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Incidence of Venous Thromboembolism in Transgender Women Receiving Oral Estradiol

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ABSTRACT

Introduction: One of the most serious known adverse effects of feminizing cross-sex hormone therapy (CSHT) is venous thromboembolism (VTE); however, no study has assessed the incidence of VTE from the hormone therapies used in the United States because previous publications on this topic have originated in Europe. CSHT in the United States typically includes estradiol with the antiandrogen spironolactone, whereas in Europe estradiol is prescribed with the progestin cyproterone acetate.

Aim: To estimate the incidence of VTE from the standard feminizing CSHTs used in the United States.

Methods: A retrospective chart review of transgender women who had been prescribed oral estradiol at a District of Columbia community health center was performed.

Main Outcome Measure: The primary outcomes of interest were deep vein thrombosis or pulmonary emboli.

Results: From January 1, 2008 through March 31, 2016, 676 transgender women received oral estradiol-based CSHT for a total of 1,286 years of hormone treatment and a mean of 1.9 years of CSHT per patient. Only one individual, or 0.15% of the population, sustained a VTE, for an incidence of 7.8 events per 10,000 person-years.

Conclusion: There was a low incidence of VTE in this population of transgender women receiving oral estradiol.

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Key Words: Transgender Persons; Hormone Replacement Therapy; Cross-Sex Hormone Therapy; Venous Thromboembolism; Gender Identity

INTRODUCTION

Cross-sex hormone therapy (CSHT) allows transgender individuals to develop secondary sex characteristics that conform to their gender identity and decreases the endogenous hormone production of their natal sex. Venous thromboembolism (VTE) is considered one of the most serious known adverse effects of feminizing CSHT owing to high levels of exogenous estrogen being administered.[1]

Early therapies to promote the feminization of male-to-female transgender patients relied on ethinyl estradiol, which was subsequently shown to have a significantly higher risk of thrombotic events than 17β-estradiol—the predominant form of estrogen used in current feminizing CSHT (estradiol will be used to refer to 17β-estradiol).[2] The available literature that analyzes the risk of VTE from CSHT has been published from data on European populations taking ethinyl estradiol or estradiol in combination with cyproterone acetate, a synthetic derivative of hydroxyprogesterone that is not approved for use in the United States. The first of these studies, published in 1997 from the Netherlands, found that 6.4% of individuals on CSHT developed a VTE; however, a large majority of this study population was receiving ethinyl estradiol.[2] Subsequent work originating in Belgium by Wierckx et al[3] found a 5.1% lifetime risk of VTE in transgender women taking largely transdermal or oral estradiol in combination with cyproterone acetate. Notably, a study examining 162 Austrian transgender women receiving only transdermal estradiol in combination with cyproterone acetate and finasteride found that none of these patients developed a VTE during a mean of 64.2 ± 38.0 months of follow-up.[4] The conclusions from this study are similar to those from studies in postmenopausal women that consistently demonstrate no increased risk of VTE from transdermally administered estradiol.[5–7] Transdermal estradiol is not commonly used in the United States as CSHT because, when combined with the antiandrogen spironolactone, one needs to apply multiple patches to successfully suppress endogenous testosterone production and reach the goal serum estradiol levels.

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The decreased efficacy of transdermal estradiol for transgender women in the United States is likely due to the absence of cyproterone acetate in U.S. hormone regimens. Cyproterone acetate is one of the most effective antiandrogens available because it lowers testosterone levels by 70% to 80% through central inhibition.[8] In addition, cyproterone acetate is the most potent progestin known as measured by endometrial proliferation. It is approximately 1,000 times more potent than progesterone and three times more potent than medroxyprogesterone.[9] Progestins such as cyproterone acetate also have been demonstrated to be necessary for the breast tissue of transgender women to fully histologically mimic that of genetically female breast tissue.[10] For these reasons, estradiol combined with cyproterone acetate has been the standard of care for feminizing CSHT in Europe for many years.[11]

No study has assessed the risk of VTE from the standard feminizing CSHTs used in the United States, which typically rely on oral estradiol with the antiandrogen spironolactone—a mineralocorticoid receptor antagonist that has no progestational activity.[12] It is unclear whether the risk of VTE differs between regimens used in the United States and Europe because the previous literature in postmenopausal women has demonstrated a higher risk of deep vein thrombosis and pulmonary embolism from combined estrogen-progestin therapies compared with unopposed estrogen therapy.[13,14] Based on these studies, we hypothesized that the standard feminizing CSHTs used in the United States would confer a lower risk of VTE than estradiol-cyproterone therapies used in Europe because American regimens lack a progestin. To better elucidate the incidence of VTE in transgender women taking estradiol without cyproterone acetate, we retrospectively assessed the number of deep vein thromboses or pulmonary emboli that were sustained by transgender women receiving CSHT at a District of Columbia community health center that specializes in transgender medicine.

METHODS

Study Design

A retrospective cohort analysis was performed to determine the incidence of VTE in transgender women receiving CSHT from January 2008 through March 2016 at a community health center in the District of Columbia. An informed consent exemption was granted by the Chesapeake Institutional Review Board.

Study Population

The patient population included individuals who identified as transgender, were older than 18 years, and had been prescribed oral estradiol. Patients who had been prescribed spironolactone, finasteride, conjugated equine estrogens, or progestins also were included in this analysis. Patients who had received prescriptions for injectable estrogens or testosterone before or during the study period were excluded.

Study Protocol

Computational methods were used to identify the number of patients within the electronic medical record who were assigned diagnosis codes related to pulmonary embolism or deep vein thrombosis and who had met the inclusion and exclusion criteria. In addition, a medical provider survey was conducted to assess the number of patients who sustained a VTE, at what dose and course in therapy these events occurred, and whether any comorbidity existed. Computational methods also were used to identify the number of individuals taking each form of CSHT. Total number of patient-years of follow-up was calculated using the amount of time from the patients' first to last medical visits. No patient identifiers were collected during this computational chart review or provider survey.

Statistical Methods

Descriptive statistics are expressed as mean ± SD.

RESULTS

General characteristics of the study population are presented in Table 1. Of the 676 transgender women, 22.8% were HIV positive, 23.6% were obese, and 21.2% were tobacco users at baseline. This study population received CSHT for a total of 1,286 years of patient follow-up and a mean of 1.9 years of CSHT per patient. Only one individual, or 0.15% of the population, sustained a VTE, for an incidence of 7.8 events per 10,000 person-years.

The individual who sustained a VTE had developed a right lower lobe segmental pulmonary artery embolism in her 20s approximately 2 years after starting CSHT at doses of estradiol 4 mg/d and spironolactone 200 mg/d. The pulmonary embolism was diagnosed at an outside facility by a computerized

Table 1. Baseline characteristics of transgender women (N = 676)*

Age (y)	33.2 ± 10.8
BMI (kg/m^2)	26.6 ± 6.8
White	339 (50.0)
African American	170 (25.1)
Race unreported or refused to report	95 (14.0)
Asian	25 (3.7)
>1 race	14 (2.1)
American Indian or Alaska Native	9 (1.3)
HIV positive	154 (22.8)
BMI ≥ 30 kg/m^2	160 (23.6)
Current smoker	143 (21.2)
Hypertension	88 (13.0)
Dyslipidemia	59 (8.7)
Diabetes mellitus	43 (6.4)
Renal disease (eGFR ≤ 60)	11 (1.6)

BMI = body mass index; eGFR = estimated glomerular filtration rate.
*Data are presented as mean ± SD or number (percentage).

Table 2. Administered cross-sex hormone therapies in transgender women (N = 676)

Oral estradiol	676 (100%)
Spironolactone	634 (93.8%)
Finasteride	112 (16.6%)
Conjugated equine estrogens	42 (6.2%)
Oral progesterone	27 (4.0%)
Intramuscular medroxyprogesterone acetate	3 (0.4%)

tomographic angiogram a few hours after the onset of hemoptysis and dyspnea. She had sustained no known trauma or immobilization preceding the development of symptoms. She had no other acquired risk factors for VTE other than a body mass index of 37 kg/m^2. She was an HIV-negative non-smoker and her only medications were CSHT. Subsequent evaluation was negative for inherited risk factors for VTE, including negative antiphospholipid antibody and no factor V Leiden or prothrombin gene mutations.

As presented in Table 2, 93.8% of the transgender women receiving oral estradiol also were prescribed the antiandrogen spironolactone and 16.6% received the antiandrogen finasteride. Conjugated equine estrogens or oral progestins were prescribed to 6.2% and 4.0% of the total study population, respectively. In addition, three patients were prescribed intramuscular medroxyprogesterone acetate in combination with oral estradiol.

DISCUSSION

This study presents the incidence of VTE in transgender women in the United States receiving oral estradiol-based CSHT, most commonly with the antiandrogen spironolactone. A significantly lower incidence of VTE was observed than previously reported in European populations receiving oral estradiol with the progestin cyproterone acetate. This lower incidence is consistent with studies in postmenopausal women that demonstrate a lower risk of VTE from unopposed estrogens compared with estrogen-progestin therapies.[13,14]

The standard protocol at our practice for CSHT in preoperative transgender women was estradiol 4 to 8 mg/d orally with spironolactone 100 to 200 mg/d. Very few individuals in our population had obtained an orchiectomy or vaginoplasty because, until recently, most local insurance plans did not cover transgender surgeries. In the patients who had obtained these procedures, estradiol typically would be decreased to 2 to 4 mg/d and spironolactone would be discontinued. The dose of estradiol for all transgender women was determined by their satisfaction with the rate of feminization and roughly based on serum hormone values. A goal serum estradiol level of 200 pg/mL and a serum testosterone level lower than 50 ng/dL were used to guide hormone dosing because these values approximately correlate to those seen in premenopausal women. If a patient had any type of upcoming surgery, she was instructed to stop estradiol 1 month before the procedure and restart only after having returned to full ambulation.

The antiandrogen finasteride was typically used only in conjunction with estradiol and spironolactone and usually only at the request of the patient who sought to increase scalp hair. Finasteride was not routinely offered as standard therapy because it is unclear how effective this agent is at promoting feminization or improving alopecia in individuals whose testosterone levels are typically already suppressed by estradiol and spironolactone. Conjugated equine estrogens were not recommended because they are produced from pregnant mares' urine and contain a mixture of estrogens. In addition, the concern for animal welfare has led many medical providers and patients to discontinue its use. The use of progestins also was not recommended at our practice because the clinical benefit of these agents for transgender women remains unclear.

Risk factors for VTE include older age, trauma or immobilization, malignancy, chronic renal disease, HIV infection, African-American race, obesity, hypertension, diabetes mellitus, tobacco use, and hyperlipidemia.[15–17] The population examined in this study is young and has a lower prevalence of obesity, hypertension, diabetes mellitus, and renal disease compared with the general American population, which might contribute to the low incidence of VTE observed. However, our population has a high prevalence of HIV and tobacco use and a large number of African-American individuals, which would be expected to increase the risk of thrombophilia. Therefore, it is unclear how this population's baseline risk factors for VTE compare with those of the general population or the wider population of transgender women in the United States.

The major limitations of this study are its retrospective nature and small sample size. Retrospective studies can underestimate incidence because patients with VTE might have been lost to follow-up. The small sample might underestimate the true risk of VTE to transgender women because the incidence of VTE observed in the present study is slightly lower than the 8 to 27 events per 10,000 person-years observed in the general population and lower than the 30 events per 10,000 person-years observed in postmenopausal women on unopposed estrogen therapy.[18,19] Our results also might underestimate the incidence of VTE if the computational chart review failed to detect these events because medical providers did not code for deep vein thrombosis or pulmonary embolism in the assessment or problem list fields of the electronic medical record. In addition, medical providers who were no longer practicing at the clinic were not surveyed for this study. The true incidence of VTE also might be underreported because asymptomatic venous thrombotic events were not detected.

This study also does not examine the incidence of VTE in transgender women receiving intramuscular or transdermal estradiol. Intramuscular estradiol is often prescribed in the United States in place of oral estradiol, and there is significant controversy regarding the risk of VTE from this route of

hormone administration. Some argue that high serum values of estradiol observed immediately after intramuscular administration can lead to a hypercoagulable state and therefore a higher risk of VTE. Others argue that, like transdermal estradiol—which in postmenopausal women and a small cohort of transgender women in Europe has been shown to not increase the risk of VTE—intramuscular estradiol avoids first-pass hepatic metabolism and therefore does not stimulate hepatic production of clotting factors as orally administered estradiol does.[20,21]

CONCLUSION

This is the first study to assess the incidence of VTE in transgender women receiving the most commonly prescribed standards of care for feminizing CSHT in the United States. Our results suggest that estradiol- and spironolactone-based CSHTs have a lower risk of VTE than the oral estradiol- and cyproterone acetate–based therapies used in Europe; however, further research that directly compares the disparate forms of feminizing CSHTs used in the United States and Europe is necessary to better identify the safest and most efficacious combinations of these agents.

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