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Review

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

Jamie D. Weinand, BS, BA, Joshua D. Safer, MD *

Transgender Medicine Research Group, Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, Boston, MA, USA

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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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* Corresponding author. Transgender Medicine Research Group, Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, 715 Albany Street, Room M-1016, Boston, MA 02118, USA. Tel.: +1 617 638 8530; fax: +1 617 638 7221.
E-mail address: jsafer@bu.edu (J.D. Safer).

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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