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REVIEW ARTICLE

A Review of Gender-Affirming Hormone Therapy for Transgender and Gender Diverse Adults in South Korea

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Recently, gender-affirming hormone therapy for gender incongruence has become an issue in various countries and organizations with various guidelines. In South Korea, several clinical treatments are also used with many possible options. These treatments include masculinizing (female-to-male [FTM]) or feminizing (male-to-female [MTF]) hormone therapies, with regimens usually driven by standards of hormonal replacement therapy for hypogonadism (i.e., hypogonadal natal men and postmenopausal women). This cross-sex hormone therapy can change patients' physical appearance to better match their gender identity and expression. Regarding masculinizing therapy, injection and transdermal gel types of testosterone are used according to international guidelines. Progesterone is utilized in the form of oral pills, injections, or intrauterine devices to suppress menstruation and avoid pregnancy. Essentially, feminizing therapy uses androgen blockers along with estrogen. This is because estrogen alone cannot exert sufficient androgen-suppressing effects. In South Korea, the most commonly used androgen blockers are spironolactone and cyproterone acetate. Gonadotropin-releasing hormone (GnRH) agonist is also available. Regarding estrogen, oral pills, injections, and transdermal gels are utilized. This review introduces these gender-affirming hormone therapies in South Korea and discusses the side effects of each regimen.

Key Words: Feminizing, Gender incongruence, Gender-affirming treatment, Masculinizing, Transgender

INTRODUCTION

Terms such as 'transgender', 'gender non-binary', 'gender mismatch', and 'genderqueer' are adjectives that refer to people whose gender identity is inconsistent with their assigned sex at birth. The World Professional Association of Transgender Health (WPATH) has stated that "the expression of gender characteristics, including identities that are not stereotypically associated with one's assigned sex at birth, is a common and culturally diverse human phenomenon that should not be judged as inherently pathological or negative." [1] Recently, gender identity disorder, which was used as a diagnostic term in the World Health Organization International Classification of Disease (ICD)-10 and the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, was converted to a new diagnostic term, 'gender incongruence' in ICD-11 [2]. Gender incongruence is defined as an individual's gender identity, role, and expression different from those assigned sex. It is no longer considered a mental disorder. Over the past decades, the number of transgender people seeking gender-affirming hormone therapy, clinical studies, and experiences have markedly increased [3] which might have contributed to recent diagnostic term change. The WPATH [1,4] and the Endocrine Society [5] have revised their guidelines of the gender-affirming hormone therapy for transgender people based on available evidence. Other societies, including the European Society [6] and Rainbow Health Ontario, in Canada [7], also have created transgender-specific guidelines to reflect local conditions according to updated evidence

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and clinical experience, different demographics of objectives, national health/insurance system, and domestically available options of medical treatment. The objective of this article is to describe current trends in clinical treatment for transgender and present available options of hormone therapy in South Korea.

GOALS AND CRITERIA OF GENDER–AFFIRMING HORMONE THERAPY

The principal purposes of gender-affirming hormonal therapy are as follows: 1) to suppress endogenous effects of sex hormones of an individual's assigned sex; 2) to induce secondary sex characteristics with replacement of endogenous sex hormone levels in accordance with the individual gender identity. This treatment consists of masculinizing (FTM; female-to-male,) or feminizing (MTF; male-to-female,) hormone therapies. Regimens are usually driven by standards of hormonal replacement therapy in hypogonadism (i.e., hypogonadal natal men and postmenopausal women). This cross-sex hormone therapy can change a patient's physical appearance to better match with their gender identity and expression. In the past, both WPATH (ver. 7) [1] and the Endocrine Society [5] recommended that hormone therapy should be started once a psychosocial assessment has been completed, especially if it is assessed by trained mental health professionals. However, recent guidelines [4,6,7] have suggested that healthcare professionals should determine which assessment approaches can best meet the needs of transgender persons and initiate gender-affirming treatments without an initial referral or evaluation from mental health professionals except if it is needed. The healthcare professional can assess transgender individual and choose an appropriate gender-affirming hormone therapy according to the following criteria: (1) they have experienced marked and sustained gender incongruence regardless of significant distress related to their gender identity; (2) they are satisfied with the diagnostic criteria for gender incongruence if required; (3) informed decision and consent have been obtained independently; and (4) assessment for other mental and physical conditions that could negatively impact treatment outcomes and discussion about possible benefits and harms of long-term hormone treatment have been completed (Table 1). Meanwhile, WPATH offers a flexible guidance considering the nature of health care in local circumstances and regulatory requirements in revised guidelines as shown in Table 1 [4].

GENDER–AFFIRMING HORMONE THERAPY

Masculinizing hormone therapy

Several forms of parenteral testosterone are used in FTM individuals to develop secondary characteristics in transgender men. Desired masculinizing effects with hormone treatment might vary from person to person. Treatment options including doses, routes, and serum hormone levels should not be uniform, but personalized to meet each patient's treatment goals following clinical response and minimize the risk associated with

Table 1. Assessment and criteria for gender-affirming hormone therapy

WPATH SOC ver. 7 (2012) [1] and Endocrine Society Clinical practice Guideline (2017) [5]
• Persistent, well-documented gender dysphoria/gender incongruence. • The capacity to make a fully informed decision and to consent for treatment. • The age of majority in each country (if younger, follow the criteria for adolescents). • Mental health concerns, if present, must be reasonably well controlled.
Revised WPATH SOC ver. 8 (2022) [4]
• Gender incongruence is marked and sustained. • Meets diagnostic criteria for gender incongruence prior to gender-affirming hormone treatment in regions where a diagnosis is necessary to access health care. • Demonstrates capacity to consent for the specific gender-affirming hormone treatment. • Other possible causes of apparent gender incongruence have been identified and excluded. • Mental health and physical conditions that could negatively impact the outcome of treatment have been assessed, with risks and benefits discussed. • Understands the effect of gender-affirming hormone treatment on reproduction and they have explored reproductive option.

SOC: Standard of Care, WPATH: World Professional Association for Transgender Health.
Adapted from World Professional Association for Transgender Health (WPATH 2012; https://www.wpath.org/publications/soc) [1], from Coleman et al. (J Transgend Health 2022; 23(Supple 1): S1-259) [4], Hembree et al. (J Clin Endocrinol Metab 2017; 102: 3869-903) [5].

Table 2. Hormone regimens in transgender persons

Drug		Dose	
		International guidelines (WPATH/ES) [4,5]	Available regimen in South Korea
Female-to-male (masculinizing) hormone regimen			
Testosterone			
Parenteral	Testosterone enanthate or cypionate (Jenasteron®)	100–200 mg IM every 2 weeks or SC/IM 50% per week	100–200 mg IM every 2 weeks or 250 mg IM every 3–4 weeks or 50–100 mg SC every week
	Testosterone undecanoate (Nevido®)	1,000 mg IM every 12 weeks or 750 mg every 10 weeks[a] 1,000 mg every 12 weeks[b,c]	1,000 mg every 12 weeks
Oral	Testosterone undecanoated[d,e]	160 mg once or twice daily	N/A
Transdermal	Testosterone gel	50–100 mg/d[a] Testosterone gel 1.6%, 50–100 mg/d[b]	Testosterone gel 2%, 30–80 mg/d (10 mg/pump)
	Testosterone nasal gel		22–33 mg/d (5.5 mg/spray)
	Testosterone transdermal patch	2.5–7.5 mg/d	N/A
Male-to-female (feminizing) hormone regimen			
Estrogen			
Oral	Estradiol (Progynova®)	2–6mg/d (oral or sublingual)	2–6mg/d (oral or sublingual)
Transdermal	Estradiol transdermal patch (new patch placed every 3–5 day)	0.025–0.2 mg/d	N/A
	Estradiol gel various	(WPATH) Daily to skin (amount applied varies to formulation and strength)[a]	Estradiol 0.1% gel, 2–6 mg/d
Parenteral	Estradiol valerate (Estradiol-Depot Injection®)	5–30 mg IM every 2 weeks or 2–10 mg IM every week	5–10 mg IM every week or 10–20 mg IM every 2 weeks
	Estradiol cypionate		N/A
Antiandrogen	Spironolactone	100–300 mg/d	100–300 mg/d
	Cyproterone acetate[d]	10 mg/d[a] 25–50 mg/d[b]	12.5–50 mg/d
	Finasteride	(WPATH) Do not recommend routine use	1–5 mg/d (not routine use)
	Dutasteride	(WPATH) Do not recommend routine use	0.5 mg/d (not routine use)
GnRH agonist	GnRH agonist GnRH agonist depot formulation	3.75–7.50 mg SC/IM monthly 11.25/22.5 mg SC/IM 3 monthly	Monthly or 3 monthly

ES: Endocrine Society Clinical Practice Guideline, GnRH: gonadotropin-releasing hormone, IM: intramural, N/A: not available, SC: subcutaneous, WPATH: World Professional Association of Transgender Health.
[a]Adapted from Coleman et al. (J Transgend Health 2022; 23(Supple 1): S1-259) [4]. [b]Adapted from Hembree et al. (J Clin Endocrinol Metab 2017; 102: 3869-903) [5]. [c]Initially 1,000 mg followed by an injection at 6 weeks then at 12 weeks intervals. [d]Not available in United State due to concerns about metabolic effects. [e]Available in Europe, but not available in WPATH or ES.

testosterone use.

Testosterone

Current options for testosterone in international guidelines and South Korea are presented in Table 2. Injection (i.e., intramuscular, or subcutaneous) and transdermal forms are commonly used preparations both in Europe and US, whereas oral administration is available in Europe, not in the US or Canada. In South Korea, currently available formulations for testosterone are injection (testosterone enanthate, testosterone undecanoate), testosterone gel (2%), and testosterone nasal gel (Table 2). Testosterone enanthate (Jenasteron®; Jaytech Biogen, Seoul, Korea, 250mg/mL/amp) is usually administered 100–200 mg every two weeks. It can be extended to 250 mg (1 amp) every 3–4 weeks. Testosterone undecanoate (Nevido®; Bayer AG, Berlin, Germany; 1,000 mg/4 mL/amp) is a long-acting testosterone. It is administered 1,000 mg initially followed by an injection 6 weeks later and then every 12 weeks. Ac-

cording to serum testosterone levels measured just before the 4th injection of testosterone undecanoate, the clinician can adjust the administrating interval at 10–20 weeks. Transdermal formulations are favorable options with the advantage of a steady state of hormone delivery. Transdermal patch is not available in South Korea. As another transdermal formulation, testosterone gel 2% (Tostrex Gel 2%®; Kyowa Kirin Ltd, Galashiels, United Kingdom) which contains 20 mg of testosterone per gram of gel is available. Each actuation of the pump dispenses 0.5 gram of gel, equivalent to 10 mg of testosterone allowed for dry skin (i.e., upper arms or shoulders). Recently, the intranasal formulation is also added to available options in South Korea. The recommended dose of testosterone nasal gel (Natesto Nasal Gel®; Haupt Pharma Amareg GmbH, Regensburg, Germany) is 11 mg of testosterone (2 pump actuations; 1 actuation per nostril) administered intranasally 2–3 times daily (total 22–33 mg).

Progestogen

Amenorrhea is usually expected within a few months (3–6 months) after initiation of testosterone treatment [8,9]. However, menstruation can be persistent for more than a year, which is inconvenient for FTM individuals. Ovulation may occur during long-term testosterone treatment with or without menstruation, resulting in unexpected pregnancy [9,10]. Moreover, contraception is recommended while using testosterone in terms of teratogenic effect on the fetus, such as hyper-androgenization [11]. Progestogens might be considered for FTM individuals who need menstrual suppression and/or contraception. For example, the administration of progestin-only oral pills, injectable progestogen (i.e., Depo-Provera®; Pfizer Limited, Sandwich, United Kingdom), and levonorgestrel intrauterine device can be performed before or concurrent with testosterone treatment and then stopped at 3–6 months after achieving amenorrhea. Progestin-only pills and injectable progestogen, including Depo-Provera® (Pfizer Limited), are no longer available in South Korea. Gonadotropin-releasing hormone (GnRH) agonists might be alternatively considered for achieving amenorrhea.

Effects of masculinizing hormone therapy

The degree and timing of virilization depend on the formulation and dose of testosterone and individual characteristics, including age upon starting hormone, genetics, and habitus [4]. Typically, expected anatomical and physiological changes can be induced within 3–6 months of testosterone treatment, including increased skin oiliness and facial/body hair, increased muscle mass and strength (particularly grip strength), increased lean body mass (1.7–6.0 kg) and body weight (2.2–3.5 kg), amenorrhea, and increased libido with clitoral growth [12,13]. Acne of the face, chest, and back, usually accompanied by hair growth, can commonly develop, or worsen in the first year of testosterone use. Then they can decline spontaneously [14,15]. Coarsening of hair and possibly androgenetic alopecia may occur over several years [14]. FTM on testosterone may experience lowering of voice within the first 3 months and significant voice deepening within 9–12 months [16,17], although the degree of change is insufficient for some patients [18,19]. As another desired change, clitoral enlargement up to 3.83–4.6 cm after 1–2 years of testosterone treatment has been reported [13,20]. Testosterone treatment associated with atrophy of the vaginal epithelium may cause vaginal dryness, itching, and painful penetration [21]. Exogenous testosterone can reduce breast glandular tissues with fibrous transformation without increasing breast size [21-23]. Most changes including fat redistribution and increased muscle mass are reversible, while deepening voice and male pattern hair loss are irreversible. There is a lack of evidence that increased doses of testosterone have a more masculine effect after reaching maximal virilization in the first two years of treatment [7,24]. Although the effect of testosterone on fertility remains unclear, it can result in reduced follicular function and developing features of polycystic ovary syndrome [21]. Therefore, international guidelines suggest counsel about fertility preservation options prior to initiating hormone therapy [4-7].

Monitoring of masculinizing hormone therapy and adverse outcomes

Standard recommended monitoring schedules for gender-affirming hormone therapy are presented in Table 3. Patients on estrogen or testosterone treatment should be evaluated and adjusted for levels of hormones, appropriate physical changes, and adverse effects every three months in the first year and subsequently every 6–12 months. If testosterone level is lower than the lower limit of the cisgender male physiologic levels, the dose can be elevated carefully. In contrast, testosterone should not be over supraphysiologic

Table 3. Follow-up and monitoring of hormone therapy

Female-to-male (masculinizing) individuals
1. Evaluate patient approximately every 3 months (with dose changes) in the first year, then every 6–12 months to monitor for virilizing and adverse effects in response to testosterone. 2. Measure serum testosterone levels every 3 months (with dose changes) until levels are at physiological range - For parenteral testosterone, the serum total testosterone should be measured mid-cycle between injections. the target level is 300–1,000 ng/dL. alternatively, measure peak and trough to ensure levels remain in the range of reference men. - For parenteral testosterone undecanoate, testosterone should be measured just before injection. If the level is < 300 ng/dL, adjust the dosing interval. - For transdermal testosterone, the testosterone level can be measured no sooner than after 1 week of daily application (at least 2 hours after application of product). 3. Measure baseline hematocrit or hemoglobin concentrations - Every 3 months (with dose changes) for the first year, then every 6–12 months. - Obtain blood pressure , body weight , cholesterol level at follow-up visit. 4. Routine bone mineral density screening after age 65 if a patient is at low risk for osteoporosis. - Screening for osteoporosis should be conducted from the age of 50 in those who stop testosterone treatment (> 5 years), have undergone oophorectomy, are not compliant with hormone therapy, or who develop risks for bone loss. 5. If cervical tissue is present, routine cervical cancer screening tests after age 20 following recommendations for cisgender women as endorsed by the Korean national cancer screening guidelines. 6. Annual chest wall and axillary examinations if mastectomy is performed. If mastectomy is not performed, then consider mammograms following recommendations for cisgender women as endorsed by the Korean national cancer screening guidelines.
Male-to-female (feminizing) individuals
1. Evaluate patient approximately every 3 months (with dose changes) in the first year, then every 6–12 months to monitor for feminizing and adverse effects in response to estrogen. 2. Measure serum estradiol and testosterone levels every 3 months (with dose changes) and maintain them at the level for premenopausal female - Serum testosterone < 50 ng/dL - Serum estradiol: target 100–200 pg/mL 3. For individuals receiving spironolactone, serum electrolytes, (in particular potassium), and kidney function(in particular creatinine), should be monitored (every 3 months in the first year and one time per year thereafter. 4. For breast cancer screening, mammography every 1 to 2 years after age 50 if breast cancer risk factors are present (e.g., estrogen or progestin use for > 5 years, positive family history, body mass index > 35 kg/m^2). Routine screening mammography for all transgender women receiving hormone therapy is not recommended. 5. For prostate cancer screening, following recommendations for non-transgender individuals as endorsed by the Korean national cancer screening guidelines. 6. Routine bone mineral density screening after age 65 if a patient is at low risk for osteoporosis.

Revised from Coleman et al. (J Transgend Health 2022; 23(Supple 1): S1-259) [4], Hembree et al. (J Clin Endocrinol Metab 2017; 102: 3869-903) [5], and Deutsch et al. (University of California San Francisco, 2016) [24].

levels (> 1,000 ng/dL) to prevent adverse effects and potential risks. Measurement of serum testosterone levels usually can be conducted at mid-cycle of administration of injectable types. Some patients experience cyclic symptoms (i.e., pelvic pain, migraines, and mood changes) in the initial hormone treatment, which are associated with wide fluctuations in testosterone levels [24,25]. When peak and trough levels of testosterone are too broad in those patients, increasing the injection frequency with a lower dose or switching to a transdermal form with less periodicity may be preferred. Polycythemia defined as hematocrit > 50% is a risk factor for adverse vascular events. It is the most common side effect in FTM individuals treated with testosterone [26,27]. Higher incidences of polycythemia with intramuscular testosterone enanthate than with other preparations have been reported [27-29]. It occurs predominantly during the first year of treatment [28]. Thus, it is crucial to monitor hemoglobin/hematocrit levels closely. In addition to polycythemia, testosterone use in FTM persons can reduce high-density lipoprotein cholesterol and elevate triglycerides, low-density lipoprotein, and inflammatory markers, which are potential risks for cardiovascular events [4,26,30]. However, it is unclear whether gender-affirming testosterone treatment increases risks of adverse cardiovascular outcomes [5]. Previous studies did not demonstrate a significant increase in cardiovascular diseases associated with short- or long-term testosterone treatments in FTM individuals [27,30-32]. Both testosterone and estradiol are essential to maintain bone mineral density (BMD). Estradiol concentrations have more effects on the maintenance of BMD than testosterone levels [33]. Estradiol concentrations can also predict fractures [33].

A Systematic Review and Meta-Analysis conducted by the Endocrine Society in 2017 demonstrated no statistically significant decrease in BMD at 12 and 24 months compared with baseline before starting masculinizing hormone therapy in FTM individuals, whereas there was an increase in BMD in MTF individuals on feminizing hormone [5,34]. BMD screening should be conducted for all transgender individuals on hormone at age 65. It can begin at age 50 in those with a high risk of osteoporosis [24]. (Table 3) Testosterone treatment does not appear to significantly increase the risk of breast cancer. However, there are several reports of FTM developing breast cancer on testosterone, even after mastectomy [35]. Clinicians should be aware of unknown risks associated with residual breast tissue and limitations of mammography in FTM individuals who undergo a mastectomy. Thus, annual chest wall and axillar examinations should be conducted. If mastectomy is not performed, consider mammography like cisgender women. Testosterone treatment is not associated with an increase of cervical cancer. However, FTM individuals are at risk of cervical cancer. They are often not included in the screening of cervical cancer such as pap smear. As with cisgender women, FTM individuals with cervical tissues should be provided with cervical cancer screening tests after age 20.

Feminizing hormone therapy

Hormone therapy for MTF persons is more complex than that for FTM persons. The general approach of feminizing therapy combines estrogen and androgen blockers. Estrogen use alone is usually insufficient to achieve desirable androgen suppression with the physiological range for females. Combination of estrogen and androgen blockers is often necessary. While androgen blockers suppress or minimize secondary male characteristics, estrogen promotes female sex characteristics.

Androgen blockers

The rationale for adding androgen blockers is twofold: 1) to lower testosterone levels to within the physiologic range of cisgender women, and 2) to reduce the amount of estrogen needed to achieve adequate physical effects. There are several options for using androgen blockers according to their mechanisms, such as suppression of pituitary gonadotropin release and subsequently reducing sex steroids (GnRH agonist), antiandrogenic effect of progestin (i.e., cyproterone acetate), directly decreasing testosterone synthesis or interfering conversion of testosterone to dihydrotestosterone which is more potent androgen (i.e., finasteride, spironolactone, cyproterone acetate), and blocking activities of androgen receptors (i.e., spironolactone, cyproterone acetate). The most common treatment regimen is a combination of estrogen and spironolactone or cyproterone acetate as an androgen blocker. Spironolactone is a potassium-sparing diuretic that can directly block peripheral androgen receptors, causing competitive inhibition of androgen and consequently suppressing testosterone synthesis. It also has a weak estrogenic effect [36]. Cyproterone acetate is commonly used in Europe and South Korea (not approved in the United States due to concerns of hepatotoxicity) as an androgen blocker. This synthetic progestin compound can suppress testosterone production and act through a decline in luteinizing hormone secretion. Cyproterone acetate has been reported to have a higher testosterone suppression efficacy than spironolactone [37]. GnRH agonist can effectively reduce testosterone levels with a low risk of adverse outcomes [38]. It can be considered when a patient has contraindication or intolerance of spironolactone or cyproterone acetate. Spironolactone (Aldactone®; Pfizer Limited) can be used at 100–300 mg/d. Cyproterone acetate (Androcur®; Bayer AG) can be used at 12.5–50 mg/d. As another option, GnRH agonist can be administrated monthly or every three months. Finasteride is one of 5-α reductase inhibitors. It was approved for treating androgenetic alopecia (1 mg) and benign prostatic hypertrophy (5 mg) by the Food & Drug Administration [39]. Finasteride does not directly suppress testosterone action or production. It is a less effective androgen blocker. Administration of 5-α reductase inhibitors such as finasteride and dutasteride may be added for those who experience scalp hair loss with standard feminizing hormone regimen or with a gonadectomy state. However, 5-α reductase inhibitors have hepatotoxic effects. Benefit of this treatment has not been firmly established. Thus, almost all international guidelines for transgender hormone treatment did not recommend their routine use [4-7]. All androgen blockers are available in South Korea.

Estrogen

The major treatment in feminizing hormone treatment is administrating estrogen. Among many different estrogenic compounds, ethinyl estradiol is a well-known risk factor for thromboembolic events. The use

of ethinyl estradiol in transgender hormone treatment is not recommended [40]. Parenteral estradiol valerate, oral estradiol valerate, and transdermal estradiol are available options in South Korea. Since risks of thromboembolic events of oral administration are higher than others [41], the transdermal route is preferred for older MTF (age > 45 years) and those with a previous history of thromboembolic events [4]. In South Korea, oral estradiol valerate (Progynova®; Bayer Weimar GmbH und Co. KG, Weimar, Germany) 1 mg or 2 mg and parenteral estradiol valerate (Estradiol-Depot Injection®; mibe GmbH Arzneimittel, Waltrop, Germany) 10 mg/mL are commonly used. While transdermal patch is not available, transdermal estradiol gel (Estreva 0.1% Gel®, Divigel 0.1% Gel®; Theramex Laboratory, Monaco, Monaco; 2.0–6.0 mg per day) can be used. Target serum estradiol level is 100–200 pg/mL, has to be maintained as level for premenopausal female.

Progestogen

Some providers argue that the use of progestogen (i.e., medroxyprogesterone acetate and micronized progesterone) in feminizing hormone therapy can improve breast development and quality of life [42,43]. However, there is currently insufficient evidence to recommend such progestogen use. One prospective study has shown that progestogen is not related to breast development [44]. A recent systematic review has demonstrated an increased risk of a thromboembolic event in transgender women prescribed progestogen with estrogen [45]. Notably, potential risks of cardiovascular disease and breast cancer have been demonstrated in postmenopausal women when progestogen is combined with estrogen according to Women's Health Initiative (WHI) studies, although the study population and objective of hormone therapy are different from transgender women [46]. Progestogen also has side effects such as weight gain, edema, and depression. International guidelines do not recommend progestogen in feminizing hormone therapy given the lack of evident benefit with long-term use [4,7].

Effects of feminizing hormone therapy

Physical feminizing effects vary depending on the dose and formulation of treatment agent and individual tolerance. Redistribution of fat mass in the gynoid region occur in the first six months, leading to female physical change [47]. Muscle mass and strength can decrease, especially in the upper limb [47]. But such changes are markedly dependent on the amount of exercise and the kind of food consumed. Softening of skin, loss of facial hair, enlargement of breast, and decreased libido, spontaneous erections and testicular volume can occur in the first 3–6 months of treatment. It has been reported that testicular volume and size are reduced approximately 25% within the first year [20] and up to 40%–50% after one year of therapy [13], which are correlated with the severity of spermatogenesis abnormality [48,49]. Even spermatogenesis might restart after discontinuation of prolonged treatment with estrogen and androgen blockers [50]. However, there are limited data to ensure the influence of these gender-affirming hormone treatments on the reversibility of fertility. Accordingly, all patients should be advised of potential reproductive effects of therapy and consulted regarding options for fertility preservation (i.e., sperm cryopreservation) prior to initiating hormones. One of the most important changes in feminizing is that breast development induced by administration of estrogen is very diverse among individuals. Most (71%) MTF patients show modest increase in breast volume (corresponding to a Tanner breast stage 2-3). About 20% of patients can reach Tanner breast stage 4-5 after two years of estrogen therapy [51]. In the same study, 58% of MTF patients were satisfied with their breast development, although the result was insufficient against individual's expectations [51,52]. There is no evidence that formulation or dose of hormone agent can affect the degree of breast size [52]. Generally, the effect of breast development is irreversible. The maximal effect reaches at two years after hormone use. Dissatisfied breast change can be enhanced by breast augmentation surgery. Estrogen does not affect voice. Many MTF people wish to receive voice and communication training.

Adverse outcomes and monitoring of feminizing hormone therapy

Avoiding supraphysiologic level of estradiol is crucial in feminizing hormone therapy, which can increase the risk of venous thromboembolism (VTE). The risk of VTE is variable according to the type, route (transdermal vs. oral), dose of hormone therapy, smoking, and underline risk factors. Based on studies of menopausal women, conjugated estrogens as well as ethinyl estradiol have a high risk of having hemostasis and thrombotic effects [53]. In addition, previous prospective and retrospective studies have shown that the incidence of

VTE is decreased in transgender women who are routinely switched to transdermal estrogen at age 40–45 or treated with estradiol patches only [31,54,55]. Thus, the use of transdermal estrogen is recommended for MTF individuals who have risk factors of VTE (i.e., age > 45 years or a previous history of VTE). Estrogen therapy can be discontinued 2–4 weeks before operation including gender-affirming surgery and restarted after a patient ambulates due to potential risk of VTE [7]. However, there is a lack of evidence for this cessation. Previous studies have found no VTE increases among MTF patients remaining on estrogen for surgery compared to patients whose estrogen therapy was discontinued preoperatively [56,57]. The effect of feminizing hormone therapy on cardiovascular risk and diabetes type II is still unclear because estrogen shows both changes in MTF patients as follows: (1) increased triglycerides, blood pressure, both subcutaneous and visceral fat, and decreased insulin sensitivity; and (2) increased high-density lipoprotein cholesterol and decreased low-density lipoprotein cholesterol concentration, which are favorable changes [58]. Evaluation of cardiovascular risk, lipid profile, and diabetes screening is also recommended. Risk factors should be managed before initiation of treatment. Theoretically, estrogen can lead to increased risk of breast cancer. Several studies have shown that risk of breast cancer in MTF patients on estrogen is much lower than that in cisgender females [59,60]. No evidence supports routine screening mammography for all transgender women receiving hormone therapy. Screening mammography every 1 to 2 years is advisable for transgender women age 50 and older with additional risk factors (e.g., estrogen or progestin use for > 5 years, positive family history, body mass index > 35 kg/m^2) [61]. Estrogen might be also associated with hepatotoxicity, cholelithiasis, and hyperprolactinemia. Moreover, cyproterone acetate use can increase the risk of hepatotoxicity, hyperprolactinemia, and mood disorder [7]. Thus, prolactin levels should be monitored for those use estrogen, especially if estrogen is combined with cyproterone acetate. Spironolactone should be used as an androgen blocker in individuals with a high risk of hepatotoxicity. Spironolactone may result in side effects, including hyperkalemia, frequency of urination, low blood pressure. There are some concerns about the development of meningiomas with prolonged use (> 2 years) and higher doses (> 10 mg daily) of cyproterone acetate [62,63]. Thus, it should be more evaluated with long-term studies.

CONCLUSION

Gender-affirming sex hormone replacement therapy inducing the transition of physical characteristics has been demonstrated to improve mental health outcomes as a cardinal concern for transgender persons [64]. In addition to this medical treatment, social and surgical interventions are associated with improved emotional health and well-being. They are now widely known as effective treatments for transgender persons [65]. In South Korea, only a few clinicians can provide gender-affirming treatments [66-68]. More clinicians should get training so that they could provide gender-affirming treatment in terms of primary health care [4,7,69,70]. Notably, clinicians should give evidence-based and individualized hormone treatment for patients seeking gender-affirming care, keep the risk and adverse effects in mind, and counsel them using proper language and terms they prefer. This review provides currently available options and updated clinical advice of hormone treatment for both MTF and FTM people in South Korea.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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