Published in final edited form as:
Best Pract Res Clin Obstet Gynaecol. 2023 February ; 86: 102296. doi:10.1016/j.bpobgyn.2022.102296.

Gender-affirming hormonal therapy for transgender and gender-diverse people—A narrative review

J. Defreyne[a,*,1], **Clara Vander Stichele**[a,1], **Sean J. Iwamoto**[b], **G. T'Sjoen**[a]

[a]Department of Endocrinology and Center for Sexology, Ghent University Hospital, Ghent, Belgium

[b]Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado School of Medicine, Anschutz Medical Campus, and Rocky Mountain Regional VA Medical Center, Aurora, CO, USA

Abstract

As the number of transgender and gender-diverse (TGD) people accessing gender-affirming care increases, the need for healthcare professionals (HCPs) providing gender-affirming hormonal therapy (GAHT) also increases. This chapter provides an overview of the HCPs interested in getting involved in providing GAHT.

Keywords

Transgender health; Gender-affirming hormonal therapy; Gender diverse

Introduction

The aim of gender-affirming care is to provide safe and effective ways for transgender and gender-diverse (TGD) people to feel comfortable living as their affirmed gender identity. Gender-affirming care goes beyond changing the physical characteristics of one's body as it also aims to improve people's overall health, including psychological well-being and self-fulfillment. In the World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) edition 8, gender-affirming hormone therapy (GAHT) was described as medically necessary [1].

Although previous studies confirmed the safety of GAHT [2,3], medical supervision over time remains necessary as GAHT may be associated with potential long-term risks [2,3]. Therefore, the WPATH SOC 8 [1] recommends monitoring and screening for adverse effects by a healthcare professional (HCP) providing GAHT.

*Corresponding author. Department of Endocrinology, Ghent University Hospital, Ghent, Belgium. Justine.defreyne@ugent.be (J. Defreyne).
[1]These authors contributed equally.

Declaration of competing interest
The authors have no conflict of interest.

Gender-affirming endocrine care can be provided by both endocrinologists and gynecologists depending on the customs of the center where the gender-affirming care is provided and the availability of HCPs involved in transgender care in a given area. In the absence of HCPs prescribing and monitoring GAHT (e.g., from a lack of knowledge or comfort), people may obtain hormones themselves and take them without medical supervision [4–7], which may lead to an increase in adverse health outcomes.

GAHT has been shown to reduce general psychopathology, depressive symptoms, and subjective gender dysphoria [8]. When questions arise, HCPs who prescribe GAHT can consult guidelines by WPATH (SOC 8) [1], the Endocrine Society [9], or the European Society for Sexual Medicine (ESSM) [10].

GAHT is generally aimed at inducing serum levels of estradiol and testosterone that fall within the reference (i.e., physiological) range for the individual's gender identity. There is currently no TGD-specific reference range for the measurement of sex steroid levels [9]; hence, we do not suggest altering GAHT based solely on the serum levels of sex steroids. GAHT can be individualized to meet the specific needs of that person, although inducing supraphysiological levels is not recommended as it may result in adverse effects [1]. In contrast, subphysiological levels may adversely impact bone health [1].

In adolescents, gonadotropin-releasing hormone agonists (GnRHa) can be used to suppress pubertal development, starting from early puberty (Tanner stage G2/B2), and this is considered a medically necessary therapy. If gender dysphoria persists, GAHT can be added to the therapy.

In the absence of evidence stating otherwise, the current recommendation is to continue GAHT lifelong, although this differs from cisgender people who go through menopause or in whom testosterone levels decrease with age [11]. It is currently unknown whether doses of GAHT should be tapered in aging TGD people. However, the cessation of GAHT may result in bone loss, particularly after the removal of the gonads [12]. Studies prospectively comparing bone density in older TGD people after stopping GAHT with prospective changes in bone density in age-matched cisgender people are currently unavailable.

Feminizing endocrine care

Feminizing hormone care typically consists of estrogen therapy, combined with antiandrogens, as long as a gonadectomy has not been performed. Estrogens are used to induce secondary female characteristics (e.g., breast growth and female body composition), whereas anti-androgens are used to suppress secondary male characteristics (e.g., body hair and male pattern hair loss) [9]. Estrogens are preferably bioidentical estrogens. Examples include 17-beta estradiol, transdermal estrogel, or estrogen patches. The use of conjugated estrogens or ethinyl estradiol (EE) has mostly been abandoned because of a higher thromboembolic risk. In addition, in people on conjugated estrogens or synthetic estrogen, the serum level of estradiol does not reflect adequate GAHT as these estrogen formulations are difficult to accurately measure by the available assays.

Estrogen therapy can consist of oral, transdermal, or parenteral estradiol. The availability and cost can differ among different regions. In TGD people aged 45 years and older or in TGD people with a history of venous thromboembolism (VTE), the use of oral estrogen therapy is not recommended because of the higher risk of developing VTE. Instead, the use of transdermal formulations (estrogel or estrogen patches) is advised [1]. Currently available research does not support routinely initiating progesterone therapy [13], and it may be associated with nearly threefold higher odds of thromboembolism [14,15] compared with not using it.

If desired, an anti-androgen agent can be initiated in addition to estrogen therapy. Anti-androgen therapy reduces the testosterone levels to levels within the reference range of cisgender women and/or blocks the androgen receptor activity, but it may also result in a lower amount of estrogen needed to achieve the desired physical effects. Frequently prescribed options include cyproterone acetate (CPA), spironolactone, or GNRHas. Some anti-androgen dosages are aimed at lowering serum testosterone levels toward female reference ranges (CPA, GNRHas), although others (spironolactone) act primarily as a receptor blocker, resulting in a smaller decrease in serum testosterone levels [16].

An important point is that people may be taking nonprescribed hormones; this may include the use of preferred agents for GAHT as well as contraceptive pills obtained from others, which may contain EE. Previous reports stated that 4.7–24% of transgender women have obtained hormones from friends [4–6] and 2–70% have purchased them online [7]. The use of GAHT obtained from nonmedical sources varies among different groups. In a sample of transgender people referred to a gender clinic [7], 23% admitted to using nonprescribed hormones. In community-based samples, this is often higher (26.8–63%) [4–6]. It is important to be aware of this and ask about nonprescribed hormone use in a nonjudgmental way as the use of hormones such as EE or the use of higher doses than recommended may lead to an increased risk for adverse health events.

Physical effects of feminizing GAHT

GAHT with estrogens and anti-androgens will induce the secondary characteristics associated with female puberty. In one study, breast development and gynoid fat deposition have been identified as the most anticipated changes in transgender women [17]. Certain physical aspects are associated with psychological well-being in TGD people, such as hair distribution pattern, breast development, and testis volume [8].

Breast–chest difference will increase within 3 months of starting GAHT [18] and will continue to increase during the first two years of GAHT [8]. Most people will achieve breast development consistent with Tanner stage 3 [8]. Before starting GAHT, body composition already differs between transfeminine people and cisgender men, with transfeminine people having less lean mass and more fat mass than cisgender men [19]. Feminizing GAHT will result in an increase in fat mass and a loss of lean mass [19–21], which is often desired. The body fat distribution changes during the first year of GAHT, with a decrease in waist-to-hip ratio and a more pronounced increase in gynoid fat and leg fat, compared with a less pronounced increase in android fat [20]. This shift in body composition and fat distribution continues during the second year of GAHT [22]. The impact of different

anti-androgen agents on breast development and body composition has not been investigated in studies with a large sample size [23]. One study found no difference in body composition in people on different types of anti-androgen therapy [24]. In addition, higher serum estrone or estrone/estradiol ratio does not reflect reduced changes in body fat or breast growth compared with those with lower serum estrone levels or estrone/estradiol ratios [25]. Therefore, these measurements are not routinely recommended in GAHT management [25].

Compared with transmasculine persons, GAHT in transfeminine people is often less effective in obtaining the desired hair pattern [8], and hair removal is required (laser and electrolysis) in addition to GAHT.

GAHT will lead to a decrease in testis volume, with a 40% and 50% reduction after 1 and 2 years, respectively [8].

Effects of feminizing GAHT on mental health

Because of all the physical changes, GAHT also results in lower scores for depression [8,26], lower subjective levels of gender dysphoria, and lower body uneasiness [8]. In the study by Fisher et al. [8], there was no statistically significant difference between depression scores in transfeminine people with versus without GAHT, although people with GAHT did observe lower levels of body uneasiness. Cross-sectional observations also revealed a higher score for gender dysphoria in transfeminine people with GAHT compared with those without [8]. Note that experiencing more gender dysphoria may also be the reason why some people initiate GAHT, whereas others with less gender dysphoria may not feel the need for GAHT.

Side effects of feminizing GAHT

Cardiovascular and metabolic health—Concern has been raised about a potentially increased cardiovascular risk in transfeminine people [27,28], with a higher number of cardiovascular deaths in TW than expected based on population prevalence [27,28] and an elevated standardized mortality rate for ischemic heart disease (1.64, (95% CI (1.43–1.87)). The majority of cardiovascular deaths occurred in current/former smokers, and the use of EE was associated with cardiovascular mortality [27]. However, there are currently no long-term prospective follow-up studies available with a substantial cohort size in TGD people adhering to current treatment regimens that are adequately powered to assess mortality risk in TGD people. Regarding cardiovascular morbidity, available results were meta-analyzed by Maraka et al. [29]; the risk of myocardial infarction, stroke, or VTE was not increased compared with people without GAHT. Earlier reviews of the literature concluded that the level of evidence was too low to allow an interpretation of morbidity and mortality risk in TGD people [29–31]. Conflicting results among different papers may be due to the differences in the type of GAHT. To date, there are no randomized controlled clinical trials available reporting on cardiovascular mortality, morbidity, and/or risk among different GAHT formulations/doses. In addition, research on cardiovascular mortality, morbidity, and/or risk that takes into account possible confounding factors (e.g., age, lifestyle factors, minority stress, body composition, dietary information, physical

activity, biochemical markers, and geographical location) may improve our understanding of the impact of GAHT on cardiovascular risk.

Because the anti-androgen agents each have a different mechanism of action, their use may also be associated with certain side effects. Spironolactone, a potassium-sparing diuretic, is mainly used as an antihypertensive agent. Side effects may include low blood pressure, higher serum potassium levels, and, in the event of dehydration, impaired renal function [1].

After initiating CPA in transfeminine people, an increase in serum lipid levels has been observed, with decreased serum HDL levels [32,33].

The impact of feminizing GAHT on insulin resistance remains unclear, with some studies reporting increases in insulin resistance [34–39] and others reporting no changes [24].

Sexual function

GAHT affects sexual functioning in transgender people. After starting GAHT, erections (spontaneous, desired, and nocturnal) usually decrease or disappear completely [40]. This may be desired by some, although others may want to maintain the erectile function. However, erections arising as a result of sexual stimulation seem more persistent [41]. Sexual desire usually decreases within 3 months after starting GAHT [42]. Whether or not this is regarded as a negative side effect varies by individual. Wierckx. et al. [42] found that only one in three people considered this distressing. Sexual desire may even increase in transfeminine people over time, reaching levels that are higher than before starting GAHT [43]. The exact mechanism for these findings has not been identified, although reduced gender dysphoria may contribute to better sexual functioning.

Fertility

After the initiation of anti-androgen therapy, reduced levels of serum testosterone will result in erectile dysfunction and reduced testicular volume. Anti-androgen therapy may result in a decrease or even absence of spermatogenesis, depending on the type of anti-androgen agent. Even in transfeminine people who did not start GAHT yet, sperm quality is often lower compared with the World Health Organization (WHO) data for the general population [44], which could be attributed to wearing tight undergarments and a tucking (hiding the penis by pulling it back between the legs) frequency of more than eight times per month. Normal spermatogenesis has been reported in 0–48% of all orchiectomy specimens [45–50]. For example, in people using GAHT with spironolactone, testosterone levels are not completely suppressed. One case report [51] described sperm cryopreservation two months after the cessation of spironolactone therapy and initiation of a regimen with follitropin alfa (a human FSH preparation) and clomiphene citrate. In papers where spermatogenesis has been reported, serum levels of testosterone were not suppressed or not reported [45–50].

It is likely that effectively suppressing serum testosterone levels by anti-androgen therapy may result in suppressed spermatogenesis in the majority of transfeminine people [52], although preliminary research by De Nie et al. [53] described restored spermatogenesis in nine transfeminine people after stopping GAHT (3–27 months after cessation).

Oncological risk

The incidence of certain types of cancers may differ in people on GAHT, particularly hormone-sensitive cancers. Although there have been cohort studies on the incidence of cancer in TGD people, large-scale epidemiological data are limited. Given the lack of specific research on TGD people, it is often advised to review the guidelines for both birth-assigned sex and identified gender and screen according to the most cautious guidelines for which there are tissue- or organ-specific recommendations. Unfortunately, TGD cancer screening rates appear to be lower compared with cisgender people (e.g., cervical cancer at 56% versus 72%, breast cancer at 33% versus 65%, and colorectal cancer at 55% versus 70%, respectively) [54]. It was hypothesized by the authors that lower cancer screening rates in TGD people were due to both patients and HCPs being unaware of how to implement screening guidelines in TGD people [54].

Data from a large retrospective cohort in transfeminine adults with a median duration of 13 years of GAHT [55] revealed lower incidence rates for breast cancer compared with cisgender women (incidence ratio 0.3), although the risk increased after starting GAHT. A retrospective study examining the available medical records on breast biopsies of 2616 transfeminine people reported six lesions described as breast cancer. The benign/malignant biopsy ratio was 88/12, which is comparable to cisgender women (90/10). Therefore, for transfeminine adults, it may be more cautious to follow the screening guidelines for breast cancer in cisgender women.

De Nie et al. [56] investigated prostate cancer risk in transfeminine people and reported a lower incidence compared with cisgender men (standardized incidence ratio 0.2), with six diagnoses out of 2281 transfeminine people with a median follow-up duration of 14 years. They started GAHT at a median age of 47 years, and four people had undergone orchiectomy at a median of 11 years prior to cancer diagnosis. The median age at the time of diagnosis was 64 years old. De Nie et al. [56] suggest a potentially preventative effect of androgen deprivation on the occurrence of prostate cancer.

In a Dutch cohort [57] of 3026 transfeminine people with a median follow-up time of 2.3 years, three testicular cancer cases were identified. In the overall group, follow-up was short because of people undergoing orchiectomy. In the group with a follow-up time of >5 years (n = 523), no testicular cancer was observed. They concluded that testicular cancer risk in transfeminine people is similar to that in cisgender men and that GAHT does not increase the risk as no cases were observed in transfeminine people with a longer follow-up period.

Gender-affirming hormone therapy in transgender women has been associated with meningiomas as well as prolactinomas. Meningiomas occur twice as much in females and are considered hormonally sensitive [58,59]. Fourteen cases of meningiomas in transfeminine people have been described [60]. In the Amsterdam cohort, eight meningiomas and nine prolactinomas were reported in a large cohort of 2810 transfeminine people [61]. The standardized incidence ratios (SIR) were higher than expected compared with population-based incidence numbers (meningioma SIR 4.1 compared with females, SIR 11.9 compared with males, prolactinoma SIR 4.3 compared with females, and SIR 26.5 compared with males) [61]. Meningiomas were predominantly diagnosed in transfeminine

people aged 45 years and older and in those who were taking CPA doses of 50 mg or over for a longer duration (59–477 months). In some cases, people were still taking CPA despite a previous gonadectomy. The increased incidence of meningiomas may be explained by the high expression of progesterone receptors in human meningiomas [62]. This phenomenon has been evaluated in a large retrospective cohort of cisgender women (n = 253 777) and transfeminine people (n = 10 876) [63]. In cisgender women using a cumulative CPA dose of <3 g, the incidence was 0, whereas the risk was 20.7 per 100.000 person-years (PY) (n = 3) in the group with a cumulative dose of >3 g. However, the risk decreased after the discontinuation of treatment. The observed rise in serum prolactin levels after initiation of GAHT in transfeminine people could also be attributed to the use of CPA as multiple studies have shown a differential effect between people taking CPA versus people not taking CPA [24,64,65].

Bone health

Sex steroids affect periosteal and endocortical bone geometry. GAHT alters the hormonal exposure at the level of the bone and plays a key role in bone turnover as well as preserving bone mineral density (BMD) [66]. It is important to include estrogens in the GAHT regimens as the use of anti-androgen therapy alone (e.g., GnRH analog monotherapy) may result in osteoporosis if it is used for a long time without adequately dosed estrogen therapy [67]. In general, prospective cohort studies [19,68,69] have shown an increase in BMD at the total hip and femoral neck, radius, lumbar spine, and total body over the first one to three years of GAHT in transfeminine people. However, cross-sectional studies show lower Z-scores in transfeminine people compared with age-matched cisgender women [69], which may be due to the lower BMD for age in transfeminine people before starting GAHT [70,71], with a diagnosis of low bone mass (Z-score ≤2) in approximately 40% [72]. Factors precipitating low bone mass include having lower serum estradiol levels and low compliance to estrogen treatment [72]. During the first 10 years of GAHT, the Z-score at the lumbar spine increased by +0.34 in a large cohort of transfeminine people (n = 543; median age = 25 years), although there was no change in lumbar spine BMD [71]. Compared to cisgender people, fracture risk is higher in older (>50 years old) transfeminine people, compared to age-matched reference cisgender men (odds ratio 1.9), but not women [73]. In younger transfeminine people, fracture risk is increased compared with age-matched reference cisgender women (odds ratio 1.49), but not men [73].

Masculinizing endocrine care

Masculinizing GAHT consists of testosterone, aimed at inducing virilization. Testosterone therapy causes the voice pitch to drop, the facial and body hair to appear in a male pattern, and the musculature to become bulkier and more pronounced [9]. Testosterone can be prescribed parenterally, trans-dermally, or orally. Parenteral formulations include testosterone esters (e.g., cypionate, enanthate) or undecanoate—subcutaneously (except for testosterone undecanoate) or intramuscularly. Transdermal formulations are testosterone gel or patches. Oral formulations include testosterone capsules [1]. Usually, starting testosterone treatment will result in the cessation of vaginal bleeding. A progestational agent or a GNRHa can be added to the treatment regimen if suppression of vaginal bleeding is desired or if vaginal bleeding does not cease [74].

Physical effects of masculinizing therapy

In the study by Masumori et al. [17], the cessation of vaginal bleeding was the most anticipated change in transmasculine people. Depending on the type of testosterone therapy, amenorrhea can be expected within three to six months (testosterone esters) and three to nine months (testosterone gel or testosterone undecanoate) [74,75]. There was no significant difference in time to amenorrhea in the study by Pelusi et al. [75], although this may be due to the small sample size (n = 45). Defreyne et al. [74] described less severe vaginal bleeding and spotting in people on testosterone undecanoate and testosterone esters compared with those receiving testosterone gel. If vaginal bleeding persisted, starting progestogens at three months resulted in a decrease in the intensity of vaginal bleeding and spotting [74].

Increasing body mass index (BMI) is related to reduced body uneasiness in transmasculine people [8]. Body composition will change within three months of starting testosterone therapy [76], and lean mass will continue to increase as fat mass decreases over the next year [20,76,77]. However, although overall fat mass decreases, visceral fat mass increases [35,78] up to 47% of the relative amount of weight gain. Overall, waist-to-hip ratio (and android-to-gynoid fat ratio) will increase [20]. After a mean duration of 10 years of testosterone therapy, lean mass remained higher in transmasculine people compared with age-matched cisgender female controls [79].

A male pattern of facial and body hair growth is associated with lower levels of subjective gender dysphoria in transmasculine people [8]. Hair growth can already increase during the first three months of testosterone therapy, and by 6 months, half of the transmasculine population in the paper by Wierckx et al. [80] had Ferriman–Gallwey (FG) scores of eight or more (a score corresponding with hirsutism in females). In the paper by Fisher et al. [8], more than 90% of the participants had an FG score of eight or over. This difference may be due to different patterns of hair growth and distribution in the Belgian versus Italian population. After 12 months, the majority of the Belgian population (80%) had scores above eight. However, they did notice a very wide inter-individual variability.

Clitoral growth is often reported, with an increase of 60% after only 3 months of testosterone therapy. The increase continues during the first two years [8].

Effects of masculinizing therapy on mental health

As in transfeminine people, GAHT in transmasculine people also results in lower scores for depression [8,26], lower subjective levels of gender dysphoria, and body uneasiness [8]. Cross-sectionally, people with GAHT versus those without GAHT had less depressive symptoms, lower levels of body uneasiness, and less gender dysphoria [8].

Side effects

Cardiovascular and metabolic health—The use of testosterone in TGD people has been linked to increased adverse cardiovascular risk and events (e.g., myocardial infarction, higher blood pressure, altered serum lipid levels, and weight gain) [81–83].

An increase in serum hemoglobin and hematocrit levels has been observed in transmasculine people during the first year of GAHT, with the most pronounced increase during the first 3 months [37,42,75,84–95]. Usually, hematocrit levels do not change after the first twelve months of GAHT [87,89–92]. Clinically significant erythrocytosis is rare [21,86,89–91], and the increase in hematocrit and hemoglobin level is generally toward cisgender male reference ranges [21,37,42,75,84–95].

Results on the impact of testosterone therapy on the development of insulin resistance are conflicting [24,34–39,75,96]. One could argue that an increase in fat mass may be responsible for changes in insulin resistance. However, a recent prospective cohort study showed no correlation between HOMA-IR and changes in visceral or total body fat mass [97].

Undesired physical effects

Testosterone therapy often leads to an increase in facial and back/chest acne [80], with up to 88% of transmasculine people experiencing acne after 6 months of treatment. The majority only had mild or moderate acne lesions. The incidence of acne tends to decrease, with only 63% experiencing mild lesions after 5 years of testosterone therapy in the study by Wierckx et al. [80]. There was no association between more severe acne and higher testosterone levels [80]. Younger people may experience more acne lesions [80]. If necessary, topical products (e.g., benzoyl peroxide gel, adapalene gel, or over-the-counter products) can be used. In more severe cases or if the acne causes distress, oral antibiotics or topical tretinoin can be prescribed. If necessary, people can be referred to a dermatologist for treatment.

Male pattern baldness may also occur in those susceptible to androgenic hair loss (1/3 experienced mild alopecia, 1/3 moderate to severe alopecia, 1/3 experienced no alopecia), and it is more common with increasing age [80]. If desired, finasteride 1 mg orally daily can be added to the treatment regimen, resulting in an improvement of one grade on the Norwood-Hamilton scale after 5.5 months of treatment (range 4–6 months) [98].

Sexual function

Testosterone treatment usually results in increased sexual desire and, for some, improved sexual satisfaction [99]. In several studies, testosterone therapy in transmasculine people was associated with an increased sexual desire [42,43,87,100]. Sexual desire after starting GAHT is often described as more urgent, more frequent, and less controllable [87,100]. However, it is possible that sexual desire may return to levels comparable to before starting GAHT after at least three years of testosterone therapy [43]. No association has been reported between sexual desire and total or free testosterone levels [42,43]. Some people may fear hypersexuality because of testosterone therapy, although only 3.6% reported a level of increased sexual desire that caused personal or relational distress [42].

Fertility

The effect of testosterone therapy on fertility in transmasculine people has not been completely determined. Although testosterone therapy will usually lead to the cessation of vaginal bleeding over time [74], there have been cohorts of transgender people becoming

pregnant shortly after stopping testosterone therapy [101]. It has been hypothesized that testosterone therapy may lead to polycystic ovarian morphology, and therefore, transmasculine people should proceed with fertility preservation before initiating GAHT. Grynberg et al. [102] reported polycystic ovarian morphology with stromal hyperplasia, enlarged ovaries, and increased ovarian follicles in pathology specimens obtained from transmasculine people who underwent gonadectomy. In contrast, De Roo et al. [103] reported no change in the distribution or number of ovarian follicles after more than one year of testosterone therapy.

Transmasculine people who want to preserve gametes after starting testosterone treatment can be reassured. In the study by Leung et al. [104], after the cessation of testosterone therapy, the average time off testosterone treatment before the occurrence of a menstrual cycle was 4 months. Twenty-six people completed 29 cycles (mean 1.1 per person) [104], and a mean of 20 oocytes was retrieved per cycle. Several studies described a higher number of oocytes being retrieved in transmasculine people compared with cisgender people [104,105], although transmasculine people often require a higher dose of gonadotropins for cycle stimulation [104,105]. An important point is that the participants in the study by Leung et al. [104] were quite young (age range 14–39 years old).

There are currently no guidelines specifying the duration of interruption of GAHT before one can safely start ovarian stimulation, and, theoretically, there could be virilization of the female fetus in the case of pregnancy shortly after stimulation. However, stopping testosterone therapy for several months may also lead to physical changes such as fatigue, feminization of the voice, and menstrual bleeding, which may induce more gender dysphoria [106].

Oncological risk

Concerns have been raised in the past about the effects of prolonged testosterone use on the incidence of gynecological cancers in transmasculine people, and there is currently no consensus on how to screen transmasculine people for gynecological cancers. Concern has been raised that exogenous testosterone may lead to increased estradiol levels [107]. With the removal of the need for sterilization to change the legal gender marker in the legislation of several countries, more people are not proceeding with gonadectomy. In addition, a lack of insurance to cover the costs of gonadectomy and availability of affirming surgeons may also lead to people not proceeding with gonadectomy. In the 2015 U S. Transgender Survey [108], 14% of the transmasculine people underwent gonadectomy and 71% initiated testosterone therapy.

In a retrospective cohort study including 81 transmasculine persons (median age 31 years old) receiving testosterone therapy (median duration 4 years) who underwent hysterectomy, no cases of endometrial hyperplasia or malignancy were reported [109]. Only one case of endometrial cancer in a transgender man has been reported [110], while there are several cases of ovarian cancer [102,111,112] and breast cancer [113–126]. The HPV prevalence in self-collected vaginal swabs of transmasculine people (16%) also appears comparable to the prevalence in cisgender women [127]. The risk of cervical cancer may be higher in transmasculine people because of a lower number of people accessing screening programs

[128]. In addition, testosterone therapy may lead to tissue epithelial atrophy and shrinkage in the genital tract, which may cause discomfort and pain upon speculum insertion and cervical screening [129]. If atrophy is present, Weyers et al. [129] suggest vaginal application of estriol or estradiol for 1–2 months before undergoing a PAP test. Studies on oncological risk in TGD people after the initiation of testosterone therapy remain inconclusive and lack power [27,28,118,121,124,130–132]. Therefore, it is advised to adhere to the screening protocols for the general population, depending on the tissues present [9]. In addition, not all TGD adults have the ability or need to receive routine medical care from a specialized TGD health clinic. All HCPs involved in primary care and gynecological and gender-affirming care should have some knowledge about the need for screening TGD people [133].

Bone health

Several prospective cohort studies [68,77] have reported an increase in BMD after initiating testosterone therapy, although one prospective study [134] reported no difference in BMD after one year of testosterone therapy. The increase was measured at the total hip, lumbar spine, and femoral neck during the first year [68]. In addition, Van Caenegem et al. [77] described a small increase in trabecular BMD at the distal radius over the first year of GAHT in a group of 23 transmasculine people. The increase in trabecular BMD may be caused by the aromatization of testosterone to estrogen as well as a testosterone-mediated increase in muscle mass, leading to higher bone remodeling due to strain on the bone. Note that Wiepjes et al. [68] described a larger increase in BMD at the lumbar spine in people aged >50 years compared with those aged <50 years old. Bone turnover markers (procollagen type I N-terminal propeptide (P1NP), alkaline phosphatase, and sclerostin) increased during the first year of GAHT but decreased in transmasculine people over 50 years old. This could be explained by an estrogen-deficient state in older transmasculine people initiating GAHT, with a positive prospective effect of an increase in serum testosterone levels on the bone [135]. It is hypothesized that the aromatization of the testosterone therapy resulted in decreased bone resorption. However, during a ten-year follow-up period (n = 543; median age 25 years old) [71], no changes in lumbar spine BMD were noted, although the Z-score increased by +0.34. These findings were confirmed in another study by Wiepjes et al. [136], where the bone geometry did not change after 5, 15, or 25 years of GAHT. Whether changes in BMD result in hard endpoints (e.g., fracture risk) was assessed by Wiepjes et al. [73], who found no increase in fracture risk in transmasculine people in the Amsterdam cohort after a median duration of 9 years of GAHT.

Conclusion

The number of people coming out as TGD and seeking gender-affirming care has increased over the past few years [137]. This inevitably results in a higher need for HCPs familiar with transgender care. However, many physicians do not feel comfortable getting involved in transgender care out of fear of inducing adverse effects related to the gender-affirming care provided [138]. The currently available guidelines [1,9,10] can assist HCPs who want to get involved in the care of TGD people. In this population, providing gender-affirming care not only results in physical changes but also reduces co-occurring psychopathology [8,139,140]. As stated earlier, the use of gender-affirming hormones without HCP supervision can lead to

adverse events. Therefore, we aim to inform HCPs about the provision of safe, effective, and lifesaving gender-affirming endocrine care.

References

[1]*. Coleman E, Radix AE, Bouman WP, Brown GR, De Vries ALC, Deutsch MB, et al. Standards of care for the health of transgender and gender diverse people, version 8. Int J Transgender Heal 2022. S1:1–259.

[2]*. Tangpricha V, den Heijer M. Oestrogen and anti-androgen therapy for transgender women. Lancet Diabetes Endocrinol 2017;5(4):291–300. [PubMed: 27916515]

[3]*. Safer JD, Tangpricha V. Care of the transgender patient. Ann Intern Med 2019;171(1):ITC1–16. [PubMed: 31261405]

[4]. Van Schuylenbergh J, Motmans J, Defreyne J, Somers A, T'Sjoen G. Sexual health, transition-related risk behavior and need for health care among transgender sex workers. Int J Transgenderism 2019;20(4):388–402.

[5]. Rotondi NK, Bauer GR, Scanlon K, Kaay M, Travers R, Travers A. Nonprescribed hormone use and self-performed surgeries: "do-it-yourself" transitions in transgender communities in Ontario, Canada. Am J Publ Health 2013; 103(10):1830–6.

[6]. Sanchez NF, Sanchez JP, Danoff A. Health care utilization, barriers to care, and hormone usage among male-to-female transgender persons in New York City. Am J Publ Health 2009;99(4):713–9.

[7]. Mepham N, Bouman WP, Arcelus J, Hayter M, Wylie KR. People with gender dysphoria who self-prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. J Sex Med 2014;11(12):2995–3001. [PubMed: 25213018]

[8]*. Fisher AD, Castellini G, Ristori J, Casale H, Cassioli E, Sensi C, et al. Cross-sex hormone treatment and psychobiological changes in transsexual persons: two-year follow-up data. J Clin Endocrinol Metab 2016 Nov 1;101(11):4260–9. [PubMed: 27700538]

[9]*. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2017;11(102):3869–903.

[10]*. T'Sjoen G, Arcelus J, De Vries ALC, Fisher AD, Nieder TO, Özer M, et al. European society for sexual medicine position statement "assessment and hormonal management in adolescent and adult trans people, with attention for sexual function and satisfaction. J Sex Med 2020;17(4):570–84. [PubMed: 32111534]

[11]. Rothman MS, Iwamoto SJ. Feminizing gender-affirming hormone therapy: special considerations for older adults. In: A Case-Based Guide to Clinical Endocrinology. Springer; 2022. p. 513–23.

[12]*. Wiepjes CM, de Blok CJM, Staphorsius AS, Nota NM, Vlot MC, de Jongh RT, et al. Fracture risk in trans women and trans men using long-term gender-affirming hormonal treatment: a nationwide cohort study. J Bone Miner Res 2020;35(1):64–70. [PubMed: 31487065]

[13]. Iwamoto SJ, T'Sjoen G, Safer JD, Davidge-Pitts CJ, Wierman ME, Glodowski MB, et al. Letter to the Editor:"Progesterone is important for transgender women's therapy–applying evidence for the benefits of progesterone in ciswomen. J Clin Endocrinol Metab 2019;104(8):3127–8. [PubMed: 30860591]

[14]. Pyra M, Casimiro I, Rusie L, Ross N, Blum C, Keglovitz Baker K, … & Schneider J (2020). An observational study of hypertension and thromboembolism among transgender patients using gender-affirming hormone therapy. Transgender Health, 5(1), 1–9. [PubMed: 32322683]

[15]. Goldstein Z, Khan M, Reisman T, Safer JD. Managing the risk of venous thromboembolism in transgender adults undergoing hormone therapy. J Blood Med 2019;10:209. [PubMed: 31372078]

[16]. Angus L, Leemaqz S, Ooi O, Cundill P, Silberstein N, Locke P, et al. Cyproterone acetate or spironolactone in lowering testosterone concentrations for transgender individuals receiving oestradiol therapy. Endocr Connect 2019;8(7): 935–40. [PubMed: 31234145]

[17]. Masumori N, Baba T, Abe T, Niwa K. What is the most anticipated change induced by treatment using gender-affirming hormones in individuals with gender incongruence? Int J Urol 2021;28(5):526–9. [PubMed: 33465834]

[18]. de Blok CJM, Klaver M, Wiepjes CM, Nota NM, Heijboer AC, Fisher AD, et al. Breast development in transwomen after one year of cross-sex hormone therapy: results of A prospective multicenter study. J Clin Endocrinol Metab 2017; 103(2):532–8.

[19]. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, et al. Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study. Osteoporos Int 2014;26:35–47. [PubMed: 25377496]

[20]. Klaver M, de Blok C, Wiepjes C, Nota NM, Dekker MJHJ, de Mutsert R, et al. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. Eur J Endocrinol 2017;178(2):163–71. [PubMed: 29183889]

[21]. Wierckx K, Van Caenegem E, Schreiner T, Haraldsen I, Fisher A, Toye K, et al. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. J Sex Med 2014;11(8):1999–2011. [PubMed: 24828032]

[22]. Mueller A, Zollver H, Kronawitter D, Oppelt PG, Claassen T, Hoffmann I, et al. Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone agonist. Exp Clin Endocrinol Diabetes 2011;119(2):95–100. [PubMed: 20625973]

[23]. Angus LM, Nolan BJ, Zajac JD, Cheung AS. A systematic review of antiandrogens and feminization in transgender women. Clin Endocrinol (Oxf). 2021;94(5):743–52. [PubMed: 32926454]

[24]. Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggiola MC. Cyproterone acetate versus leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. Clin Endocrinol (Oxf). 2016;85:239–46. [PubMed: 26932202]

[25]. Tebbens M, Heijboer AC, T'Sjoen G, Bisschop PH, den Heijer M. The role of estrone in feminizing hormone treatment. J Clin Endocrinol Metab 2022;107(2):e458–66. [PubMed: 34632510]

[26]. Aldridge Z, Patel S, Guo B, Nixon E, Pierre Bouman W, Witcomb GL, et al. Long-term effect of gender-affirming hormone treatment on depression and anxiety symptoms in transgender people: a prospective cohort study. Andrology 2021;9(6):1808–16. [PubMed: 32777129]

[27]. Asscheman H, Giltay EJ, Megens JAJ, van Trotsenburg MAA, Gooren LJG. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 2011;164(4):635–42. [PubMed: 21266549]

[28]. Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Langstrom N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 2011;6(2):e16885. [PubMed: 21364939]

[29]*. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, Davidge-Pitts CJ, Nippoldt TB, Prokop LJ, et al. Sex steroids and cardiovascular outcomes in transgender individuals: a systematic review and meta-analysis. J Clin Endocrinol Metab 2017;102(11):3914–23. [PubMed: 28945852]

[30]. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clin Endocrinol (Oxf). 2010;72(1):1–10. [PubMed: 19473174]

[31]. Gooren LJG, Giltay EJ. Review of studies of androgen treatment of female-to-male transsexuals: effects and risks of administration of androgens to females. J Sex Med 2008;5(4):765–76. [PubMed: 17971101]

[32]. Fung R, Hellstern-Layefsky M, Tastenhoye C, Lega I, Steele L. Differential effects of cyproterone acetate vs spironolactone on serum high-density lipoprotein and prolactin concentrations in the hormonal treatment of transgender women. J Sex Med 2016;13(11):1765–72. [PubMed: 27693265]

[33]. Sofer Y, Yaish I, Yaron M, Bach MY, Stern N, Greenman Y. Differential endocrine and metabolic effects of testosterone suppressive agents in transgender women. Endocr Pract 2020;26(8):883–90. [PubMed: 33471679]

[34]. Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ. Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 1994;79(1):265–71. [PubMed: 8027240]

[35]. Elbers JMH, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, et al. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin Endocrinol (Oxf) 2003;58(5):562–71. [PubMed: 12699437]

[36]. Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, et al. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. J Psychosom Res 2015;78(4):399–406. [PubMed: 25691225]

[37]. Auer MK, Cecil A, Roepke Y, Bultynck C, Pas C, Fuss J, et al. 12-months metabolic changes among gender dysphoric individuals under cross-sex hormone treatment: a targeted metabolomics study. Sci Rep 2016;6:37005. [PubMed: 27833161]

[38]. Auer MK, Ebert T, Pietzner M, Defreyne J, Fuss J, Stalla GK, et al. Effects of sex hormone treatment on the metabolic syndrome in transgender individuals: focus on metabolic cytokines. J Clin Endocrinol Metab 2018;103(2):790–802. [PubMed: 29216353]

[39]. Shadid S, Abosi-Appeadu K, De Maertelaere A-S, Defreyne J, Veldeman L, Holst JJ, et al. Effects of gender-affirming hormone therapy on insulin sensitivity and incretin responses in transgender people. Diabetes Care 2020;43(2).

[40]. Bartolucci C, Gómez-Gil E, Salamero M, Esteva I, Guillamón A, Zubiaurre L, et al. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. J Sex Med 2015;12(1):180–8. [PubMed: 25401972]

[41]. Bettocchi C, Palumbo F, Cormio L, Ditonno P, Battaglia M, Selvaggi FP. The effects of androgen depletion on human erectile function: a prospective study in male-to-female transsexuals. Int J Impot Res 2004;16(6):544–6. [PubMed: 15175636]

[42]. Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, et al. Sexual desire in trans persons: associations with sex reassignment treatment. J Sex Med 2014;11(1):107–18. [PubMed: 24165564]

[43]. Defreyne J, Elaut E, Kreukels B, Fisher AD, Castellini G, Staphorsius A, et al. Sexual desire changes in transgender individuals upon initiation of hormone treatment: results from the longitudinal European network for the investigation of gender incongruence. J Sex Med 2020;17(4).

[44]. De Nie I, Meißner A, Kostelijk EH, Soufan AT, Voorn-de Warem, den Heijer M, et al. Impaired semen quality in trans women: prevalence and determinants. Human Reprod 2020;35(7):1529–36.

[45]. Schneider F, Neuhaus N, Wistuba J, Zitzmann M, Heß J, Mahler D, et al. Testicular functions and clinical characterization of patients with gender dysphoria (GD) undergoing sex reassignment surgery (SRS). J Sex Med 2015;12(11): 2190–200. [PubMed: 26559385]

[46]. Sirachai Jindarak, Kasama Nilprapha, Taywin Atikankul, Apichai Angspatt, Pornthep Pungrasmi, Seree Iamphongsai, et al. Spermatogenesis abnormalities following hormonal therapy in transwomen. BioMed Res Int 2018;2018:1–5.

[47]. Leavy M, Trottmann M, Liedl B, Reese S, Stief C, Freitag B, et al. Effects of elevated β-estradiol levels on the functional morphology of the testis-new insights. Sci Rep 2017;7:39931. [PubMed: 28045098]

[48]. Matoso A, Khandakar B, Yuan S, Wu T, Wang LJ, Lombardo KA, et al. Spectrum of findings in orchiectomy specimens of persons undergoing gender confirmation surgery. Hum Pathol 2018;76:91–9. [PubMed: 29555572]

[49]. Adeleye AJ, Reid G, Kao CN, Mok-Lin E, Smith JF. Semen parameters among transgender women with a history of hormonal treatment. Urology 2019;124:136–41. [PubMed: 30312673]

[50]. Jiang DD, Swenson E, Mason M, Turner KR, Dugi DD, Hedges JC, et al. Effects of estrogen on spermatogenesis in transgender women. Urology 2019;132:117–22. [PubMed: 31310772]

[51]. Alford AV, Theisen K, Kim N, Bodie J, Pariser J. Successful ejaculatory sperm cryopreservation after cessation of long-term estrogen therapy in a transgender female. Urology 2019;136:e48–50. [PubMed: 31465795]

[52]. Vereecke G, Defreyne J, Van Saen D, Collet S, Van Dorpe J, T'Sjoen G, et al. Characterisation of testicular function and spermatogenesis in transgender women. Hum Reprod 2021;36(1):5–15. [PubMed: 33257947]

[53]. de Nie I Andrological care in transgender women: Perspectives for (new) life after transition. 2022.

[54]. Kiran T, Davie S, Singh D, Hranilovic S, Pinto AD, Abramovich A, et al. Cancer screening rates among transgender adults: cross-sectional analysis of primary care data. Can Fam Physician 2019;65(1):e30–7. [PubMed: 30674526]

[55]. De Blok CJM, Wiepjes CM, Nota NM, Van Engelen K, Adank MA, Dreijerink KMA, et al. Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in The Netherlands. BMJ 2019;365:1652.

[56]. de Nie I, de Blok CJM, van der Sluis TM, Barbé E, Pigot GLS, Wiepjes CM, et al. Prostate cancer incidence under androgen deprivation: nationwide cohort study in trans women receiving hormone treatment. J Clin Endocrinol Metab 2020;105(9):e3293–9. [PubMed: 32594155]

[57]. de Nie I, Wiepjes CM, de Blok CJM, van Moorselaar RJA, Pigot GLS, van der Sluis TM, et al. Incidence of testicular cancer in trans women using gender-affirming hormonal treatment: a nationwide cohort study. BJU Int 2022;129(4):491–7. [PubMed: 34390620]

[58]. Mindermann T, Wilson CB. Age-related and gender-related occurrence of pituitary adenomas. Clin Endocrinol (Oxf). 1994;41:359–64. [PubMed: 7893282]

[59]. Mancini I, Rotilio A, Coati I, Seracchioli R, Martelli V, Meriggiola MC. Presentation of a meningioma in a transwoman after nine years of cyproterone acetate and estradiol intake: case report and literature review. Gynecol Endocrinol 2018;34(6):456–9. [PubMed: 29105524]

[60]. Ter Wengel PV, Martin E, Gooren L, Den Heijer M, Peerdeman SM. Meningiomas in three male-to-female transgender subjects using oestrogens/progestogens and review of the literature. Andrologia 2016;48(10):1130–. [PubMed: 26888610]

[61]. Nota NM, Wiepjes CM, De Blok CJM, Gooren LJG, Peerdeman SM, Kreukels BPC, et al. The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. Brain 2018;141(7):2047–54. [PubMed: 29688280]

[62]. Gil M, Oliva B, Timoner J, Maciá MA, Bryant V, de Abajo FJ. Risk of meningioma among users of high doses of cyproterone acetate as compared with the general population: evidence from a population-based cohort study. Br J Clin Pharmacol 2011;72:965–8. [PubMed: 21627676]

[63]. Weill A, Nguyen P, Labidi M, Cadier B, Passeri T, Duranteau L, et al. Use of high dose cyproterone acetate and risk of intracranial meningioma in women: cohort study. bmj 2021:372.

[64]. Defreyne J, Nota N, Pereira C, Schreiner T, Fisher AD, den Heijer M, et al. Transient elevated serum prolactin in Trans women is caused by cyproterone acetate treatment. LGBT Heal 2017.

[65]. Nota NM, Dekker MJHJ, Klaver M, Wiepjes CM, van Trotsenburg MA, Heijboer AC, et al. Prolactin levels during short- and long-term cross-sex hormone treatment: an observational study in transgender persons. Andrologia 2017;49(6): e12666.

[66]. Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 2017;95:11–9. [PubMed: 27845262]

[67]. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J Clin Endocrinol Metab 2015;100(2):E270–5. [PubMed: 25427144]

[68]. Wiepjes CM, Vlot MC, Klaver M, Nota NM, de Blok CJM, de Jongh RT, et al. Bone mineral density increases in trans persons after 1 Year of hormonal treatment: a multicenter prospective observational study. J Bone Miner Res 2017; 32(6):1252–60. [PubMed: 28370342]

[69]. Gava G, Mancini I, Alvisi S, Seracchioli R, Meriggiola MC. A comparison of 5-year administration of cyproterone acetate or leuprolide acetate in combination with estradiol in transwomen. Eur J Endocrinol 2020;183(6):561–9. [PubMed: 33055297]

[70]. Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman JM, et al. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. Bone 2013;54:92–7. [PubMed: 23369987]

[71]*. Wiepjes CM, de Jongh RT, de Blok CJM, Vlot MC, Lips P, Twisk JWR, et al. Bone safety during the first ten years of gender-affirming hormonal treatment in transwomen and transmen. J Bone Miner Res 2019;34:447–54. [PubMed: 30537188]

[72]. Motta G, Marinelli L, Barale M, Brustio PR, Manieri C, Ghigo E, et al. Fracture risk assessment in an Italian group of transgender women after gender-confirming surgery. J Bone Miner Metabol 2020;38(6):885–93.

[73]*. Wiepjes CM, de Blok CJM, Staphorsius AS, Nota NM, Vlot MC, de Jongh RT, et al. Fracture risk in trans women and trans men using long-term gender-affirming hormonal treatment: a nationwide cohort study. J Bone Miner Res 2019;35(1): 64–70. [PubMed: 31487065]

[74]. Defreyne J, Vanwonterghem Y, Collet S, Iwamoto SJ, Wiepjes CM, Fisher AD, et al. Vaginal bleeding and spotting in transgender men after initiation of testosterone therapy: A prospective cohort study (ENIGI). Int J Transgender Health 2020;21(2):163–75.

[75]. Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, et al. Effects of three different testosterone formulations in female-to-male transsexual persons. J Sex Med 2014;11(12):3002–11. [PubMed: 25250780]

[76]. Haraldsen IR, Haug E, Falch J, Egeland T, Opjordsmoen S. Cross-sex pattern of bone mineral density in early onset gender identity disorder. Horm Behav 2007;52(3):334–43. [PubMed: 17604029]

[77]. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, et al. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). Eur J Endocrinol 2015;172(2):163–71. [PubMed: 25550352]

[78]. Elbers JMH, Asscheman H, Seidell JC, Megens JAJ, Gooren LJG. Long-term testosterone administration increases visceral fat in female to male transsexuals. J Clin Endocrinol Metab 1997;82(7):2044–7. [PubMed: 9215270]

[79]. Van Caenegem E, Wierckx K, Taes Y, Dedecker D, Van de Peer F, Toye K, et al. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. J Clin Endocrinol Metab 2012;97(7):2503–11. [PubMed: 22564669]

[80]. Wierckx K, Van de Peer F, Verhaeghe E, Dedecker D, Van Caenegem E, Toye K, et al. Short-and long-term clinical skin effects of testosterone treatment in trans men. J Sex Med 2014;11(1):222–9. [PubMed: 24344810]

[81]. Irwig MS. Cardiovascular health in transgender people. Rev Endocr Metab Disord 2018;19(3):243–51. [PubMed: 30073551]

[82]. Alzahrani T, Nguyen T, Ryan A, Dwairy A, McCaffrey J, Yunus R, et al. Cardiovascular disease risk factors and myocardial infarction in the transgender population. Circ Cardiovasc Qual Outcomes 2019;12(4):e00559.

[83]. Kyinn M, Banks K, Leemaqz SY, Sarkodie E, Goldstein D, Irwig MS. Weight gain and obesity rates in transgender and gender-diverse adults before and during hormone therapy. Int J Obes 2021;45(12):2562–9.

[84]. Emi Y, Adachi M, Sasaki A, Nakamura Y, Nakatsuka M. Increased arterial stiffness in female-to-male transsexuals treated with androgen. J Obstet Gynaecol Res 2008;34(5):890–7. [PubMed: 18834347]

[85]. Fernandez JD, Tannock LR. Metabolic effects of hormone therapy in transgender patients. Endocr Pract 2015;22(4): 383–8. [PubMed: 26574790]

[86]. Jacobeit JW, Gooren LJ, Schulte HM. ENDOCRINOLOGY: long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. J Sex Med 2007;4(5):1479–84. [PubMed: 17635694]

[87]. Costantino A, Cerpolini S, Alvisi S, Morselli PG, Venturoli S, Meriggiola MC. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. J Sex Marital Ther 2013;39(4):321–35. [PubMed: 23470169]

[88]. Vita R, Settineri S, Liotta M, Benvenga S, Trimarchi F. Changes in hormonal and metabolic parameters in transgender subjects on cross-sex hormone therapy: a cohort study. Maturitas 2018;107:92–6. [PubMed: 29169588]

[89]. Defreyne J, Vantomme B, Van Caenegem E, Wierckx K, De Blok CJM, Klaver M, et al. Prospective evaluation of hematocrit in gender-affirming hormone treatment: results from European Network for the Investigation of Gender Incongruence. Andrology 2018;6(3):446–54. [PubMed: 29602229]

[90]. Velho I, Fighera TM, Ziegelmann PK, Spritzer PM. Effects of testosterone therapy on BMI, blood pressure, and laboratory profile of transgender men: a systematic review. Andrology 2017;5(5):881–8. [PubMed: 28709177]

[91]. Jacobeit JW, Gooren LJ, Schulte HM. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. Eur J Endocrinol 2009;161(5): 795–8. [PubMed: 19749027]

[92]. Mueller A, Haeberle L, Zollver H, Claassen T, Kronawitter D, Oppelt PG, et al. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. J Sex Med 2010;7(9): 3190–8. [PubMed: 20584125]

[93]. Schlatterer K, Yassouridis A, Von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. Arch Sex Behav 1998;27(5): 475–92. [PubMed: 9795728]

[94]. Jarin J, Pine-Twaddell E, Trotman G, Stevens J, Conard LA, Tefera E, et al. Cross-sex hormones and metabolic parameters in adolescents with gender dysphoria. Pediatrics 2017;139(5):e20163173. [PubMed: 28557738]

[95]. Olson-Kennedy J, Okonta V, Clark LF, Belzer M. Physiologic response to gender-affirming hormones among transgender youth. J Adolesc Heal 2017;62(4):397–401.

[96]. Berra M, Armillotta F, D'emidio L, Costantino A, Martorana G, Pelusi G, et al. Testosterone decreases adiponectin levels in female to male transsexuals. Asian J Androl 2006;8(6):725–9. [PubMed: 16855767]

[97]. Klaver M, van Velzen D, de Blok C, Nota N, Wiepjes C, Defreyne J, et al. Change in visceral fat and total body fat and the effect on cardiometabolic risk factors during transgender hormone therapy. J Clin Endocrinol Metab 2022;107(1): e153–64. [PubMed: 34415999]

[98]. Moreno-Arrones OM, Becerra A, Vano-Galvan S. Therapeutic experience with oral finasteride for androgenetic alopecia in female-to-male transgender patients. Clin Exp Dermatol 2017;42(7):743–8. [PubMed: 28691187]

[99]*. Holmberg M, Arver S, Dhejne C. Supporting sexuality and improving sexual function in transgender persons. Nat Rev Urol 2019;16(2):121–39. [PubMed: 30375495]

[100]. Bockting W, Benner A, Coleman E. Gay and bisexual identity development among female-to-male transsexuals in North America: emergence of a transgender sexuality. Arch Sex Behav 2009;38(5):688–701. [PubMed: 19330439]

[101]. Light AD, Obedin-Maliver J, Sevelius JM, Kerns JL. Transgender men who experienced pregnancy after female-to-male gender transitioning. Obstet Gynecol 2014;124(6):1120–7. [PubMed: 25415163]

[102]. Grynberg M, Fanchin R, Dubost G, Colau J-C, Brémont-Weil C, Frydman R, et al. Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population. Reprod Biomed Online 2010;20(4):553–8. [PubMed: 20122869]

[103]. De Roo C, Lierman S, Tilleman K, Peynshaert K, Braeckmans K, Caanen M, et al. Ovarian tissue cryopreservation in female-to-male transgender people: insights into ovarian histology and physiology after prolonged androgen treatment. Reprod Biomed Online 2017;34(6):557–66. [PubMed: 28372892]

[104]. Leung A, Sakkas D, Pang S, Thornton K, Resetkova N. Assisted reproductive technology outcomes in female-to-male transgender patients compared with cisgender patients: a new frontier in reproductive medicine. Fertil Steril 2019; 112(5):858–65. [PubMed: 31594633]

[105]. Adeleye AJ, Cedars MI, Smith J, Mok-Lin E. Ovarian stimulation for fertility preservation or family building in a cohort of transgender men. J Assist Reprod Genet 2019;36(10):2155–61. [PubMed: 31435820]

[106]. Cho K, Harjee R, Roberts J, Dunne C. Fertility preservation in a transgender man without prolonged discontinuation of testosterone: a case report and literature review. F&S Reports 2020;1(1):43–7. [PubMed: 34223211]

[107]. van Trotsenburg MA. Gynecological aspects of transgender healthcare. Int J Transgenderism 2009;11(4):238–46.

[108]. James S, Herman J, Rankin S, Keisling M, Mottet L, Anafi M. The report of the 2015 US transgender survey. 2016.

[109]. Hawkins M, Deutsch MB, Obedin-Maliver J, Stark B, Grubman J, Jacoby A, et al. Endometrial findings among transgender and gender nonbinary people using testosterone at the time of gender-affirming hysterectomy. Fertil Steril 2021;115(5):1312–7. [PubMed: 33583596]

[110]. Urban RR, Teng NNH, Kapp DS. Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance. Am J Obstet Gynecol 2011;204(5):e9–12. [PubMed: 21354550]

[111]. Dizon DS, Tejada-Berges T, Koelliker S, Steinhoff M, Granai CO. Ovarian cancer associated with testosterone supplementation in a female-to-male transsexual patient. Gynecol Obstet Invest 2006;62(4):226–8. [PubMed: 16804313]

[112]. Hage JJ, Dekker J, Karim RB, Verheijen RHM, Bloemena E. Ovarian cancer in female-to-male transsexuals: report of two cases. Gynecol Oncol 2000;76(3):413–5. [PubMed: 10684720]

[113]. Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. Clin Breast Cancer 2011;11(6):417–9. [PubMed: 21831723]

[114]. Nikolic DV, Djordjevic ML, Granic M, Nikolic AT, Stanimirovic VV, Zdravkovic D, et al. Importance of revealing a rare case of breast cancer in a female to male transsexual after bilateral mastectomy. World J Surg Oncol 2012;10(1):280. [PubMed: 23273269]

[115]. Eismann J, Heng YJ, Fleischmann-Rose K, Tobias AM, Phillips J, Wulf GM, et al. Interdisciplinary management of transgender individuals at risk for breast cancer: case reports and review of the literature. Clin Breast Cancer 2019; 19(1):e12–9. [PubMed: 30527351]

[116]. Nadia Barghouthi, Jennifer Turner, Jessica Perini. Breast cancer development in a transgender male receiving testosterone therapy. Case Rep Endocrinol 2018:1–3.

[117]. Chotai N, Tang S, Lim H, Lu S. Breast cancer in a female to male transgender patient 20 years post-mastectomy: Issues to consider. Breast J 2019;25(6):1066–70. [PubMed: 31273889]

[118]. Jacoby A, Rifkin W, Zhao LC, Bluebond-Langner R. Incidence of cancer and premalignant lesions in surgical specimens of transgender patients. Plast Reconstr Surg 2021;147(1):194–8. [PubMed: 33370065]

[119]. Katayama Y, Motoki T, Watanabe S, Miho S, Kimata Y, Matsuoka J, et al. A very rare case of breast cancer in a female-to-male transsexual. Breast Cancer 2016;23(6):939–44. [PubMed: 26660332]

[120]. Gooren LJ, van Trotsenburg MAA, Giltay EJ, van Diest PJ. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. J Sex Med 2013;10(12):3129–34. [PubMed: 24010586]

[121]. Gooren L, Bowers M, Lips P, Konings IR. Five new cases of breast cancer in transsexual persons. Andrologia 2015; 47(10):1202–5. [PubMed: 25611459]

[122]. Burcombe RJ, Makris A, Pittam M, Finer N. Breast cancer after bilateral subcutaneous mastectomy in a female-to-male trans-sexual. Breast 2003;12(4):290–3. [PubMed: 14659317]

[123]. Brown GR. Breast cancer in transgender veterans: a ten-case series. LGBT Heal 2015;2(1):77–80.

[124]. Brown GR, Jones KT. Incidence of breast cancer in a cohort of 5,135 transgender veterans. Breast Cancer Res Treat 2015; 149(1):191–8. [PubMed: 25428790]

[125]. Kuroda H, Ohnisi K, Sakamoto G, Itoyama S. Clinicopathological study of breast tissue in female-to-male transsexuals. Surg Today 2008;38(12):1067–71. [PubMed: 19039630]

[126]. Tanini S, Fisher AD, Meattini I, Bianchi S, Ristori J, Maggi M, et al. reportTestosterone and breast cancer in transmen: case reports, review of the literature, and clinical observation. Clin Breast Cancer 2019.

[127]. Reisner SL, Deutsch MB, Peitzmeier SM, White Hughto JM, Cavanaugh TP, Pardee DJ, et al. Test performance and acceptability of self-versus provider-collected swabs for high-risk HPV DNA testing in female-to-male trans masculine patients. PLoS One 2018;13(3):e0190172. [PubMed: 29538411]

[128]. Peitzmeier SM, Khullar K, Reisner SL, Potter J. Pap test use is lower among female-to-male patients than non-transgender women. Am J Prev Med 2014;47(6):808–12. [PubMed: 25455121]

[129]*. Weyers S, Garland SM, Cruickshank M, Kyrgiou M, Arbyn M. Cervical cancer prevention in transgender men: a review. BJOG An Int J Obstet Gynaecol 2021;128(5):822–6.

[130]. Van Kesteren PJM, Asscheman H, Megens JAJ, Gooren LJG. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 1997;47(3):337–43. [PubMed: 9373456]

[131]. Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, et al. Long-term evaluation of cross-sex hormone treatment in transsexual persons. J Sex Med 2012;9(10):2641–51. [PubMed: 22906135]

[132]. Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. Eur J Endocrinol 2013; 169(4).

[133]. Iwamoto SJ, Grimstad F, Irwig MS, Rothman MS. Routine screening for transgender and gender diverse adults taking gender-affirming hormone therapy: a narrative review. J Gen Intern Med 2021;36(5):1380–9. [PubMed: 33547576]

[134]. Gava G, Armillotta F, Pillastrini P, Giagio S, Alvisi S, Mancini I, et al. A randomized double-blind placebo-controlled pilot trial on the effects of testosterone undecanoate plus dutasteride or placebo on muscle strength, body composition, and metabolic profile in transmen. J Sex Med 2021;18(3):646–55. [PubMed: 33531255]

[135]. Vlot MC, Wiepjes CM, de Jongh RT, T'Sjoen G, Heijboer AC, den Heijer M. Gender-affirming hormone treatment decreases bone turnover in transwomen and older transmen. J Bone Miner Res 2019;34(10):1862–72. [PubMed: 31099910]

[136]*. Wiepjes CM, Vlot MC, de Blok CJM, Nota NM, de Jongh RT, den Heijer M. Bone geometry and trabecular bone score in transgender people before and after short-and long-term hormonal treatment. Bone 2019;127:280–6. [PubMed: 31271934]

[137]. Reisner SL, Poteat T, Keatley J, Cabral M, Mothopeng T, Dunham E, et al. Global health burden and needs of transgender populations: a review. Lancet 2016;388(10042):412–36. [PubMed: 27323919]

[138]. Snelgrove JW, Jasudavisius AM, Rowe BW, Head EM, Bauer GR. Completely out-at-sea with two-gender medicine: a qualitative analysis of physician-side barriers to providing healthcare for transgender patients. BMC Health Serv Res 2012;12(1):110. [PubMed: 22559234]

[139]. Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. J Sex Med 2014;11(1):119–26. [PubMed: 24344788]

[140]. Dhejne C, Van Vlerken R, Heylens G, Arcelus J. Mental health and gender dysphoria: a review of the literature. Int Rev Psychiatry 2016;28(1):44–57. [PubMed: 26835611]

Practice points

- Gender-affirming hormone therapy effectively reduces psychological distress in transgender people.
- Healthcare professionals willing to get involved in transgender care can consult the WPATH Standards of Care edition 8, the endocrine society guidelines “Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline,” and the ESSM position statement “Assessment and Hormonal Management in Adolescent and Adult Trans People, With Attention for Sexual Function and Satisfaction.”
- In the absence of healthcare professionals prescribing gender-affirming hormonal therapy, people may resort to other ways of obtaining hormonal therapy, which can put them at risk of adverse health events.

Research agenda

- Long-term large-scale prospective follow-up studies on people adhering to currently prescribed GAHT regimens are lacking.
- Cross-sectional prospective cohort studies comparing different treatment modalities would enhance our knowledge on the specific effects of each component of GAHT.
- It is important to include TGD people to determine research questions relevant to the TGD population.