The Female-to-Male Medical Treatment

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26.1 On the Way to Medical Treatment

Transsexualism refers to a condition where an individual identifies with a gender that differs from the assigned sex [1]. Transsexual subjects may suffer from gender dysphoria, which is the distress caused by the feeling of being born to the wrong biologic sex. Gender dysphoria is undoubtedly a complex and multifaceted problem that requires a multidisciplinary approach for its diagnosis and treatment [2]. It goes without saying that the goal of the therapy is to harmonize physical appearance with gender identity [3]. In order to do so, treatments need to be customized, as some individuals need cross-sex hormone therapy and surgery to alleviate their gender dysphoria, others need only one of these treatment options, and some need neither [2].

Having said that before starting any medical or surgical treatment, the diagnosis of gender dysphoria should be established by a mental health professional [3]. The World Professional Association for Transgender Health (WPATH), formerly known as the Harry Benjamin International Gender Dysphoria Association [4], has drafted Standards of Care for the diagnosis and treatment of transsexual individuals [2]. The WPATH Standards of Care indicate that, beside gender dysphoria, the other criteria for cross-sex hormone therapy prescription to adult transsexuals include: (i) capacity to make a fully informed decision and to consent for treatment, (ii) age of majority, and (iii) prior management of coexisting medical or mental health concerns.

Gender dysphoria is not always a straight forward diagnosis. As a result, the prescription of cross-sex hormone therapy is accompanied by a period of time during which the patient lives as a person of the desired sex. This real-life experience is essential for providing insight into the new sex status, confirming the diagnosis, considering surgery [5]. Before starting the therapy, patients should be educated on its risks and adverse effects as well as on what could be their realistic and unrealistic expectations about outcomes. Moreover, patients should be counselled about the available options for fertility. Lastly, an informed consent should be obtained.

26.2 The Female-to-Male Medical Treatment

26.2.1 Androgens

In female-to-male (FtM) transsexuals, cross-sex hormone therapy aims at reducing female secondary sex characteristics and at inducing male secondary characteristics. This therapy is based on the use of testosterone. Testosterone is

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available in different forms, including intramuscular (i.m.) injections, topical gels, patches, buccal tablets, and implantable pellets (Table 26.1). The dose of testosterone required to virilize biological females is generally slightly higher than that used as replacement therapy in hypogonadic men [6]. Common dosage ranges are reported in Table 26.1. Finding the right type of hormone therapy is a challenging task, given that there are no prospective or retrospective studies indicating what is the optimal formulation and dose of hormones. As a result, any prescription of cross-sex hormone therapy is primarily based on expert opinions [3]. In the second place, hormone therapy should be continued after sex-reassignment surgery to maintain virilization and prevent osteoporosis. Nevertheless, there are no recommendations as to what age cross-sex hormone administration must be continued, and there is presently no evidenced-based recommendation on risks/benefits of continuing/stopping hormones. Often, cross-sex hormone treatment is maintained for lifetime, for FtM themselves are usually reluctant to stop administration of hormones worrying that the secondary sex characteristics of the acquired sex will diminish [7]. Moreover, testosterone treatment does not require any interruption before sex-reassignment surgery or any other surgical procedure [6]. Although there have been no reports that the long-term administration of testosterone increases mortality and morbidity [8], FtM subjects seem to have a higher risk of cardiovascular diseases (CVD) [9]. Therefore, before starting any FtM cross-sex hormone therapy, it is recommended to ensure that patients do not have comorbid conditions that could be exacerbated by hormonal treatments (Table 26.2) [3, 10]. In addition, before starting such therapy, FtM people should be strongly advised to give up smoking and to lose weight as a measure to reduce their cardiovascular risk [3, 9, 11].

Table 26.1 Hormones used in female to male treatment and potential disadvantages

Testosterone	Dosage range	Disadvantages
Oral		
Testosterone undecanoate	160–240 mg/day	Variable clinical response
Transbuccal		
Buccal tablets	30 mg twice daily	Gum-related adverse effect
Transdermal		
Testosterone gel 1 %	2.5–10 g/day	Potential transfer to a female partner or child
Testosterone patch	2.5–7.5 mg/day	Skin irritation, musky odor
Parenteral		
Testosterone esters (enanthate or cypionate)	100–200 mg i.m. every 2 weeks or 50–100 mg i.m. every wk	Requires i.m. injections, peaks and valleys in serum T levels
Mixture of testosterone esters	1 ampoule i.m. every two wks	
Testosterone undecanoate	1,000 mg every 12 weeks	Requires i.m. injections of a large volume
Subcutaneous		
Testosterone pellets	3–6 pellets; dose and regimen vary with formulation	Requires surgical incision for insertion; pellets may extrude spontaneously

Table 26.2 Contraindications to cross-sex hormone therapy in female-to-male transsexual patients

Absolute (*very high risk of serious adverse outcomes*)
Pregnancy
Unstable coronary artery disease
Active substance abuse
Breast or uterine cancer
Erythrocytosis (hematocrit >50 %)
Severe liver dysfunction
Relative (*moderate to high risk of adverse outcomes*)
Coronary artery disease
Hyperlipidemia
Severe obstructive sleep apnea
Refractory migraine headaches
Uncontrolled hypertension
Heavy tobacco use
Obesity
Advanced age

26.2.2 Intramuscular Injections

The i.m. administration of testosterone esters, such as testosterone enanthate and testosterone

cypionate, is the preferred and most widely used treatment modality for providing testosterone replacement in FtM subjects [3, 12]. Injectable testosterone esters do not undergo first-pass metabolism and thus do not cause hepatotoxicity. Moreover, esterization allows for a sustained release of testosterone from the site of injection to the blood. Consistent with it, i.m. injectable testosterone esters have been recommended due to their lipophilicity, resulting in the storage and gradual release from the oil-based vehicle in which they are administered and limiting the need for frequent injections [13]. Testosterone enanthate and testosterone cypionate are almost interchangeable, apart from the fact that they may be mixed with different oils, so some individuals may tolerate one better than the other. Other i.m. injectable formulations of testosterone esters include a mixture of short- and long-acting testosterone esters and testosterone undecanoate. The testosterone mixture, also known as *Sustanon*, is an oil-based blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate [14]. On the other hand, testosterone undecanoate is a newly marketed formulation of i.m. injectable testosterone in oil, which allows for only four yearly injections [15]. Nevertheless, each dose of testosterone undecanoate consists of 4 ml which may require multiple simultaneous injections, without considering that it is much more expensive and currently unavailable in the United States. Limitations of i.m. injectable testosterone esters include high peak levels of androgens in the first few days after an injection (except for testosterone undecanoate), which can be ameliorated by reducing the dosing interval while maintaining the same total dose [12]. Moreover, due to the variability in absorption between users, some subjects may experience fluctuations in energy [16]. In the third place, injection site reactions are frequent side effects [16]. In addition to this, due to the viscous nature of the vehicle in which testosterone is delivered and the muscularity of the injection site, a long, large-gauge needle is required to administer the drug, which can be a barrier to someone [12].

26.2.3 Topical and Transdermal Preparations

Transdermal testosterone is available in either patches or gels, and both reproduce normal testosterone levels better than injectable preparations. Both are absorbed quickly when applied and produce a temporary drug depot in the skin, whereby testosterone diffuses into the circulation, peaking at 4 h and decreasing slowly over the rest of the day. Clinical studies have demonstrated that gels allow for longer-lasting serum testosterone levels as compared to transdermal patches [17]. Notwithstanding these clear advantages, transdermal testosterone preparations are often poorly effective to induce rapid and complete amenorrhea and may translate to a lessened change in physical appearance and virilization [12]. In addition to this, patches cause skin irritation in 2 patients out of 3 [16], while gels put patients at risk of testosterone transmission with skin contact. This is particularly worrisome if the transfer occurs in children, where it may cause penile or clitoral enlargement, premature development, and aggressive behavior [16, 18]. Lastly, all transdermal formulations of testosterone can be quite costly for patients who cannot apply prescription insurance benefits for this elective therapy.

26.2.4 Oral Preparations

Oral testosterone is occasionally used in Europe while it is not available in the United States due to its risk of hepatotoxicity [16, 19]. The safest oral formulation is testosterone undecanoate, but it is still less effective than intramuscular or transdermal testosterone and much more expensive than testosterone enanthate and testosterone cypionate. Moreover, testosterone undecanoate bioavailability seem to be affected by food and dietary fat content.

26.2.5 Transbuccal System

Testosterone may also be taken by buccal tablets, which release it as excipients are slowly hydrated

in the mouth [16]. These buccal systems release testosterone in a pulsatile manner, which is similar to endogenous testosterone secretion. Peak testosterone levels are reached rapidly, and the steady state is achieved by the second dose. The advantages of this route of administration include avoidance of first-pass hepatic metabolism and patient compliance, since it is well tolerated. On the other hand, though, transient mouth and gum reactions, as well as a bitter taste or other forms of dysgeusia, are the chief complaints. At the moment, its use in FtM transsexuals is limited.

26.2.6 Subcutaneous Testosterone Implants

Implants of crystalline testosterone can be inserted into the subcutaneous tissue to maintain adequate serum testosterone levels for up to 6 months [16]. The chief adverse events with testosterone pellets include pellet extrusion, minor bleeding, and infection, which are not frequent and may also result in pellet extrusion.

26.2.7 Progestins

Progestins may be used with testosterone if menses do not cease [20]. At the beginning of FtM cross-sex hormone therapy, medroxyprogesterone can be given by i.m. injection at a dose of 150 mg every 3 months in addition to testosterone, and it is usually discontinued once the patient has had 3–6 months of testosterone therapy [12]. Progestins may be also indicated in order to avoid endometrial hyperplasia in those rare patients who take testosterone for more than 3 years and are not willing to undergo hysterectomy [6].

26.3 Effects of Female-to-Male Medical Treatment

26.3.1 Physical Changes

The degree of changes that are induced by hormone therapy is highly variable for fully mature adult genetic females, and outcome predictive criteria are scarce. Physical changes depend on medication, as well as on their dose and route of administration, and on individual sensitivity [6]. Androgen effects are in fact primarily mediated by their specific receptors, whose polymorphism can be responsible for different responses to steroid hormones in different subjects [21]. Treatment duration is also an important variable to consider when evaluating physical changes, given that at least 2 years of therapy are necessary to get the full effect of the treatment [22]. The first physical changes appear after 3–6 months of testosterone therapy, and they include menses cessation, facial and body hair increase, oiliness of skin, libido increase, clitoral enlargement, and muscle and fat mass redistribution [3]. Then over a long period of time, ovaries undergo polycystic transformation [23, 24], and endometrium may become either hyperplastic or atrophic [24]. Endocrinologists should closely monitor the physical signs of masculinization for judging the efficacy of the treatment. It has also to be noted that the physical changes induced by sex hormone transition are usually accompanied by an improvement in mental well-being and a better quality of life [25]. Unrealistic expectations include skeletal changes and male distribution of body fat changes.

26.3.2 Menses Cessation

Menses arrest is a very important goal of the FtM cross-sex hormone therapy. In the vast majority of recipients, testosterone therapy interrupts the menses after 3–6 months from the start, especially if it is administered i.m. [26]. If this is not achieved, as in the cases of transdermal testosterone administration, progesterone therapy can be added to the therapy in order to stop menstrual flow [12, 20].

26.3.3 Hair Growth and Skin Sebum Production

It is well known that sex steroids regulate the skin pilosebaceous unit, as both the sebaceous

gland epithelial cells and the hair follicle mesenchymal cells contain androgen receptors [27]. Here, androgens promote hair growth and skin oiliness, and, in case of an excess of androgenic activity, hirsutism and acne usually develop [28, 29]. So androgen treatment in FtM transsexuals results in the induction of facial hair growth and the increase in sebum production, which can be usually seen after 4 months and continue to develop beyond 1 year [30]. Acne occurs in approximately 40 % of the subjects, and it is usually most pronounced on the back and shoulders rather than in the face [30]. The degree of hirsutism can be generally predicted from the degree and pattern of hair distribution in male members of the same family. Likewise, androgenic alopecia, which affects approximately 50 % of the patients [31], is influenced by genetic background.

26.3.4 Clitoral Enlargement

Clitoral enlargement occurs in all the recipients but its degree varies. The younger the patient is at the start of androgen administration, the more it is encountered [32]. In approximately 5–8 % of people, the clitoral length may reach up to 6 cm and become sufficient for vaginal intercourse [20].

26.3.5 Libido Increase

Most FtM subjects report an increase in the frequency of masturbation, sexual desire, arousal, and sexual fantasies after testosterone administration [33]. Solitary or dyadic sexual desires have been found to correlate positively with testosterone levels [34], while they are inversely associated with LH levels [33]. Unfortunately, there has been little focus so far on the sexual health of transsexuals after sex-reassignment surgery. In one of the very few papers on this issue, Costantino and colleagues reported that sexual parameters such as kissing, arousal, and sexual fantasies returned to baseline levels after surgery. This can be probably ascribed to the fact that in Italy phalloplasty or metoidoplasty are not routinely performed in every center, which may have generated dissatisfaction, failed expectations, and ultimately contributed to the decrease of some aspects of sexual function after surgery [34].

26.3.6 Breast

Androgen effects on breast differ widely from one subject to the other. In most FtM transsexuals, long-term testosterone administration markedly reduces the glandular tissue while promoting connective tissue formation [35]. These changes are similar to the mammary involution that is observed at the end stage of the menopause [35]. The effects on breast are likely to reflect the simultaneous action of androgens and estrogens, which are generated by androgen peripheral aromatization. Sometimes, FtM people utilize the breast-binding technique to flatten their breast and create a male chest contour before sex-reassignment surgery.

26.3.7 Ovaries

Exogenous androgens in FtM transsexuals induce the morphological feature characteristic of the polycystic ovary disease, often encountered in polycystic ovarian syndrome (PCOS) [36]. In these cases the ovaries are enlarged probably in relation to the high number of antral follicles as well as to the hyperplasia of both theca interna and connective tissue.

26.3.8 Endometrium

It is not entirely clear what are the effects that androgen have on the uterus. Having said that androgen receptors are detected in the epithelial cells and connective tissue of the endometrium, during all the phases of the menstrual cycle [37]. Here, the effect of long-term androgen administration is quite variable ranging from endometrial hyperplasia to atrophy [24]. The pathophysiological mechanisms leading to

endometrial hyperplasia during androgen therapy remain debated. Nevertheless, one possible explanation is that the chronic lack of progesterone accompanying hyperandrogenemia and anovulation might stimulate endometrial proliferation and hyperplasia [37].

26.3.9 Body Composition

It is well known that men, on average, have less fat mass and that its distribution is more central or intra-abdominal than that of women [38]. On the other hand, premenopausal women have more fat, whose distribution is more gluteal/femoral. In addition, women generally have more subcutaneous fat [38, 39], while men carry more visceral fat [40]. Consistent with this, it has been demonstrated that FtM cross-sex hormone therapy causes a reduction in subcutaneous fat and an increase in thigh muscle area as well as visceral fat [41]. Moreover, testosterone treatment would also lead to an increase in BMI and in lean mass. The increase in lean body mass is on average 4 kg, and the increase in body weight is usually above 7 kg [20].

26.3.10 Voice

Voice deepening occurs after 6–10 weeks of androgen administration and is irreversible [32].

26.4 Side Effects of Female-to-Male Medical Treatment

26.4.1 Cardiovascular Events

There are no adequate data yet to assess the long-term cardiovascular risks of testosterone therapy in the general population [42]. The same could obviously be said for the risks of such a therapy in FtM transsexuals [43]. On one hand, there is some evidence that patients with testosterone deficiency have a higher risk of CVD [44], as treatment with testosterone has been shown to improve lipid profiles [45, 46] and insulin resistance [45, 46] and to increase the time to ST depression during stress testing [47]. On the other hand, though, other studies have demonstrated that there is a clear association between testosterone therapy and risk of serious, adverse cardiovascular-related events, including nonfatal myocardial infarction, which could be ascribed to the induction of an atherogenic lipid profile [3, 43], to the increase in plasma total homocystein [48] and C-reactive protein levels [7]. This discordance can only be partly explained by the notion that the effects of endogenous and exogenous testosterone may differ [49]. Going back to FtM transsexuals, in a recent meta-analysis of 16 studies that included 651 FtM subjects, testosterone treatment was associated with a significant decrease in high-density lipoprotein levels and a modest increase in systolic blood pressure. However, testosterone did not have any significant effect on cardiovascular outcomes such as death, stroke, myocardial infarction, or venous thromboembolism [43]. This is consistent with long-term studies from the Netherlands that did not find any increase in the risk for cardiovascular mortality in patients taking cross-sex hormone therapy [8]. In conclusion, in spite of current limitations, the most important issue raised by all these apparently conflicting findings is that testosterone effects may partly depend on the population that is being treated with it. Therefore, since cardiovascular risk increases with aging, in both FtM transsexuals and hypogonadic males treated with testosterone, glucose, lipid profile, and blood pressure should be monitored regularly and managed according to established guidelines [2, 3].

26.4.2 Cancer

Malignancies related to cross-sex hormone treatment of transsexuals have so far, fortunately, been a rare occurrence. Nevertheless, they are a concern in FtM subjects treated with long-term testosterone therapy [50], given that androgens are converted to estrogens [51], which could then increase the risk of breast or ovarian cancer. FtM transsexuals receiving androgen treatment

have in fact high circulating 17β-estradiol levels, coming from the peripheral aromatization of testosterone [50]. A direct effect of testosterone on the tissues expressing the androgen receptors cannot be excluded [51]. The vast majority of FtM subjects undergo mastectomy as part of their sex-reassignment therapy. In those who have not undergone mastectomy, clinicians should be aware of the potential development of breast carcinoma. In addition, Endocrine Society guidelines suggest that total hysterectomy and oophorectomy should also be considered as a part of the sex-reassignment surgery in FtM transsexuals [3].

26.4.2.1 Breast Cancer

Although some authors have reported an association between circulating testosterone levels and the risk of developing breast cancer in postmenopausal women [52], according to the North American Menopause Society, there are no randomized controlled trials of sufficient size and duration to conclusively assess if testosterone has an effect on breast cancer risk in postmenopausal women [53]. Accordingly, almost all long-term follow-up studies of women with hyperandrogenism from PCOS, which is characterized by the simultaneous presence of high circulating androgen and estradiol levels, do not provide evidence of a higher breast cancer risk in these women [54, 55]. In FtM transsexuals, three cases of breast cancer have been reported so far. These were all cases where supraphysiologic doses of testosterone were used [51, 56].

26.4.2.2 Ovarian Cancer

Thus far, three cases of ovarian carcinoma have been reported in testosterone-treated FtM transsexuals who had not undergone sex-reassignment surgery [57, 58]. Having too much high androgen levels, as it may have happened in these subjects, is one of the putative mechanisms underlying the development of ovarian cancer, given that ovarian epithelial cells express androgen receptors [59] and experimental data show that testosterone may increase ovarian tumor growth [60]. In addition to this, exogenous testosterone would in any case promote the development of polycystic ovaries [23], which are more likely to develop malignancies. Therefore, although there are no epidemiological studies showing a higher incidence of ovarian cancer in FtM transsexual as compared to the general population, it seems reasonable to suggest that androgen-treated FtM people should undergo laparoscopic oophorectomy after a successful transition to the male role [20].

26.4.2.3 Endometrial Cancer

Prolonged testosterone exposure can lead to an increase in endogenous estrogen levels and the risk of endometrial hyperplasia [24], but whether this condition could represent a premalignant lesion is unknown [61]. Although there has been no report of cases of endometrial cancer in FtM transsexuals, bleeding should not be neglected [3].

26.4.2.4 Tumors of Other Organs

Rare cases of hormone-dependent tumors in organs such as the lung, colon, bladder and brain (in particular meningiomas) have also been reported in transsexuals, but not in numbers that could suggest a causative link between their development and cross-sex hormone therapy [46].

26.4.3 Osteoporosis

Sex steroids are important regulators of bone metabolism and bone mineral density. Since postmenopausal women and hypogonadal men have an increased risk of fractures, long-term bone health is a matter of concern in the treatment of transsexual persons especially after gonadectomy. In FtM transsexuals, it is well documented that androgens protect the bone from estrogen deprivation [62]. This positive effect on bone turnover can be ascribed to both a direct effect of testosterone on bone mass and an indirect effect that is due to the aromatization of testosterone to estradiol [7]. A bone histomorphometric study carried out in 15 FtM

transsexuals, who had undergone hysterectomy with bilateral ovariectomy and had been treated with 250 mg testosterone i.m. every fortnight for an average of 39 months, showed intact trabecular bone structure, increased cortical thickness, and low bone turnover indices as compared to 11 healthy men and 8 postmenopausal women [62]. Consistent with it, it has been found an inverse relationship between serum LH concentrations and bone mineral density, so that serum LH could be used as an indicator of the adequacy of sex steroid administration [63]. At the moment, it is not known whether and when cross-sex hormone therapy can be discontinued, without inducing an unacceptable risk of osteoporosis and bone fractures. Unfortunately, fracture data in transsexual men and women are not available. Otherwise, vitamin D and calcium supplementation should be initiated according to standard guidelines for the general population.

26.4.4 Mortality

In FtM transsexuals, the use of testosterone at doses similar to those used for hypogonadal men seems to be safe, and deaths are not significantly different from those expected [8]. In contrast to male-to-female, in FtM, transsexuals, the external causes of death (suicide, illicit drugs, and AIDS) are extremely rare [8].

26.5 Monitoring and Safety of Female-to Male Medical Therapy

During cross-sex hormone therapy, a continuous medical supervision by a trained endocrinologist is strongly recommended, as androgens may produce serious adverse effects. In the vast majority of cases, risks come from and are worsened by the intentional or unintentional use of either too elevated or inadequate doses of sex hormones to maintain normal physiology [3]. Transsexual subjects tend to self-administer higher hormonal doses in order to achieve more rapid physical changes and therefore to obtain better results. Therefore, once the treatment has been started, the most important rule is avoiding supraphysiological doses of androgens, which may sensibly increase the risk of cardiovascular diseases, including thromboembolic events as well as of other adverse effects. In the second place, total testosterone and estradiol levels should be monitored regularly in order to maintain total testosterone plasma concentrations within the normal range for men (320–1,000 ng/dl) [3], and this goal should be shared with patients [64].

Regular clinical and laboratory monitoring of androgen administration should be scheduled at baseline and every 3 months during the first year and then once or twice yearly. Patient history, drug history, current complaints, and patient ideas, concerns, and expectations should always be evaluated. The physical examination should focus on secondary sex characteristics as well as on the monitoring of body weight and blood pressure. Laboratory tests that include complete blood count, renal and liver function, and lipid and glucose metabolism should be performed. Other exams such as ECG or DEXA should be considered in selected patients. ECG should be performed in smokers or hypertensive patients during the first year of follow-up, whereas DEXA should be taken into account at baseline if there are other risk factors for fracture or in patients older than 60 years, especially if they have stopped cross-sex hormone therapy and have had gonadectomy [3]. An ultrasound scan of the abdomen should be periodically performed in patients who have not undergone ovarian removal. If breast and cervical tissue are present, FtM people should be followed according to screening guidelines as recommended by the American Cancer Society and by the American College of Obstetricians and Gynecologists, respectively [3]. A standard monitoring plan for FtM transsexuals on testosterone therapy is found in Table 26.3.

Lifestyle changes, such as eating healthy food, giving up smoking, and taking regular exercise, should be strongly encouraged in FtM transsexual persons to avoid cardiovascular complications.

Table 26.3 Clinical assessment and follow-up of MtF transsexuals during cross-hormone therapy

Assessments	Timing of clinical and laboratory assessment
Routine health questions focused on risk factors and medications	Baseline
Karyotype in case of a surgical reassignment or according to clinical indication	
HBsAg, HBsAb, HCV, HIV, TPHA	
Complete physical examination including: Blood pressure, body weight Extent of masculinization Palpation of breast for masses Examinations of genitalia	Baseline, every 3 months after starting treatment for the first year Every 6–12 months after the first year
Laboratory investigation including: Creatinine, blood urea Liver function tests Fasting glucose and lipid profile CBC, hemoglobin LH, total testosterone, estradiol	Baseline, every 3 months after starting treatment for the first year Every 6–12 months after the first year
ECG	Within the first year of hormone treatment
Bone mineral density	At baseline if risk factors are present and at age 60 in low-risk people
Lower abdomen ultrasound	After 2–3 years of testosterone therapy waiting hystero-adnexectomy
Cervical PAP test	In case of prolonged androgen treatment
Mammography	Annually after age 50

CBC complete blood count, *HBsAg* hepatitis B surface antigen, *HBsAb* hepatitis B surface antibody, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *TPHA* treponema pallidum hemagglutination, *LH* luteinizing hormone, *ECG* electrocardiogram, *PAP* papanicolaou

Conclusion

Transsexualism is a rare condition of unknown cause that is accompained by gender dysphoria, whose diagnosis should be first assessed by an experienced mental health professional [3].

Although hormonal treatment with androgens is an indispensable tool to alleviate gender dysphoria in FtM people, by inducing and mantaining male characteristics [3], cross-sex hormone therapy can be associated with many potentially serious long-term complications [33].

Comparative and long-term multicenter follow-up studies are necessary to test the efficacy of different regimens and dosing of cross-sex hormones and its potential risks and benefits.

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