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Review

# Hormone therapy in transgender adults is safe with provider supervision; A review of hormone therapy sequelae for transgender individuals

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ABSTRACT

*Introduction:* Some providers report concern for the safety of transgender hormone therapy (HT).
*Methods:* This is a systematic literature review of HT safety for transgender adults.
*Results:* Current literature suggests HT is safe when followed carefully for certain risks. The greatest health concern for HT in transgender women is venous thromboembolism. HT among transgender men appears to cause polycythemia. Both groups experienced elevated fasting glucose. There is no increase in cancer prevalence or mortality due to transgender HT.
*Conclusion:* Although current data support the safety of transgender HT with physician supervision, larger, long-term studies are needed in transgender medicine.


## Introduction

Access to healthcare for transgender individuals is limited, and some providers report concern for the safety of hormone therapy (HT) for transgender individuals [1]. This review article seeks to provide an overview of current knowledge in transgender medicine as it relates to the safety of hormone therapy (HT) for transgender adults. A severe limitation in this field is the lack of large-cohort studies to study the long-term effects of hormone therapy [1]. Current guidelines and medical knowledge provided in this review are the result of a small number of studies; the studies with the greatest statistical power are listed first in each section. Much of the existing data on transgender HT are from case reports, however these provide less reliable insight into the association of HT and long-term health outcomes. Case reports are provided for the completeness of this review and due to the limitations of this field, however these are listed last.

## Methodology

This literature review was conducted searching the terms “transgender” and “transsexual” on the electronic PubMed database by a single author over March 9–12, 2014, which retrieved 1881 articles from 1967 to 2014. Articles that had a primary research project or literature review designed to assess some aspect of the safety of hormone therapy for transgender individuals were considered, as well as papers from select bibliographies, to clarify existing limited knowledge on topics in hormone therapy for which there is limited to no research among transgender individuals on HT. Case reports were used when other long-term studies were not available, which is a significant limitation in this field. Where not otherwise mentioned, study controls are non-transgender individuals, who are not on hormone therapy, and study participants are transgender individuals who either are initiating or continuing HT.

## Cardiovascular profile

### *Venous thrombosis events may be estrogen related and therefore a concern for MTF transgender individuals*

The greatest concern among male-to-female (MTF) transgender individuals is the potential increase in thromboembolic events

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associated with estrogen therapy. In one of the largest studies to-date, Asscheman et al. (2014), observed the lowest reported rate of 1% of adults experiencing VTE among 1076 MTF individuals for an average follow of 5.4 years [2]. Other compelling data suggest that the incidence of venous thromboembolism (VTE) among transgender women appears associated with the presence of a hypercoaguable risk factor, including the use of an especially thrombogenic estrogen (ethinyl estradiol) which is no longer used [3]. Gooren et al. (2008), reported no increase in VTE among 2236 male-to-female (MTF) transgender individuals on HT from 1975 to 2006 compared with controls, with the exception of those who used ethinyl estradiol, for which there was a 6–8% incidence [4]. Additionally, while Wierckx et al. (2013) observed 5% of 214 MTF individuals to have a VTE within the first three years of estrogen therapy, 10 out of 11 of these women had at least one VTE risk factor such as smoking, immobilization due to gender confirmation surgery, or a hypercoaguable disorder [5]. Wierckx et al. (2012), previously found a 6% incidence of VTE among transgender women ($n = 50$) after an average of 11.3 years on HT, and released with their data a recommendation to discontinue estrogen therapy a minimum of 2 weeks minimum prior to any surgery, coupled with increased mobility after the surgery, to minimize this VTE risk factor [6]. The incidence of VTE events among transgender men did not change compared to female and male controls in these studies in Asscheman et al. (2014) ($n = 523$ study participants), Gooren et al. (2008) ($n = 876$), Wierckx et al. (2013) ($n = 138$) and Wierckx et al. (2012) ($n = 79$) [2,4–6].

Venous thrombosis events (VTE) were reported in MTF individuals as early as 1976, when a 29-year old transgender woman with no history or risk factors for VTE presented with pulmonary embolism after beginning estrogen therapy of diethylstilbestrol (DES) [7]. A 1978 paper also observed an occlusion of the middle cerebral artery during estrogen therapy in a transgender woman, where the patient was reported using mestranol, a 3-methyl ether of ethinyl estradiol [8].

### *Elevated cerebrovascular disease and myocardial infarctions for MTF individuals*

Similar to the previous reports of VTE events among MTF individuals on estrogen therapy, data suggest that transgender women may have an elevated risk of vascular events compared to female controls. Wierckx et al. (2013) ($n = 214$) reported an incidence of MI among MTF adults that matched that of male controls, but exceeded female controls; three transgender women experienced a myocardial infarction (average 48 years old) within two years of estrogen therapy [5]. In the same study, an increase in cerebrovascular disease and transient ischemic attack (TIA) among MTF adults was also observed in the same study, as compared to male controls; five transgender women on estrogen therapy (average 7.2 years) experienced one of these conditions (average 51 years old).

Wierckx et al. (2012) also examined 100 transgender men and women and found that 6% of transgender women had cardiovascular health problems after an average of 11.3 years on estrogen therapy [6]. These included 2 reports of MI, 1 report of TIA, and 1 case of venous ulcer where ethinyl estradiol was used. The other two cases were suggested to be less related to the individual's estrogen therapy, including peripheral arterial disease due to complications of diabetes and a MI before HT. Futhermore, 5 out of 6 of these transgender women smoked for an average of 24 years, and the authors suggested that both smoking risk and the known role of estrogen hormone replacement therapy in increased risk TIA and VTE might play a role in these cases. Such a role has been outlined in previous literature [9].

The rates of CVD/TIA and MI among transgender men did not change compared to male controls in the above studies of Wierckx et al. (2013) ($n = 138$) and Wierckx et al. (2012) ($n = 79$) [2–6].

### *VTE risk may be lessened by use of transdermal estrogen in MTF adults*

The "first-pass" hypothesis of liver metabolism of estrogen proposes that there is a decrease of thromboembolic and other cardiovascular events with the use transdermal as opposed to oral estrogen therapy [10–12]. In Ott et al. (2010), 162 transgender women were followed for a mean of 64.2 months, and there were no reports of VTE while using transdermal 17β estradiol [13]. Wilson et al. (2009) also observed increases in inflammatory markers (cytokine IL-6, IL-1 and IL-8, clotting factors FV11 and FVIX and superoxide dismutase) consistent with this hypothesis for MTF individuals taking oral estrogen, but not for those taking transdermal estrogen [14].

The rates of VTE among transgender men did not change compared to male controls in the above studies of Ott et al. (2010) ($n = 89$) [13].

### *Estrogen therapy may be safe even for MTF adults who have hypercoagulable mutations*

Estrogen therapy in transgender adults may be safe even in the presence of hypercoaguable gene deficiencies. In Ott et al. (2010), no VTE events were reported among the same 162 MTF and 89 FTM individuals followed, despite observation of activated protein C resistance and deficiency in 7% and 4%, respectively [13].

The effects of other clotting related gene mutations in conjunction with estrogen therapy in transgender adults have not been as well studied. One case report noted that an MTF individual who experienced a myocardial infarction and VTE on heparin was deficient in antithrombin III, and that this individual's deficiency was corrected when HT was stopped [15].

### *Isolated case studies of cardiovascular incidents among transgender adults are inconclusive*

There are four case reports of sudden death of transgender individuals on estrogen therapy since 1988, however the isolated nature of these case studies provides little conclusive evidence of the likelihood of the link between estrogen and these conditions. These reports include the earliest case of the death of a 22 year old MTF transgender individual by arrhythmogenic right ventricular dysplasia [16], along with complications in previously healthy MTF individuals: VTE, atherosclerosis, and syncope [17,18]. There are also two reports in the literature of idiopathic intracranial hypertension (IIH) among transgender men after initiating HT [19,20].

Individual case reports among FTM individuals are also inconclusive, and include a 32 year old FTM individual on testosterone therapy who died suddenly after two years from ischemic heart disease as a result of coronary stenosis [21].

## Oncology

### *No increase in cancer prevalence among transgender individuals on HT*

While some guidelines for transgender medical care express concerns for elevated cancer risk with certain hormone regimes, current data suggest that the risk of cancer may not rise.

Although studies are small, overall cancer incidence in transgender men and transgender women to-date has not been found

to be different than their respective male and female controls [5]. There are no reports of change in breast cancer specific risk among transgender individuals on estrogen compared to secular trends of male breast cancer incidence. Rates are lower relative to secular trends of female breast cancer rates. Gooren et al. (2013) reported that among 795 FTM individuals there was a breast cancer rate of 5.9 cases per 100,000 person-years and of 4.1 cases per 100,000 person-years among 2307 MTF persons [22]. In Kuroda et al. (2008), no breast carcinoma was found among FTM individuals ($n = 56$) who had been on estrogen for an average of 11 months, while one breast carcinoma was found in among those FTM individuals ($n = 130$) who were not on estrogen [23].

Rather than elevated cancer risk, studies such as Miller et al. (1986) ($n = 32$) and Perrone et al. (2009) ($n = 30$) suggest that the result of testosterone therapy in FTM individuals is tissue atrophy of the epithelium of the cervix [24] and endometrium [24,25], with maintenance of corpus luteum in ovaries even after one year of therapy [24]. Gardner et al. (2014), observed that in surgical endometrium tissues obtained from 15 FTM there was no increase in either the genes related to endometrial proliferation or endometrial malignancy [25]. Estrogen receptors (ERα and ERβ) were also observed in another study ($n = 16$) to decrease in the vaginal epithelium of transgender men [26].

There are reports of hyperplasia in female reproductive tract tissues of FTM individuals on testosterone therapy however these studies are lower powered. In an English-language abstract of the Russian-language paper by Mikhaĭlichenko et al. (2013), it was reported that hormone therapy resulted in hyperplasia of female reproductive tract and breast tissues among FTM individuals, as well as metaplasia in prostate tissue in MTF individuals [27]. Similar results were reported in Ikeda et al. 2013 who suggested that among FTM individuals ($n = 11$) on testosterone, hyperplasia increased in the ovarian stroma and the ovarian cortex was thickened [28].

There are several case reports of prostate cancer in transgender women [29,30]. A comprehensive study among the medical records of 2306 orchidectomized MTF individuals reported an overall rare but possible incidence of prostate cancer of 0.04%, limited by decreased screening and younger average age of 29.3 among these individuals at the start of therapy [31].

Additionally, there are ten case reports of breast cancer development among MTF individuals on estrogen since 1968 [23,32–37].

Similarly, within the last 50 years only 4 cases of breast cancer in FTM individuals have been recorded [38]. Pseudoangiomatous stromal hyperplasia, the condition of a rare benign breast connective tissue lesion found typically only in women and men with gynecomastia, was encountered among 2 FTM individuals [39]. Uterine and invasive cervical cancer was reported in one FTM individual [40].

There are three case reports of MTF individuals with meningioma while on estrogen HT involving intracranial [41], tuberculum sellae [42], and an olfactory groove locations [43], and one case report of a pituitary adenoma [44]. There are no reports in the literature of any of the following estrogen-related growth factor tumors: hemangioma, angiomyolipoma, or focal nodular hyperplasia.

## Mortality

*No direct increase in mortality due to HT in transgender adults*

The three largest studies to date on mortality and transgender hormone therapy suggest no direct increased risk in mortality. A large study in 15 different centers of over 2000 transgender adults found no increase in mortality compared to controls [2]. Gooren et al. (2008) monitored 2236 MTF and 876 FTM individuals on HT and observed no change compared to controls [3]. Asscheman et al. (2011) reported that over an average of 18.5 years among 966 MTF and 365 FTM individuals, MTF did have a 51% increase in mortality compared to secular data [45]. However, these differences were attributable to outside causes such as the increased incidence of suicide, AIDS, substance abuse and cardiovascular disease; notably there was also no increase in cancer mortality among these individuals. The authors found no increase in mortality of FTM individuals.

## Laboratory values

*Changes in triglycerides and cholesterol with MTF HT; inconclusive changes among FTM HT*

Roberts et al. (2013) ($n = 55$) reported elevated median triglyceride levels of 120 mg/dL among MTF adults compared to both male (80 mg/dL median) and female (60 mg/dL median) control groups, with the range of participant values spanning from 34.2 to 242.6 mg/dL [46]. Cholesterol (LDL) levels among MTF individuals resembled female controls. In Jacobeit et al. (2009), transgender men ($n = 17$) monitored for a 3 year period observed decreases in plasma cholesterol, decreases in LDL and no change in HDL [47].

Meyer et al. (1986) reported no significant changes among MTF individuals ($n = 18$) in triglycerides or total cholesterol, and among FTM individuals ($n = 14$) there were reported small increases in triglycerides and total cholesterol to the upper limit of normal of female controls [48]. The study authors also observed that among subjects, plasma cholesterol and triglycerides rose with an increase in testosterone dose.

*Hematocrit and hemoglobin; increases among FTM individuals, no change in transgender women*

Jacobeit et al. (2009) also observed that among FTM individuals on testosterone therapy, hematocrit and hemoglobin increased as compared to controls but were within normal ranges [49]. Roberts et al. (2013) reported that for MTF adults on estrogen therapy the values of hemoglobin and hematocrit were similar to female controls [48].

*Liver function tests; no change on HT in transgender adults*

In Roberts *et* al, 2013 among MTF individuals, alkaline phosphatase, potassium and creatinine values resembled male controls [48]. Liver enzymes did not change appreciably among FTM adults as reported by Jacobeit et al. (2009) [49]. Hampl et al. (1986) observed that among 6 transgender men on HT for 3 months there was no decrease in liver function [49].

*BUN and creatinine; MTF levels similar to male controls*

Roberts et al. (2013) reported no difference in blood urea nitrogen values among the same 55 MTF adults compared to both male and female control groups and no difference in creatinine values compared to non-transgender male controls [48].

*Uric acid; estrogen may elevate uric acid excretion with MTF HT*

Yahyaoui et al. (2008) found that fractional excreted of uric acids (FEUC) levels increased among 22 MTF individuals and decreased among 47 FTM individuals after two years of HT, supporting their hypothesis of increased fractional excretion of uric acid (FEUA) with rising estrogen [50]. Uric acid levels decreased in the MTF

individuals compared to their baseline after one year due to this greater excretion, and increased among the FTM individuals compared to their baseline due to less excretion. The study authors found no clear link between testosterone and FEUA.

## Glycemia, metabolism and insulin sensitivity

### *Worsened glycemic metabolism for transgender adults on HT*

Most studies on glycemic control in transgender individuals on HT report increased insulin resistance and fasting glucose.

Wierckx et al. (2013) observed an increased in type 2 diabetes among both FTM and MTF individuals [5]. Gooren et al. (2008) reported decreased insulin sensitivity among both MTF and FTM individuals on HT, as well as elevated fasting insulin on MTF HT [4]. Bosinski et al. (1997) reported a higher rate of PCOS and non-classical congenital adrenal hyperplasia among 12 FTM individuals prior to HT, suggesting a pre-existing metabolic risk in this population [51]. Whether these metabolic parameters relate to hormone therapy or simply a general response to change in body hormones remains to be studied. Polderman et al. (1994) studied glycemic control of 18 MTF and 13 FTM individuals using a glucose-clamp technique whose results also suggested that HT in both groups could increase insulin resistance [52]. A lower powered 1986 study of 6 FTM individuals reported no change for these adults on HT in respect to with insulin sensitivity [51].

Only small studies are available for leptin, adiponectin, and ghrelin. Transgender men had decreased adiponectin levels while transgender women had decreased leptin [53]. Prior animal studies have reported that both are associated with insulin resistance, and that adiponectin may have a protective effect against elevated triglycerides [54]. Among 15 MTF non-diabetic individuals in Resmini et al. (2008), MTF individuals had leptin levels lower than female controls and higher than male controls [53]. Adiponectin was also lower among 11 FTM individuals. There were no differences in ghrelin among the groups.

### *Body mass index and fat redistribution among transgender adults*

Both transgender men and women experienced changes in body mass index; Asscheman et al., 1989 observed minor weight gain and weight loss for both FTM ($n = 122$) and MTF ($n = 303$) individuals [47]. Within this study, only the FTM transgender individuals experienced a weight gain of more than 10% of their body weight on HT, and all 21 of these individuals were obese at the start of the study.

Elbers et al. (1999) found increases in thigh muscle mass on MRI among FTM ($n = 17$) individuals after 12 months of hormone therapy [55]. FTM individuals also had a decrease in overall subcutaneous fat deposition, however they showed greater visceral fat deposition, demonstrating fat redistribution. The reverse was true for MTF individuals ($n = 20$) in the study, where imaging showed increases in subcutaneous fat after 12 months of therapy but decreases in visceral fat and thigh muscle mass. The study authors noted that while hormone therapy is reported to cause fat redistribution, the exact role of both testosterone and estrogen in weight is unclear.

## Bone mass

### *Increased osteopenia in transgender women on HT*

Studies with the greatest statistical power show increased rates of osteopenia in transgender women on HT, however these may be limited by including participants who used anti-androgens for one year before starting estrogen therapy. Wierckx et al. (2012) examined 100 transgender men and women after a mean of 10 years on HT; 25% of transgender women experienced osteoporosis whereas transgender men did not [6]. Decreased bone mass has been reported at the lumbar spine [56], hip and radius regions [57]. There are a lack of fracture data available in transgender individuals. Wierckx et al. (2012) suggested that this decrease in bone mass could be due to either increased screening of MTF individuals, anti-androgen therapy itself (as noted in the decreased bone mass of non-transgender men on anti-androgens), or prior clinical practices of administering an anti-androgen for one year before the start of estrogen therapy [6]. Additionally, transgender women in Wierckx et al. (2012) had lower estrogen levels than female controls which may account for their relative rise in osteopenia [6]. Mueller et al. (2011) observed that among 84 MTF treated with estrogen therapy there was no increased risk of osteoporosis. This group also concluded that previous studies finding decreases in bone mass were those that began anti-androgen therapy alone for the first year without concomitant use of estrogen [58]. Also supporting this finding is Ruestche et al. (2005), who found that among 24 MTF individuals, those who had decreased bone mass ($n = 5$) were only those noncompliant with their estrogen therapy [59].

## Pituitary

There are reports of enlarged pituitary glands among MTF individuals on HT [60], as well as six case reports of prolactinoma [61–64]. Prolactin levels have also been reported to be elevated among MTF individuals during long-term HT [60].

## Other considerations

### *Androgen deprivation in MTF individuals may decrease sexual desire, FTM HT may increase it*

Wierckx et al. (2014) used survey data to elucidate a self-reported decrease in sexual desire among two-thirds of MTF adults ($n = 214$) and a self-reported increase in sexual desire among two-thirds of FTM individuals ($n = 138$) who had undergone either HT or gender confirmation surgery [65]. Nevertheless, an earlier study reported that while self-reported decreased sexual desire was experienced in one-third of a group of 62 MTF individuals, this level was similar to a group of pre-menopausal female controls [66]. A subsequent study of MTF individuals with self-reported decreased sexual desire began a testosterone patch used to treat decreased sex drive in cisgender women. All subjects found that their sexual desire improved without masculinizing effects, and none of the transgender women discontinued the testosterone [67].

### *Autoimmune conditions with a female prevalence in transgender women on HT*

There are two case reports of systemic lupus erythematosus occurring in MTF individuals with no prior history of autoimmunity deficits; one case presented with SLE 1 year after starting estrogen injections, and another after 20 years on HT [68,69].

## Conclusions

Compiled evidence from this literature review suggests that HT for transgender individuals is safe without a large risk of adverse events when followed carefully for a few well-documented medical concerns as follows. The primary concern among MTF individuals on estrogen therapy is the possibility of developing thrombogenic complications [2–7]. Therefore, educating MTF individuals and their

providers for preventative ways to minimize risk of thromboembolic events might be the most important long-term assessment of transgender women in order to minimize the risk of adverse effects of HT. Suggested risk modifications from groups studying VTE among MTF individuals include addressing any hypercholesterolemia, hypertension or smoking use that a patient might have. Hypercoaguable risk factors, including the use of a thrombogenic estrogen, ethinyl estradiol, have been associated with many of the cases of reported VTE, and as such the risk of these adverse events may continue to decline as the usage of this drug diminishes [3]. Other health outcomes for transgender women may include increased triglycerides [48] and decreased sexual desire [65].

There are multiple case reports of conditions associated with MTF HT, including the incidence of meningiomas [43–45], benign pituitary tumors and prolactinomas [61–65] along with the occurrence of autoimmune conditions with a female predominance, such as systemic lupus erythematosus [69,70]. However, the data are too limited to make any type of conclusion or recommendation.

Transgender men did not experience the increase in thrombogenic complications that some transgender women reported [2,4–6].

Both transgender men and women experienced an increase in insulin resistance, fasting glucose and changes in body fat redistribution [4,5,47,53,54]. Adipocyte-derived hormone levels may reflect changes in insulin sensitivity on hormone therapy, as transgender men had decreased adiponectin levels while transgender women had decreased leptin, both associated with insulin resistance [52,53].

Although modest, current research supports the view that there is no significant increase in cancer prevalence among transgender individuals on HT [5,23,24,47]. The majority of research on the effect of testosterone specifically on female reproductive tissues may suggest that there is no elevated risk for hyperplasia among FTM individuals, however such a guideline is preliminary as research to-date is contradictory [25–30].

Transgender individuals should also not exclude surveillance for cancers unique to their natal sex; transgender women have presented with prostate cancer, and transgender men with uterine and cervical cancer [31–33,42]. Both MTF and FTM individuals have presented with breast cancer [34–41].

The Standards of Care (SOC) released by the World Professional Association for Transgender Health (WPATH) report that the greatest risk factor of MTF HT to be VTE and increased triglycerides, which is supported by this literature review [70]. The greatest risk factor of FTM HT reported by WPATH SOC is polycythemia, which differs slightly from the only very small increases of hematocrit among transgender men observed in the literature on HT [69]. The guidelines established by the Endocrine Treatment of Transsexual Persons of the Endocrine Society are also supported by this literature review [71]. The seven suggested items to monitor listed include screening for cancers of the sex assigned at birth, breast cancer screening of MTF individuals, BMD tests, cardiovascular and laboratory profile monitoring, as well as the prolactin levels of MTF individuals [71]. Finally, this review would also support caution for patients with potential hormone sensitive conditions, with contraindication to HT in the presence of cancers that are sensitive to estrogen and testosterone [71]. This review would not support the recent 2014 USA Food and Drug Administration (FDA) requirement that testosterone products display a warning for the risk of VTE, deep vein thrombosis and pulmonary embolism [72].

With the exception of a few large-cohort and long-term studies, much of the existing knowledge about the health impact of transgender HT is based on case reports. While these provide clues to effects of transgender HT, there is a strong need for future research of greater cohort size to be undertaken in order to address this critical gap.

## Conflicts of interest

The authors declare they have no conflicts of interest.

## Appendix I. Terminology

*Author's note:* In some instances, studies reviewed inappropriately referred to MTF individuals as "transsexual men", referred to FTM individuals as "women", or otherwise referred to transgender individuals by their natal sex. These discrepancies were confirmed and corrected after communication with the original author of the work or by further analyzing the manuscript. The definitions of these terms as used in this paper are below.

*FTM*: female to male transgender, transgender man. FTM individuals are those whose natal sex is female, and transition to their identified and lived male gender.

*Gender confirmation surgery* – any surgery to alter function or appearance of tissues from natal sex to sex of the individual's identified and lived gender identity.

*Hormone therapy (HT)*: HT in this paper for FTM individuals typically involves testosterone HT. HT for MTF individuals involves estrogen and anti-androgens, such as spironolactone.

*MTF*: male to female transgender, transgender woman. MTF individuals are those whose natal sex is male, and transition to their identified and lived female gender.

*Transgender* – a term to describe an individual whose gender identity is different than natal sex.

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