Management of Transsexuality in an Outpatient Gynecologic Area

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12.1 Introduction

At present, people with sexual identity disorders are increasingly appearing in the world. A clear increase in the prevalence of transgender individuals is consistently observed in all studies that have been conducted over the past 50 years [1–3]. This fact indicates that the society has increased tolerance to people with nontraditional sexual orientation and gender identity. In this regard, transsexuals feel more openly and often seek professional help [4].

Despite the improvement of the overall situation, in many countries where transsexualism is considered a mental disorder, society, by and large, is simply not ready to treat people tolerant and understanding [5]. While acknowledging the improvement in the situation with transsexual medical care in countries with advanced human rights protection, it must be recognized that there are multifactorial problems around the world that are associated with providing medical care to this group of patients.

Transgenders remain one of the most underserved subgroups in many countries around the world. Unemployment rate, clinical depression, anxiety disorders, interpersonal violence, family abandonment, physical and mental violence, suicide risk, substance abuse, and serious diseases such as human immunodeficiency virus (HIV) are the highest among these population groups [6–9].

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Phobic attitudes against trans people are present in many health facilities [10–12]; noted the inaccessibility of medical assistance, the lack of qualified medical professionals, and high cost of services [13, 14]; inconsistency of existing mechanisms to assist transgender people with the principles of human rights, imperfection of the legal system among others [12, 14]. The shortage of skilled health workers and medical information on trans-health care is quoted as one of the main reasons for understanding the limitations suffered by trans-people seeking medical care [15, 16]. And, as a result of this inaccessibility to qualified medical care combined with the frequent suicidal mood and long social disadaptation, some individuals carry out hazardous practices for their health such as attempt to self-castration and uncontrolled hormone therapy [17, 18].

Transsexual subjects need to receive an effective and safe treatment. The goal of such therapies is to rehabilitate them as a member of the society in the gender area with which they are identified. According to the "Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People," the options for medical treatment include:

- Changes in gender expression and role (which may include episodic or permanent life in another gender role that coincides with gender identity person).
- Hormone therapy for feminization or masculinization of the body.
- Surgical correction for the purpose of changing primary and/or secondary sexual characteristics.
- Psychotherapy in order to explore gender identity, role, and self-expression, work with the negative impact of sexual dysphoria and stigma on mental health, facilitate internal phobia, and increase social support and mutual assistance.
- Improvement of body image or development of stress resistance [19].

12.2 Clinical Management of Transgender People

Medical services for transgenders should be provided by a multidisciplinary team consisting of a psychologist, social worker, psychiatrist, endocrinologist, and surgeon (gynecologist, plastic surgeon, urologist) [20]. The psychologist and psychiatrist should diagnose transsexualism and recommend hormonal treatment; the endocrinologist, in turn, initiates and controls cross-sex hormonal treatment and participates in determination of indications for surgery. Finally, the surgeon must be responsible for the gender-affirming operation that is required to complete the transsexual transition [19, 20].

With the accumulation of experience, medical specialists recognized that although some people require both hormone therapy and surgical procedures to alleviate gender dysphoria, others need only one of these treatments, and others do not require any of them. In some cases, with psychotherapeutic support, subjects cease to feel the need to undergo feminizing or masculinizing surgeries. Some patients may need hormonal treatment, the possibility of changing the gender role, but not surgical correction; others may need to change their gender role along with

surgical correction, but not hormonal treatment. Thus, the treatment of this condition became more individualized [19].

Feminizing or masculinizing drug therapy is based on the administration of exogenous hormones that cause changes in physical appearance [18]. Since hormone therapy is inexpensive compared to surgery and very effective in the development of secondary sexual characteristics (e.g., facial and body hair in transgender men (female-to-male, FTMs) or breast growing in transsexual women (male-to-female, MTFs)), hormone therapy is often the first and sometimes the only intervention available to transgender people who seek to develop male or female characteristics according to their gender identity. In some cases, hormone therapy may be required before sex-affirming operation [12, 16]. The change in the physical characteristics of a person with hormone therapy is considered a necessary medical intervention for many transgender people and can alleviate the psychological suffering associated with gender dysphoria, reduce mental disorders, and improve the quality of life of patients [20, 21]. The effectiveness of hormone therapy in the elimination of mental disorders associated with gender dysphoria has been largely confirmed by clinical practice and evidence of low level [22–24]. According to the Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, the following criteria must be met for conducting gender-affirming hormone therapy in adults: persistent, well-documented gender dysphoria/gender discrepancy, the ability to take a fully informed decision and consent to treatment, and age of majority in a particular country; mental health problems, if any, should be sufficiently well controlled [19].

12.3 Management and Therapeutic Options for Transgender Adults

12.3.1 Male-to-Female Transsexual Subjects

Patients with MTF transformation need complex hormone therapy aimed at suppressing secondary sexual characteristics inherent in the inborn sex and the induction of sexual features compatible with gender identification. The main hormones in gender-affirming therapy for transgender women are estrogens. For these purposes, pharmacological preparations of estrogens, including oral, injectable, transdermal, and intravaginal forms as monotherapy or in combination with progestins, are used in a variety of dosages and administration routes [17]. According to the latest recommendations, preferable are oral conjugated equine estrogens or 17β-estradiol and transdermal 17β-estradiol [20].

Before the initiation of therapy, it is recommended a routine blood test with blood cell count and basic metabolic panel (glucose, liver enzymes, electrolytes, and lipids). The measurement of testosterone, prolactin, and hemostasis is also recommended [25].

It is important to rule out family history of breast cancer and to encourage the patient in the need for breast self-control. The personal history of breast cancer or

other estrogen-dependent neoplasms are absolute contraindications for the use of estrogen therapy [26]. It is necessary to explain to patients the possibilities of hormone therapy, the risks of complications, and the effects that hormone therapy cannot achieve. It is also necessary to discuss with the patient the possibility of maintaining fertility [27, 28].

The effects of feminizing estrogen therapy in the first 3–12 months in transgender women are breast growth, some redistribution of adipose tissue according to the female type, a weakening of the musculature of the upper body, softening of the skin, a reducing of skin oiliness, a decrease in hair growth on the body, and less erections [26, 29–31]. With time, atrophy develops in the testis and prostate.

The full effect of hormone therapy on physical appearance in transgender people may not be attained in the first 2 years of therapy. However, the complete disappearance of the changes induced by the hormones of their biological sex is almost impossible to achieve.

Estrogen monotherapy does not lead to a decrease in testosterone levels in MTF transgenders up to standard female values [25, 29], and most studies highlighted the need to prescribe additional antiandrogenic drugs [29, 32, 33]. It is noteworthy that some progestins, such as cyproterone acetate, may have antiandrogenic properties [17, 26, 34]. Data exist on the effect of cyproterone acetate reducing or eliminating the effects of androgens on target organs such as the growth of hair on the face and body and the production of skin sebaceous glands. Moreover, this drug may induce a weakening of sexual desire [34] and stimulate the growth of mammary glands [35].

Spironolactone and flutamide are drugs that block the effects of testosterone at the androgen receptor level [36]. Different studies report good results using these drugs with a testosterone-suppressive goal in the schemes of MTF hormone therapy [35, 37]. Gonadotropin-releasing hormone (GnRH) agonists in combination with estrogen have shown in some studies a high efficacy and safety achieving an antiandrogenic effect in MTF patients [17, 38, 39].

Additionally, data exist on the combined use of 5-alpha-reductase inhibitors (finasteride and dutasteride). These drugs block conversion of testosterone to potent androgenic dihydrotestosterone and therefore may provide a more pronounced feminizing effect [40]. Inhibitors of 5-alpha-reductase may be a good choice for intolerance or the presence of contraindications to the use of spironolactone. 5-Alpha-reductase inhibitors may also be an option for use as monotherapy in patients requiring partial feminization or for those who have signs of virilization against antiandrogen therapy or gonadectomy [41].

Cross-sex therapy should be selected individually, paying special attention to the characteristics and wishes of each patient, and be effective and as safe as possible. Gender-affirming hormone therapy in MTF transsexuals is carried out in two stages. The first stage—before—sex reassignment surgery is aimed at the reverse development of secondary sexual characteristics of the inborn sex and the formation of those that are specific for selected sex, and the second stage—after orchiectomy—is necessary for further feminization of the patient and prevention of post-castration

syndrome development. Commonly, cross-sex therapy should be started at least 6 months before the planned surgical intervention and ceased 3–4 weeks before surgery since prolonged immobilization may increase the risk of thromboembolism. After surgery, when physical activity is recovered, hormone therapy should be resumed [25].

Recently the North American Endocrine Society published the recommended therapeutic doses and routes of administration to achieve the feminizing effect [20] (Table 12.1).

Exceeding the recommended daily dosage of estrogens is allowed for a short period of time in case of insufficient decrease in testosterone levels with lack of antiandrogenic effects and insufficient growth of the mammary glands [17]. The most dangerous adverse event of estrogen therapy in MTF transgenders is thromboembolism. From 2% to 6% of MTF individuals during the first year of therapy will develop thrombotic complications; however, frequency decreases to 0.4% afterward [17]. In addition, single cases of pulmonary artery embolism [42] and cerebral thrombosis [43] have been published. The higher risk of thrombosis is associated with oral administration of ethinyl estradiol [17, 26, 33], smoking, and the presence of cardiovascular and thrombophilic diseases [20, 44]. By oral route, estrogens undergo active metabolism in the liver that stimulates the production of coagulation factors and triglycerides [25]. Parenteral forms of estrogen administration bypass this first step, reducing the risk of thrombotic complications, and are the forms of choice for patients in the age group over 40 years [45]. In spite of this concern, administration of oral ethinyl estradiol to MTF transgenders at a dose of 0.03–0.1 mg/day in the composition of COC appears to be safe with a good feminizing effect [17, 25].

A slightly increase of prolactin level in the blood has been detected in some MTF transgenders. However, in cases of significant excess of prolactin and galactorrhea, prolactinomas should be ruled out [29].

Table 12.1 Recommended therapeutic doses and routes of administration to achieve the feminizing effect in MTF transgender individuals (Endocrine Society, US)

First stage before the operative removal of gonads			
Drug	Dose	Route	Freq.
17β-Estradiol	2.0–6.0 mg/day	Oral	Per day
Estradiol valerate	2.0–6.0 mg/day	Oral	Per day
17β-Estradiol patches/gel	0.025–0.2/day	Transdermal	Per day
Estradiol valerate/cypionate	5–30 mg	Intramuscularly	Every 14 days
Estradiol valerate/cypionate	2–10 mg	Intramuscularly	Every week
Antiandrogens			
Cyproterone acetate	25–50 mg/day	Oral	Per day
Cyproterone acetate	3.75 mg/month	Subcutaneously	Every month
Spironolactone	100–300 mg/day	Oral	Per day
Gonadotropin-releasing hormone agonists	11.25 mg	Subcutaneously	Monthly for 3 months

Interestingly, a large percentage of depression (10%) in MTF transgenders under hormone therapy has been reported [17].

At the second stage, after surgical removal of the gonads, estrogen monotherapy is usually continued. However, some patients even after the surgery have excessive growth of hair on the face and body. Such patients can be recommended to continue taking antiandrogen [26].

Individuals under MTF hormone therapy should be checked to evaluate the efficacy and safety of such a therapy. It is recommended a clinical assessment every 3 months during the first year of therapy and then every 6–12 months [17, 46]. The physical examination includes weight, blood pressure, breast augmentation, hair body involution, redistribution of fat deposits, and testicular atrophy (if not removed). Blood samples should be performed every 6–12 months to determine the level of LH, FSH, testosterone, estradiol, prolactin, hepatic serum enzymes, blood coagulation factors and lipid profile, and blood count. The levels of serum estradiol and testosterone should ideally correspond to those of premenopausal women (100–200 pg/mL and <50 ng/dL, respectively) [47]. Finally, bone absorptiometry and breast ultrasound should be performed regularly (Fig. 12.1).

12.3.2 Female-to-Male Transsexual Subjects

The goal of hormone therapy in FTM transgenders is the development of secondary sexual characteristics, inherent to men. Masculinizing effect can be achieved by using various testosterone pharmacological preparations [29, 33, 35]. The aim of

First control	6-12 months monitoring (every 3 month during 1 st year of therapy)
Weight	Weight control
Blood pressure	Blood pressure
Hemogram	Physical examination (breast augmentation, hair body involution, redistribution of fat deposits and testicular atrophy)
Metabolism (glucose, liver enzymes, electrolytes and lipid profile)	Hemogram
	Metabolism (hepatic serum enzymes, lipid profile)
	Blood coagulation factors
Testosterone, prolactin	LH, FSH, testosterone, estradiol, prolactin
Hemostasis	**3-5 years monitoring**
EKG, Abdominal ultrasound	Bone absorptiometry
	Breast ultrasound

Fig. 12.1 Management of MTF transgender subjects

cross-sex hormone replacement therapy in this case is to achieve normal male testosterone blood levels, usually within the range of 320–1000 ng/dL [48].

Commonly, in the management of FTM transgenders, therapeutic doses and routes of administering testosterone vary upon subjects. Injectable preparations of short-acting testosterone esters, injections of long-acting forms of testosterone undecanoate, transdermal patches and testosterone gels, subcutaneous implants, and oral testosterone undecanoate are prescribed.

Table 12.2 records the recommendations of the Endocrine Society for cross-sex therapy in FTM transgenders [20].

Injections of short-acting testosterone do not mimic the physiological circadian rhythms of testosterone production, and it is not uncommon that in the first days of use, supraphysiological levels were observed leading to the development of adverse effects, such as aggressiveness, increased libido, and sweating [49]. These supraphysiological peaks of testosterone and most of its adverse effects are not present with the long-acting injectable forms which are significantly better tolerated by patients [50]. However, the use of long-acting forms of testosterone is often limited by their high cost compared to the short-acting forms. On the other hand, transdermal testosterone systems simulate the physiological daily rhythms and have a reasonable cost [17].

Expected effects of testosterone therapy include increased muscle mass; fat tissue redistribution; voice change; body hair growth on the face, chest, and abdomen; clitoral size increase; and increased libido [29, 48]. The cease of menstrual function often occurs in 2–3 months from the beginning of testosterone therapy. In case of persisting uterine bleeding, the use of progestins or even endometrial ablation has been suggested [51]. In addition, gonadotropin-releasing hormone agonists or medroxyprogesterone may be administered to stop menstrual function before starting treatment with testosterone.

Testosterone replacement may be associated with adverse effects in FTM transgenders. Among them, acne, weight gain, aggressiveness, increased sexual desire, and hypertension are the most common [52]. Cases of venous thrombosis and thromboembolism, deterioration of lipid profile, polycythemia, insulin resistance, atherosclerosis, and breast and ovarian cancer have been also reported [29, 53]. In this sense, the results from the European Network for the Investigation of Gender Incongruence corroborate that current treatment modalities for transgenders are effective and carry a low risk for side effects and adverse events at short-time follow-up [54].

Table 12.2 Recommended therapeutic doses and routes of administration to achieve the masculinizing effect in FTM transgender individuals (Endocrine Society, US)

Drug	Dose (mg)	Route	Frequency
Testosterone enanthate/cypionate	100–200	Intramuscularly	Every 14 days
Testosterone enanthate/cypionate	100–200	Subcutaneously	50% dose weekly
Testosterone undecanoate	1000	Intramuscularly	Every 12 weeks
Testosterone gel 1.6%	50–100	Transdermal	Per day
Testosterone patches	2.5–7.5	Transdermal	Per day

First control		6-12 months monitoring (every 3 month during 1 st year of therapy)	
	Weight		Weight control
	Blood pressure		Blood pressure
	Hemogram		Physical examination (breast augmentation, hair body involution, redistribution of fat deposits and testicular atrophy)
	Metabolism (glucose, liver enzymes, electrolytes and lipid profile)		Hemogram
			Metabolism (hepatic serum enzymes, lipid profile)
			Blood coagulation factors
	Testosterone, prolactin		LH, FSH, testosterone, estradiol, prolactin
	Hemostasis	3-5 years monitoring	
			Bone absorptiometry
	EKG, Abdominal ultrasound		Breast ultrasound

Fig. 12.2 Management of FTM transgender subjects

Regular clinical and physical examinations to assess the development of signs of virilization and to detect adverse effects of hormone therapy every 3 months during the first year of therapy and thereafter every 6–12 months are recommended. Along with these clinical controls, blood pressure and weight should be recorded, and blood analysis should be performed including assessment of serum testosterone levels every 3 months until blood levels in healthy men are reached and LH, FSH, estradiol, blood cell count, and lipid profile each 3 months during the first year of therapy and 6–12 months thereafter.

In cases of lack of compliance with hormone therapy, violations of treatment schedules, or failure of hormonal replacement action, the actual risk of osteoporosis is high. For such patients, osteoporosis needs to be screened and absorptiometry recommended.

Oophorectomy and hysterectomy are recommended after hormonal transition. If mastectomy has been performed, a regular peri- and subareolar survey is mandatory; if not performed, mammogram is recommended [19, 55] (Fig. 12.2).

12.4 Conclusions

Mental health is improved through comprehensive gender-based treatment, including psychologic actions, real-life experience, hormone therapy, and surgical operations [34, 56]. Subjects who underwent sex reassignment surgery should be under supervision of an endocrinologist to monitor the adequacy of the hormone replacement therapy for the rest of their life. Only a properly selected dose of hormonal

replacement can prevent the development of adverse effects caused by the removal of gonads, i.e., post-castration syndrome [20].

For many transgender adults, surgery, which proves gender identity, can be a necessary step toward the goal of a successful life in accordance with the desired role of men or women. The type of gender-affirming operation is divided into two main categories: those that directly affect the reproduction ability and those that do not affect fertility. The first include surgery to remove the penis and testicles in men and the removal of the uterus and gonads in women. Operations that affect fertility are often regulated by laws. Other gender-affirming operations such as rhinoplasty that do not directly affect fertility are not so strictly regulated.

Sex reassignment surgical options for transwomen include non-genital surgeries such as breast augmentation, liposuction, facial feminization surgery, lipofilling, voice feminization surgery, thyroid cartilage reduction, and gluteal augmentation. Genital feminizing surgeries include bilateral orchiectomy, penectomy, and options for remodeling the genital tract via clitoroplasty, vaginoplasty, and/or vulvoplasty.

Similarly, transmen may undergo bilateral total or partial mastectomy, chest contouring, liposuction, lipofilling, liposurgery, and/or pectoral implants. Genital masculinizing surgeries include metoidioplasty (lengthening and straightening of the testosterone-enlarged clitoris to create a neophallus), phalloplasty, urethral lengthening and scrotal reconstruction with insertion of testicular prostheses with or without hysterectomy, and/or bilateral salpingo-oophorectomy [57].

For the last 10 years, sex reassignment surgical methods have significantly improved. Reconstructive surgery on the genitals, preserving neurological sensitivity, is at present time the standard, and the level of patient satisfaction after surgical correction is currently very high [21].

Finally, despite the growing awareness, the reduction of stigmatization, and the positive trend in the medical care of the transgender population, physicians and transgenders need to overcome many obstacles before reaching the long-term goal of achieving high standards of care for members of this diverse social group. Health facilities should include formal training on transgender health issues and help patients make choices from the full range of available health services, according to their clinical needs and the goals of gender expression. Further study of the etiology, pathogenesis, and manifestations of transsexualism, as well as profound understanding by physicians, especially endocrinologists, psychiatrists, and therapists, of this issue, will allow diagnosis and treatment at an earlier time, faster to withdraw patients from chronic stress, which, ultimately, will allow transgender patients to maximally improve their health, psychological well-being, and self-actualization.

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