Transgender Medicine and Risk of Venous Thromboembolism

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Abstract

Gender dysphoria refers to psychological distress that results from an incongruence between gender identity and sex assigned at birth. Administration of sex hormones is most often used as a first step to develop and maintain physical characteristics consistent with gender identity. Gender-affirming hormone treatment is considered beneficial for the quality of life and reduction of depression. However, estrogen and androgen-lowering hormone therapies used in transwomen are in particular associated with increased risk of venous thromboembolism. In this review, introduced by a clinical case, we provide an overview of the currently available medical therapies in transgender medicine, and put the associated increased risk of venous thromboembolism into perspective.

Keywords

- transgender
- hormone replacement therapy
- venous thromboembolism
- venous thrombosis
- pulmonary embolism

Introduction

People who are diagnosed with gender dysphoria experience distress due to an incongruence between their gender identity and sex recorded at birth (►Table 1). It is estimated that there are 25 million transgender and gender-nonbinary individuals worldwide.[1] Mostly, as the first step in transitioning, sex hormones are administered to develop and maintain physical characteristics consistent with gender identity.[2] Life-long gender-affirming hormone therapy (GAHT) is common. Gender reassignment surgeries are optional to further align psychical appearance. However, long-term GAHT is associated with a significant risk of venous thromboembolism (VTE), but simply advising against GAHT for individuals with preexisting increased VTE risk will deprive them from the (psychological) benefits of GAHT. Some suggest the possibility of concomitant long-term antithrombotic therapy to reduce VTE risk, but this requires a careful consideration of the balance between benefits and risks (i.e., bleeding). In this review, introduced by a clinical case, we outline the current medical interventions available, and highlight the impact of medical therapies in transgender medicine on the risk and prevention of VTE.

Clinical Case

A 46-year-old transwoman was referred to our center of expertise on gender and sex for a second opinion about gender-affirming hormone treatment. She was diagnosed with gender dysphoria 3 years before. She had not initiated GAHT due to the increased thromboembolic risk explained to her by the attending endocrinologist. She was known with heterozygous factor V Leiden. Her family history included a sister with factor V Leiden and her mother was diagnosed with breast cancer at the age of 50 years. Our patient did not smoke and had a body mass index (BMI) of 23 kg/m^2. Two years prior to her visit, she had undergone facial feminization surgery and, more recently, a breast augmentation which was complicated by a thrombophlebitis at the intravenous infusion site. Because of male pattern hair loss and returning facial hair she is reconsidering the use of GAHT and she also would like to undergo additional facial feminization

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Table 1 Terms and definitions[2]

Cisgender, non-transgender	Adjectives for individuals whose gender identity is aligned with sex recorded at birth
Gender-affirming or gender-conforming hormone treatment and surgery	Medical/surgical interventions performed to align appearances with gender identity
Gender dysphoria	Mental health term for the discomfort felt by some transgender individuals due to lack of alignment between gender identity and sex recorded at birth
Gender expression	How an individual communicates gender identity internally and to others
Gender identity	An individual's internal sense of one's own sex
Transgender, transsexual, gender-nonbinary, gender incongruent, gender nonconforming, genderqueer	Adjectives for individuals whose gender identity is not aligned with sex recorded at birth
Transgender women, transwomen	Individuals who self-identify as female, but whose sex was assigned male at birth
Transgender men, transmen	Individuals who self-identify as male, but whose sex was assigned female at birth

Note: Adopting language specific to transgender health care that includes definitions with consensus is essential for communicating with patients and within the medical field.

surgery. Due to her known increased VTE risk she is requesting a second opinion on the safety of hormone replacement therapy (HRT), as well as for perioperative advice.

Current Gender-Affirming Hormone Treatment

Transgender Women

Gender-affirming hormone treatment is considered beneficial for the quality of life and reduction of depression,[3] but high-quality data are limited.[4] Currently, there are two main classes of medications used in transwomen, namely, estrogen therapies and androgen-lowering hormone therapies (►**Table 2**). The synthetic estrogen ethinyl estradiol was a widely used estrogen in Europe prior to 2003. However, given safety concerns regarding thromboembolic risk and cardiovascular disease, most clinics have switched to oral or transdermal (or intramuscular) estradiol.[5] Studies comparing efficacy between routes of estradiol application in transgender women are sparse.[6] Depending on the outcome

Table 2 Gender-affirming hormone regimens in transgender individuals

	Effect	Route of administration	Drug and dose
Transgender females			
Estrogens	Feminization (breast growth, reduction in facial and body hair, softening of skin, change in body composition)	Oral	Estradiol valerate: 2–6 mg/d
		Transdermal	Estradiol patch: 0.025–0.2 mg/d
			Estradiol gel 0.06%: 0.75–1.5 mg/d
			Estradiol spray: 1.53–4.59 mg/d
Antiandrogens	Additional suppressing of testosterone into the female range	Oral	Cyproterone acetate: 10–50 mg/d
			Spironolactone: 100–300 mg/d
		Parenteral	Triptorelin: 3.75 mg (SC) monthly/11.25 mg 3 monthly
Progesterone	Alleged enhancement of breast development	Oral	Progesterone: 200 mg/d
Transgender males			
Testosterone	Masculinization (male pattern hair growth, muscle development, cessation of uterine bleeding)	Transdermal	Testosterone gel: 20–100 mg/d
		Parenteral	Testosterone esters: 250 mg (IM) every 2–3 wk
			Testosterone undecanoate: 1,000 mg (IM) every 10–12 wk
Progesterone	Additional suppression of uterine bleeds	Oral	Lynestrenol: 5 mg/d Medroxyprogesterone: 5–10 mg/d
		Parenteral	Medroxyprogesterone: 150 mg (IM) every 12 wk

measure, no significant difference in effect was observed.[7] Transgender women often require the addition of medication to lower testosterone levels into the female range.[8] Until recently, in most European countries, oral cyproterone acetate, an androgen receptor blocker with some progesterone-like activity, was predominantly prescribed. However, since the publication of reports of increased risk of meningiomas,[9] association with depression, and increased risk of hyperprolactinemia,[10] gonadotropin-releasing hormone (GnRH) agonists to lower testosterone concentrations are now most commonly used by transgender women. In the United States, spironolactone is often prescribed due to its antiandrogen effect in high dosage. Some transgender women may request progesterone to enhance breast development; yet, no clinical studies to date have demonstrated this effect. Furthermore, there are concerns that high-dose progesterone increases thromboembolic risk based on studies in cisgender postmenopausal women,[11] and therefore its use is not incorporated in routine clinical practice.

Transgender Men

In transgender men, the GAHT to induce virilization is testosterone. Different testosterone formulations may be used (►Table 2). Mostly prescribed are the injectable testosterone esters and long-acting testosterone undecanoate, or topical testosterone gel. If menstrual bleeding does not stop after initiation of testosterone, a progesterone such as oral lynestrenol or medroxyprogesterone might be considered.

Gender-Nonbinary Individuals

For gender-nonbinary individuals, medical interventions vary depending on the person's dysphoria and often a personalized treatment plan will be made taking into consideration both efficacy and safety issues.

General Concerns

Estrogen and testosterone therapy will need to be continued lifelong to maintain the achieved feminization and virilization and to avoid symptoms of hypogonadism, especially when gonadectomy has been performed. After optional gonadectomy, androgen-lowering therapy in transwomen can be stopped. GAHT in transgender individuals is generally considered to be safe.[12] However, long-term data are scarce. A recent retrospective cohort study on five decades of 4,568 adult transgender people receiving GAHT showed an increased mortality risk regardless of treatment type—standardized mortality ratio (SMR) of 1.8 (95% confidence interval [CI]: 1.6–2.0) for transgender women compared with general population men; SMR of 2.8 (95% CI: 2.5–3.1) for transgender women compared with general population women; SMR of 1.8 (95% CI: 1.3–2.4) for transgender men compared with general population women; and SMR of 1.2 (95% CI: 0.9–1.6) transgender men compared with general population men. The cause-specific mortality risk gives no indication to a specific effect of GAHT. Social stressors have been suggested to be important contributors. Monitoring, optimizing, and, if necessary, treating medical morbidities and lifestyle factors remain utmost importance in this specific population.[13] Therefore, next to fertility preservation counseling, prior to initiation, medical professionals should evaluate transgender individuals for conditions that can be exacerbated by estradiol therapy. Next to thromboembolic risk factors as explained in detail later, for transwomen this includes hormone-sensitive cancers, coronary artery disease, cerebrovascular disease, hyperprolactinemia, dyslipidemia, and cholelithiasis. Potential long-term side effects of GnRH agonists (when gonadectomy is not performed) are not yet known for this population. For transmen, supplemental testosterone prescribed by any route of administration appears not to be associated with increased VTE risk based on large retrospective cohort studies in cisgender men (adjusted odds ratio [OR]: 0.90, 95% CI: 0.73–1.12).[14] Data on VTE risk in transgender men are limited to retrospective observational series which show no increase in the risk of thrombosis or cardiac events with testosterone use.[15] Therefore, no additional precautions targeted to modify VTE risk are necessary in transgender men. Medical conditions that are influenced by testosterone therapy and needed monitoring are extensively reviewed elsewhere[16] and include several cardiovascular risk factors (e.g., dyslipidemia, hypertension, sleep apnea, and polycythemia). Since gonadectomy is not always performed, cancers of ovary and uterus can still occur and thorough counseling on relevant screening programs is important.

Thromboembolic Risk in Transgender Women

Circumstantial Evidence

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important contributor to disability and/or death, with incidence increasing by age from 0.1 per 1,000 per year in young cisgender women, to 0.72 per 1,000 per year in cisgender women older than 50 years, to 3.84 per 1,000 per year in cisgender women older than 80 years.[17] Although specific data on thrombotic risk in transgender individuals are still very limited, data on the effects of postmenopausal HRT in cisgender women are abundantly present and it is biologically plausible that these can be extrapolated to some extent to transgender women.[18–20] A two- to fourfold increased VTE risk associated with HRT was consistently demonstrated in large nested case–control studies of more than 500,000 and 80,000 individuals, respectively,[21,22] as well as in the unique and very large placebo-controlled randomized Womens Health Initiative (WHI) clinical trials.[23] The WHI trials were specifically designed to test the effects of postmenopausal HRT, including 27,347 postmenopausal women aged 50 to 79 years. The observed increased VTE risk can be explained by an estrogen-mediated procoagulant shift in the hemostasis system through increases of coagulation factors II, VII, VIII, X, and fibrinogen, as well as decreases of levels of antithrombin and protein S, and increased activated protein C resistance,[24] also observed in transwomen on GAHT.[25] Notably, in cisgender women other risks for thrombosis further increase the risk associated with oral estrogen. Odds ratios for VTE in obese

cisgender women taking HRT increased from 2.6 (95% CI: 2.1–3.3) to 5.4 (95% CI: 2.9–10.0), and in cisgender women with inherited thrombophilia like factor V Leiden or a G20210A prothrombin mutation from 3.3 (95% CI: 2.6–4.2) to 8.0 (95% CI: 5.4–11.9).[18,20] Cisgender women with a previous history of thrombosis who received HRT had even up to a 10% annual incidence of recurrent thrombosis.[19] On the other hand, several studies showed that transdermal estrogens carry minimal or no thrombotic risk (relative risk: 1.0 [95% CI: 0.9–1.1]), even in women with a prior history of thrombosis.[18] The latter can be explained by the fact that transdermal estrogens have minimal effects on hemostatic variables such as thrombin generation and activated protein C resistance, possibly due to the absence of a first-pass effect in the liver.[26]

Studies in Transgender Women

Although data of VTE risk in transgender women are much less comprehensive, the smaller cohort and retrospective studies available seem to confirm the increased VTE risk associated with oral GAHT. For example, the largest cohort study published to date investigated more than 2,800 U.S. transgender women and more than 2,100 U.S. transgender men for a period of 4 years, and matched them to cisgender women in a 1:10 ratio.[27] In transgender women, the 2- and 8-year VTE risk differences were 4.1 and 16.7 per 1,000 person-years, respectively, relative to cisgender men, and 3.4 and 13.7 per 1,000 person-years relative to cisgender woman. The adjusted hazard ratio for VTE with oral estrogen use for transwomen was 3.2 (95% CI: 1.5–6.2) and 2.5 (95% CI: 1.2–5.0), compared with matched cisgender men and cisgender woman, respectively. A recent meta-analysis on VTE risk in transgender women included 18 studies, collectively providing information on 11,542 individuals.[28] The (absolute) overall pooled VTE incidence was 2 per 1,000 person-years (95% CI: 1–3%), which is similar to the incidence rates for VTE in transgender women found in an earlier meta-analysis of 2.3 (95% CI: 0.8–6.9) per 1,000 person-years.[29] Again, transdermal estrogen therapy was not associated with a procoagulant phenotype. Both meta-analyses are, however, affected by large and significant heterogeneity (($I^2 = 88.2\%$, $p < 0.0001$, and $I^2 = 74\%$; $p = 0.0039$, respectively). Interestingly, in these studies, the VTE risk increased with longer duration of GAHT use, which differs from HRT in cisgender women in whom VTE risk is highest in the first year of use and decreases over time. In addition, it is suggested that different types of estrogen may have different procoagulant profiles. There is some evidence that conjugated equine estrogen and 17β-estradiol may be safer than ethinyl estradiol, although this is based on smaller observational studies with no head-to-head comparisons and some conflicting results.[30–32]

Advice for Clinical Practice

Although absolute VTE risk is low, the two- to fourfold increased VTE risk associated with oral GAHT in transgender women becomes clinically relevant when other VTE risk factors are present. Additional VTE risk factors and associated relative risks are summarized in ►Table 3. Current guidelines do not address questions regarding transgender women with additional VTE risk factors who will start with GAHT, and individual risk factors should be weighed against optimal GAHT treatment. Although discontinuation of HRT is relatively easily advised in cisgender women with a history of VTE or known inherited thrombophilia, this is not the case for transgender women as the benefit of GAHT is much more pronounced. Therefore, it seems reasonable to advise GAHT associated with the lowest possible VTE risk in patients with risk factors that moderately increase VTE risk (►Table 3). Of note, relative VTE risks will increase when multiple risk factors are present. For example, when oral GAHT is combined with obesity or the presence of heterozygous factor V Leiden or G20210A prothrombin mutation, relative VTE risks are 5.4 (95% CI: 2.9–10.0) and 8.0 (95% CI: 5.4–11.9), respectively.[20] In line, the recent thrombophilia guideline of ASH suggests to consider thrombophilia testing in cisgender women who want to start HRT when they have first- or second-degree relatives with known high-risk thrombophilia such as antithrombin and protein C or protein S deficiency and to not start HRT in those who are positive for these defects (ASH Draft Recommendations for Thrombophilia Testing; ►Table 3). This is extrapolated from studies on the overall risk for VTE,[33] impact of inherited

Table 3 VTE risk factors and associated relative risks on first VTE event

VTE risk factor	RR VTE (95% CI)
Oral estrogens	2.22 (1.12–4.39)[18]
Transdermal estrogen	1.0 (0.9–1.1)[18]
Oral estrogen and progesterone	4.28 (2.49–7.34)[18]
Testosterone	0.90 (95% CI, 0.73–1.12)[14]
First degree relative with VTE	2.38 (1.43–3.85)[34]
Obesity[a]	2.6 (2.1–3.3)[20]
Heterozygous factor V Leiden or G20210A prothrombin mutation[a]	3.3 (2.6–4.2)[20]
Protein S deficiency	5.37 (2.70–10.67)[45]
Protein C deficiency	7.51 (3.21–17.52)[45]
Homozygous factor V Leiden	11.5 (6.8–19.3)[46]
Malignancy	14.91 (8.9–24.95)[47]
Antithrombin deficiency	16.3 (9.9–26.7)[45]
Compound heterozygous factor V Leiden and G20210A prothrombin mutation	20.0 (11.1–36.1)[46]

Abbreviations: CI, confidence interval; RR, relative risk; VTE, venous thromboembolism.

[a]In cisgender women, other risks for thrombosis further increase the risk associated with oral estrogen. Odds ratios for VTE in obese cisgender women taking HRT increased from 2.6 (95% CI: 2.1–3.3) to 5.4 (95% CI: 2.9–10.0), and in cisgender women with inherited thrombophilia like factor V Leiden or a G20210A prothrombin mutation taking hormone replacement therapy from 3.3 (95% CI: 2.6–4.2) to 8.0 (95% CI: 5.4–11.9).[18,20]

thrombophilia,[34,35] and estimated effect of HRT on VTE risk,[18] as well as based on an estimated reduction of more than 10 VTE events per 1,000 patient years in high-risk thrombophilia, prevented by this screening strategy and subsequent avoidance of HRT in women with high-risk thrombophilia. In all other individuals starting with HRT, thrombophilia testing is not recommended.

In individuals with a very high VTE risk (e.g., history of VTE, the presence of several VTE risk factors or high-risk thrombophilia), the benefits of GAHT should therefore be carefully weighed against the high VTE risk. Because of the important benefits of GAHT in transgender women, treatment should be individualized. As an alternative to discontinuation of GAHT, risks and benefits of concomitant administration of pharmacological thromboprophylaxis by means of anticoagulation could be considered, particularly for women who have a history of VTE. The expected incidence of bleeding during long-term vitamin K antagonist (VKA) therapy is approximately 2 to 5% per year for major bleeding, and 0.5 to 1% per year for fatal bleeding.[36,37] Direct oral anticoagulants (DOACs) are associated with lower bleeding risks (RR: 0.61, 95% CI: 0.45–0.83).[38] Three to 12 months of treatment of VTE with DOAC was associated with 1.1% major bleeding complications, compared with 1.8% in VKA-treated patients.[38] Extended duration treatment (i.e., secondary prevention of unprovoked VTE with reduced DOAC dose) has been demonstrated effective with an even lower bleeding risk of 0.2 to 0.4% major bleeds.[39,40] However, primary prevention with a DOAC and concomitant use of GAHT has not yet been investigated and cannot be recommended at present.

Perioperative Management

The annual number of gender-affirming surgeries continues to increase. There remains, however, a lack of evidence-based guidelines related to perioperative VTE prophylaxis for transgender individuals. While symptomatic VTE incidence is estimated at less than 1 to 2% for cisgender surgical patients, little is known about the incidence for the transgender surgical patient.[41] Next to optimizing adjustable risk factors (e.g., BMI), discontinuing GAHT in the perioperative period has historically been recommended to reduce VTE risk after gender-affirming surgery.[42] Most surgeons withhold hormone therapy from 2 to 6 weeks preoperatively, and resume GAHT once patients are reliably ambulating (generally 2–3 weeks after surgery). However, GAHT cessation could also lead to adverse emotional and physiologic effects, including an exacerbation of gender dysphoria.[43] There is little evidence to support the discontinuation of masculinizing hormones; however, data on the risk of feminizing hormones in the perioperative setting are conflicting and often based on outdated studies not addressing the types of estrogens most often used at present.[44] Current evidence does not support routine discontinuation of all gender-affirming hormone therapies prior to surgery, particularly given the lack of information on risks associated with resuming these medications after they have been stopped. Nowadays, shared-decision making is advised, taking into consideration general risk factors (e.g., pelvic surgery, immobility, age, morbidities) of perioperative VTE, together with detailed information on GAHT (e.g., administration route and dosing), to balance and outweigh the risks together.

Conclusion

Gender-affirming hormone treatment is associated with several health risks. Individuals using GAHT for feminization are at increased risk for VTE with certain treatment regimens, and individuals using GAHT for masculinization should be monitored for cardiovascular risk factors. Taken together, the circumstantial evidence derived from large postmenopausal HRT studies in cisgender women, combined with a plausible biologic substrate (i.e., the procoagulant hemostasis effects of estrogen) and similar preliminary evidence in smaller transgender studies make that VTE risk should be taken into account in every transgender individual who desires feminization. Of note, despite the increased relative risk, in most individuals, absolute risks remain low. Therefore, concomitant risk factors for VTE should be weighed against the benefits and risks of different types of GAHT. In case of a significantly increased VTE risk and/or multiple risk factors, this should be discussed with the individual patient and treatment should be individualized accordingly, with transdermal estrogens having no increased VTE risk. There is no evidence for routine primary anticoagulant prophylaxis in patients on oral estrogens. However, as we know that GAHT improves mental health for transgender patients significantly, in very high VTE risk transgender woman in whom oral estrogen is indicated, after careful weighing of bleeding and VTE risk, anticoagulant thromboprophylaxis could be considered. In our patient described in the introduction, an increased VTE risk is present due to the presence of heterozygous factor V Leiden; therefore, we advised transdermal estrogen administration in combination with a GnRH agonist. Discontinuation of GAHT preoperative can be discussed with the patient, but standard prophylactic measures peri/postoperative will most likely suffice.

Conflict of Interest

The authors declare that they have no conflict of interest.

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