Care of World Professional Association for Transgender Health 7th edition

1. Persistent, well-documented gender dysphoria
2. Capacity to make a fully informed decision and to consent for treatment
3. Age of majority in a given country
4. If significant medical or mental health concerns are present, they must be reasonably well controlled

Moreover, before starting treatment, it is recommended to evaluate and address conditions that can be exacerbated by this treatment, as thromboembolic diseases (*very high risk*), macroprolactinoma, severe liver dysfunction, breast cancer, coronary artery disease, cerebrovascular disease, and severe migraine headaches (*moderate to high risk*) [6]. Pretreatment schedule is reported in Table 10.2.

Cessation of tobacco use should be strongly recommended, in order to avoid an increased risk of cardiovascular complication and thromboembolism [6].

10.3 Cross-Sex Hormonal Regimens in MtF Individuals

10.3.1 Antiandrogens Treatment

Several agents are commercially available to inhibit androgen secretion or action. The most commonly used drug in Europe is cyproterone acetate (CPA, 50 mg once or twice daily, see also Table 10.3), a progestational agent with antiandrogenic properties [6, 12, 13]. Spironolactone (50–100 mg twice daily), a diuretic with antiandrogenic proprieties – mostly used in the United States (where CPA is not available) – has antiandrogenic effects by directly inhibiting testosterone secretion and androgen binding to the androgen receptor [14, 15].

GnRH agonists, injected monthly (3.75 mg) or every 3 months (11.25 mg), could be also considered a good alternative for their efficacy in reducing testosterone levels and their low risk of adverse effects [16]. However, they are extremely costly, and therefore their use is limited.

Table 10.2 Monitoring schedule for MtF GD individuals

Pretreatment
Physical examination: weight, blood pressure, waist, body mass index, hair distribution, balding pattern
Fasting lipid, renal and liver function, glucose, glycosylated hemoglobin, complete blood count, serum estradiol, testosterone, prolactin
For those taking spironolactone: electrolytes
If osteoporosis risk exists (previous fracture, family history, glucocorticoid use, prolonged hypogonadism), in older than 60 years: bone mineral density according to natal sex
During first year of treatment, *every 3 months*
Physical examination: weight, blood pressure, waist, body mass index, hair distribution, balding pattern, breast development
Fasting lipid and liver function, glucose, serum estradiol, testosterone, prolactin[a]
Electrolytes (for those taking spironolactone)
During second year of treatment, *every 6 months*
Physical examination: weight, blood pressure, waist, body mass index, hair distribution, balding pattern, breast development
Fasting lipid and liver function, glucose, glycosylated hemoglobin, complete blood count, hemoglobin, serum estradiol (ideal <200 pg/ml) and testosterone (ideal <55 ng/dl), prolactin[a]
Electrolytes (for those taking spironolactone)
PSA and digital rectal prostate exam (in older than 50 years)
After genital reassignment surgery (*when requested*), *every 12 months*
Physical examination: weight, blood pressure, waist, body mass index, hair distribution, balding pattern, breast development
Fasting lipid and liver function, glucose, glycosylated hemoglobin, complete blood count, hemoglobin, serum estradiol (ideal <200 pg/ml) and testosterone (ideal <55 ng/dl), prolactin[b]
Additional screening
Bone mineral density according to natal sex (if osteoporosis risk exists)
PSA, digital rectal prostate exam according to establish guidelines for biological sex
Mammogram/breast ultrasound according to establish guidelines for assigned sex

MtF male to female, *GD* gender dysphoria
[a]At least annually
[b]At least every 2 years

Nonsteroidal antiandrogen, such as flutamide (50–75 mg/day), which blocks binding of androgens to the androgens receptor, can be theoretically used; it induces gonadotropin secretion and, consequently, increases testosterone and estradiol

Table 10.3 Cross-sex hormone treatment protocols in MtF GD individuals

Antiandrogens regimens	
Cyproterone acetate	50–100 mg/d
Spironolactone	100–200 mg/d
GnRH analogs	3.75 mg sc/monthly or 11.25 mg sc/3 months
Estrogens regimens in MtF GD individuals	
Oral estradiol	2–6 mg/d
17-β estradiol patch	100–400 mcg/24 h (changing the patch as directed once or twice weekly)
17-β estradiol hemihydrate gel	2 mg twice daily
17-β estradiol gel	3–4.5 mg daily

levels (which can be desirable in this circumstance). However, for its liver toxicity and undemonstrated efficacy in GD population, its use is not recommended [6].

Finally, finasteride (5 mg daily) – which inhibits the conversion of testosterone to 5α-dihydrotestosterone – can be used as additional antiandrogen, particularly to slow male pattern balding.

10.3.2 Estrogens Treatment

A wide range of estrogenic compounds can be used (see also Table 10.3). Typical GD estrogen dosage needs to be two to three times as high as the recommended doses for hormone replacement therapy in postmenopausal women [14].

Oral or transdermal 17-beta-estradiol is the treatment of choice. As transdermal estradiol seems to have a lower thromboembolic risk, it should be particularly considered for individuals which are at highest risk for thromboembolic events (i.e., those older than 40 years, smokers, and/or with diabetes or liver disease) [6, 17, 18].

As oral ethinyl estradiol has been reported associated with a 20-fold increased risk of venous thrombosis – particularly in subjects over 40 years [19] – and with a threefold increase in cardiovascular mortality [9], it should be avoided. Moreover, the impossibility to monitor its blood levels represents an additional important and practical limitation for its use.

Many patients ask for injectable estrogens, but avoidance of intramuscular dosing is rationalized by the prolonged time to reach steady state and the potential for abuse of this formulation [14].

Moreover, often clients believe that progestins have a fundamental role for their feminization, particularly for breast development. However, they should have informed that progestagens' role is – in natal female – to prepare uterus for conception and breast for lactations. No evidences of additional feminization effects are available in transsexual populations [4, 7]. In addition, they have many side effects of which patients should be aware of, e.g., water retention and consequent elevation of blood pressure and weight gain, detrimental lipid changes, and depression [8]. Last but not least, breast cancer and cardiovascular diseases have been reported when used in postmenopausal women together with estrogens [20].

10.3.3 Approach in Specific Conditions

10.3.3.1 Partial Sex Reassignment

In clients wishing only partial sex reassignment, with only antiandrogens, it is fundamental to perform a careful medical supervision in order to mitigate the consequence of the induced hypogonadism, e.g., osteoporosis, obesity, loss of muscle mass and strength, cardiovascular risk, and depression.

10.3.3.2 After Genital Reassignment Surgery

On the other hand, if the patients choose to undergo genital reassignment surgery, estrogen treatment should be carried on, in order to avoid signs and symptoms correlated to hypogonadism and to avoid osteoporosis. Some subjects still complain for male typical sexual hair growth, and antiandrogens may remain effective, although their dose may be reduced compared to presurgery.

10.3.3.3 Prior and After an Elective Surgical Intervention

It is advisable to stop CHT 3–4 weeks prior to any elective surgical intervention, e.g., genital reassignment surgery. In fact, immobilization is a thrombogenic risk factor, and sex steroids may aggravate this risk. Once fully mobilized

following the surgical procedure, the client may resume hormonal therapy [21].

10.3.3.4 Postmenopausal Age

Up to now, there is no consensus if CHT has to be stopped when client gets older, mirroring the postmenopausal milieu, and no data are available on this regard [7].

10.4 Adequacy Treatment Monitoring

According to the Endocrine Society guidelines [6], clinical and laboratory monitoring have to be performed every 3 months during the first year of CHT and then every 6–12 months, as reported in Table 10.2.

Routine cancer screening is recommended as in non-transsexuals individuals (breast, colon, prostate [6]).

Both estradiol and testosterone levels have to be monitored regularly in order to avoid supraphysiological levels and to minimize the risk of adverse effects [4].

Adequacy of estrogens levels could be monitored by measurement of serum estradiol levels when oral, transdermal, and intramuscular estradiol or its esters are used, but not with conjugated or synthetic estrogens. As daily stable levels are achieved after 1 week of therapy with transdermal or oral formulation, serum levels may be checked at any time during the treatment. When injectable formulations are used, serum levels have to be sampled in the middle between two injections [4]. Theoretically, serum estradiol should be maintained at the mean daily for premenopausal women (<200 pg/ml), and testosterone levels should be in the female range (<55 ng/dl) [6]. Treatment doses should be adjusted accordingly. Moreover, body feminization changes should be monitored in order to guide treatment [4].

10.5 Efficacy of CHT in MtF Individuals

10.5.1 Breast Formation

Increase in breast size usually begins within the first 3–6 months after initiation of CHT and achieves the maximum by 2 years of therapy [22]. It has been reported, from clinical experience, that only in one-third of patients it reaches cup B and that this is quantitatively satisfactory in 40–50 % of the subjects [23]. The remaining 50–60 % judge their breast formation as insufficient [23]. This may be also the consequence of the fact that the attained size could be disproportional to the male-typical chest and height of the subjects. Therefore, many clients ask for augmentation mammoplasty.

10.5.2 Skin

Often clients complain of dry skin and brittle nails, as a result of decreased sebaceous glands activity due to androgen deprivation [24].

10.5.3 Body Hair

CHT induces a reduction of sexual hair growth and hair shaft diameter. This decrease reaches a maximum after 4 months treatment with CHT, but then does not progress further [13]. Usually hair become thinner and less pigmented [24]. However, facial hairs are resilient to CHT particularly in Caucasian clients, and usually additional measures – electrolysis or laser treatment – to eliminate beard are almost always necessary. Electrolysis is effective but painful and potentially scarring. Laser is less uncomfortable but is most effective for people with dark hair.

Sexual hair on others parts of the body responds more satisfactorily, usually within 1–2 years of CHT, and, then, only waxing is required [24].

10.5.4 Body Composition

A decrease of lean body mass and an increase of subcutaneous fat deposits are observed [25]. It is therefore fundamental to encourage a healthy lifestyle.

10.5.5 Voice

CHT has no effects on voice on MtF individuals. Speech therapy can be considered an option to develop a voice within the frequency ranges for a biologic female [26]. Alternatively, laryngeal surgery may be considered in order to change the pitch of the voice, even it reduces its range.

10.5.6 Testes and Prostate

Testes and prostates become atrophy. Sometimes testis may cause discomfort as they enter in the inguinal canal.

10.5.7 Sexual Effects

Decrease of libido and spontaneous erections and male sexual dysfunction, often desired by patients, are usually observed within 1–3 months after starting CHT [6].

10.6 Adverse Effects of CHT

Serious adverse effects have been reported with long-term CHT.

10.6.1 Bone Health

Different studies have reported that estrogens are able to preserve adequately bone mineral density in MtF individuals [27, 28]. However, recently, some authors have observed a high prevalence of osteoporosis and osteopenia in their samples, which may be also related to an inadequate estrogenization of patients studied [9, 29].

An inverse relationship between serum luteinizing hormone levels and bone mineral density has been observed [7, 30]. Therefore, although based on limited evidence, a serum concentration of LH within the normal range may be a reliable marker of adequate dosing [7, 31].

10.6.2 Cardiovascular Health

In the general population, males have a higher cardiovascular risk when compared to females, and the risk in women increases only with cessation of estrogen production with menopause [23]. However, protective effects of exogenous estrogens have been refuted by the large randomized trials (Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative) [32].

Data on cardiovascular effects of estrogens in MtF GD are still conflicting. A large morbidity and mortality study by van Kesteren et al. showed no increase in cardiovascular risk [17]. However, two more recent cohort studies reported an increase of mortality for cardiovascular diseases in MtF individuals [9, 33]. Interestingly, ethinyl estradiol use, as well as smoking habit and dyslipidemia were found in the Dutch study associated with cardiovascular events [9]. This result stresses the concept that transsexual individuals, under CHT, have to avoid ethinyl estradiol, as well as needs to be addressed to a healthy lifestyle.

Remarkably, in androgen-treated FtM subjects, no increased cardiovascular mortality was observed [9]. Therefore, CHT seems to have more deleterious effect on cardiovascular risk in MtF than in FtM subjects [10].

Regarding metabolic profile, it has been reported that estrogens induce in MtF clients favorable changes with increase of high-density lipoprotein cholesterol (HDL) and decrease of low-density lipoprotein cholesterol (LDL) [34]. However, the latter may be also associated with transition to smaller, denser, and more deleterious LDL (high in triglyceride content) [34]. In addition, CHT induces in MtF individuals an increase of weight, body mass index, total body, fat, blood pressure, triglycerides, and markers of insulin resistance [34–37]. Finally, oral therapy – but not the transdermal one – has been observed associated to an increase of inflammatory and hemostatic markers (such as interleukin-6, C-reactive protein, and factor IX) [38, 39].

10.6.3 Venous Thromboembolic Disease

An increased risk of venous thromboembolism (VTE) has been reported since 1989 in a large cohort of MtF transsexuals during CHT with ethinyl estradiol and CPA [18]. This result has been confirmed in some group later study, reporting a 20-fold increased VTE risk, even if a lower incidence was observed with transdermal estrogens [17]. Different studies have emphasized the more deleterious effect of ethinyl estradiol on VTE risk, probably linked to effects on activated protein C resistance and due to its molecular structure than first-pass liver effect [18]. It has also been reported that rates of thromboembolic events are higher in older than 40 years, similarly to figures seen in biological female treated with estrogens [18, 40, 41].

All these data taken together stress the point that the use of ethinyl estradiol has to be avoided, and transdermal preparations have to be preferred, particularly in those older than 40 years. In addition, according to the Endocrine Society Guidelines, thrombophilia screening in transsexual individuals starting CHT should be limited to those with a personal of family history of VTE [6, 42].

10.6.4 Hyperprolactinemia

Estrogens treatment can induce hyperplasia of pituitary lactotropic cells. Therefore, it should not surprise that prolactin increases to over 1,000 mU/l in up to 20 % of MtF persons during estrogen treatment, associated with enlargement of pituitary gland [17, 18]. Usually, levels of prolactin return to normal range after reducing or discontinuing estrogens. Despite several reports of prolactinomas in transsexuals persons are available [43–46], the overall risk of prolactinoma could be considered very low. Moreover, given the high frequency of occult prolactinoma formation and the apparent rarity of prolactinoma in genetic males during CHT, a direct link between exogenous estrogens and prolactinoma induction cannot be drawn [13].

However, it is suggested to check prolactin levels before starting CHT and then at least annually during the first year and, after, every 2 years (see also Table 10.2). If levels of prolactin are extremely high and increase despite stable or reduced levels of estrogens, a pituitary magnetic resonance imaging (MRI) has to be considered. In fact it should be taken into account that the majority of hyperprolactinemia symptoms (such as hypoactive sexual desire, sexual dysfunction, gynecomastia) are usually not apparent in MtF transsexual persons. Careful attention should be taken for those treated with psychotropic drugs, which can contribute to increase prolactin levels.

10.6.5 Cancer Risk

It is difficult to have a reliable figure of tumor prevalence in GD persons having received CHT for many years. Moreover, it is quite impossible to establish a potentially causal relationship because case–control analysis would be needed.

Breast cancer has been reported in relatively few cases of hormonally treated MtF transsexuals [47–51]. Therefore, the risk in MtF population seems to be quite low, even if a definite conclusion cannot be reached. As in biological women, routinely breast self-examination, as well as mammogram/breast ultrasounds, according to establish guidelines for assigned sex, should be suggested.

Despite what expected with the androgen deprivation therapy, prostate cancer has been observed in few MtF subjects receiving CHT treatment [52–55]. This happened specially – but not always – in those starting treatment after the age of 50 years, inducing some authors to doubt if the cancer was present before the initiation of CHT. Prostate-specific antigen (PSA) levels as well as digital rectal prostate exam should be checked according to establish guidelines for biological sex [6].

10.6.6 Reproductive Health

Regarding effect of CHT on male fertility, CHT leads to decreased spermatogenesis and eventually to azoospermia [56]. It has been reported that protracted exposure of the testes to estrogen is

associated with testicular damage [57–59], and restoration of spermatogenesis after long-lasting treatment has not been studied [6].

Therefore, clients requesting hormonal reassignment need adequate information about options available to preserve (e.g., banking of spermatozoa) their fertility potential, before treatment takes place [6].

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