

Deep vein thrombosis in a transgender woman

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■ Cite as: *CMAJ* 2017 April 3;189:E502-4. doi: 10.1503/cmaj.160408

A 44-year-old woman presented to a rural emergency department with a one-day history of a painful and swollen left leg. She had no chest pain or shortness of breath. The previous day, she taken an eight-hour flight, followed by an eight-hour car journey. She had not consumed any alcohol while travelling. One week earlier, the patient had sprained her left ankle and was now walking with the aid of crutches. Her past medical history included male-to-female transgender treatment with genital reconstruction surgery, which included orchidectomy, in 1998. Since her surgery, the patient was on high-dose estrogen therapy (25-mg intramuscular injections of estradiol weekly) and taking 200 mg of progesterone orally each day. She was a nonsmoker. She had no history of hypertension, hyperlipidemia, diabetes, clotting disorders, cancer or recent surgery. Her family history was negative for thrombosis.

On physical examination, the patient was in no apparent distress and had stable vital signs. Her body mass index was 25. There was mild pitting edema and redness of the left ankle. She had tenderness anterior and posterior to the lateral malleolus and slight discomfort with calf palpation. There was no tenderness above the knee. No varicosities were noted. The range of motion in the left ankle was reduced.

A radiograph of the ankle showed prominent soft tissue swelling, but no acute fracture. No blood tests were done. A presumptive diagnosis of soft tissue injury was made. A cast was not applied owing to the low probability of fracture and to encourage mobility. The patient was discharged with an air boot, and lower leg venous Doppler ultrasonography was arranged for the following day in a facility one hour away.

Ultrasonography showed a thrombus in the left posterior tibial vein. A diagnosis of distal deep vein thrombosis (DVT) was made, and the patient was started on rivaroxaban (15 mg twice daily for three weeks, then 20 mg daily for three months).

At this point, a treatment dilemma arose regarding risk management for preventing recurrent venous thromboembolism. Although several factors could have provoked our patient's DVT — ankle injury immobilization during a lengthy journey and use of estrogen therapy — stopping a reversible risk factor such as hormone treatment is common practice. However, for this woman, stopping exogenous hormones risked causing her distress concerning her physical and physiologic identity. In the 15 years since her surgery,

KEY POINTS

- Estrogen treatment is an intermediate risk factor for deep vein thrombosis in otherwise healthy people.
- Estrogen administered transdermally appears to be safer than estrogen taken orally in relation to the risk of thrombosis and thromboembolism.
- Hormone treatment with estrogen for male-to-female patients carries a small risk of thromboembolism — the minimal safe dosage should be used, tailored to the patient's age.

she had never stopped hormone treatment, although she had tried different formulations. The patient sometimes used estradiol gel instead of estradiol injections, because she found injections painful. However, the gel made her feel generally unwell, and she preferred injections for long-term maintenance. Thus, although she was aware of the risk of thrombosis, which initiated her visit to the emergency department, she wanted to stay on estrogen treatment.

Like many people with gender dysphoria, she did not have a regular family physician nor ongoing monitoring of her medications. Having had negative experiences with physician care, she preferred to read about her condition and to rely on information from the transgender community.

In discussion with the patient, a decision was made to change her estrogen treatment to a transdermal estradiol patch (50 µg), and her oral progesterone was stopped. A three-month course of rivaroxaban was completed. One year later, the patient had no recurrence of DVT and feels well. She is contemplating seeing a family physician.

Discussion

Venous thromboembolism (VTE), the collective term for DVT and pulmonary embolism, is a relatively common disorder, with an incidence of about one to two cases per 1000 population. The incidence in male-to-female people is increased up to 20-fold owing to the use of cross-sex hormone treatment, particularly estrogen.¹ Treatment of VTE is twofold: active treatment, to suppress the episode of acute thrombosis, and secondary prevention, to prevent new episodes.

Box 1: Risk of recurrence of venous thromboembolism according to provoking factor^{3,4}

Provoking factor	Risk of recurrence, %	
	Within 1 yr of stopping therapy	Within 5 yr of stopping therapy
Recent surgery	1	3
Nonsurgical trigger (estrogen, pregnancy, leg injury, flight length > 8 h)	5	15
Unprovoked venous thromboembolism	10	30
Cancer	15	–

Management of VTE

Anticoagulation is the mainstay of treatment for pulmonary embolism and proximal vein DVT. However, controversy exists regarding optimal management of DVT in the calves.² Given the risk of propagation, pulmonary embolism and recurrence, doing nothing is unacceptable. A systematic review of 6 randomized controlled trials (RCTs) and 25 observational studies concluded that either observation with elastic compression stockings and serial imaging surveillance, or anticoagulation therapy are acceptable management options.² When anticoagulation is determined necessary, a 2016 guideline recommended direct anticoagulants, such as oral rivaroxaban, based on six RCTs and meta-analysis.³ Determining appropriate treatment requires consideration of provoking factors and patient preferences.

Risk of recurrent VTE depends on the location of thrombosis and its underlying cause. The risk of recurrence for distal DVT is about half that of proximal DVT or pulmonary embolism.¹ The risk is highest for unprovoked VTE, intermediate from a nonsurgical risk factor (estrogen therapy, pregnancy, flights longer than 8 h, leg injury) and low if VTE is provoked by surgery (Box 1).^{3,4}

Estrogen and VTE

Estrogen is an intermediate reversible risk factor for VTE. Women with hormone-associated VTE are generally advised to stop hormone treatment. Baglin and colleagues⁵ suggest it may be reasonable to continue hormone treatment while receiving anticoagulation therapy, but to cease hormone treatment before stopping anticoagulation therapy. They propose that for select women with a strong clinical indication, the option of continuing hormonal treatment in addition to anticoagulation may be warranted. No trials have assessed the safety of this option.⁵

The risk of VTE with estrogen is related to the formulation of estrogen prescribed. Orally administered estrogens increase the risk of thrombosis owing to an altered balance between anticoagulant and procoagulant factors, and the risk is greatest in the first year of treatment. A meta-analysis of observational studies involving women after menopause showed a superior safety profile for transdermal therapies.⁶

Box 2: Useful resources for the care of transgender patients

- Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgenderism* 2012;4:165-232.
- Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal, et al. Endocrine treatment of transsexual persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2009;9:3132-54.
- Good practice guidelines for the assessment and treatment of adults with gender dysphoria. London (UK): Royal College of Psychiatrists; 2013. Available: www.rcpsych.ac.uk/usefulresources
- Canadian Professional Association for Transgender Health. Available: www.cpath.ca/home/

Transgender hormone therapy and risk of VTE

High rates of VTE in male-to-female people have been attributed to historic use of ethinyl estradiol, which is no longer recommended.¹ The aim of treatment is to maintain an age-appropriate physiologic range of hormones, which can be monitored with estradiol levels. Transdermal estrogen formulations are recommended, particularly for patients more than 40 years of age. If oral preparations are preferred, nonsynthetic estrogens, such as estradiol valerate or estradiol, are advised.¹ Several studies note, however, that estrogen therapy may be misused within this cohort of patients.⁷ Patients may mistakenly use ethinyl estradiol, as available in the oral contraceptive pill,¹ or take estrogen at higher than recommended doses,⁷ as in our patient's case. The risk of adverse events increases with higher doses, especially those resulting in supraphysiologic levels.⁸ It is advisable to stop hormone treatment for two weeks prior to major surgery, and to resume treatment after full mobilization.¹

Our patient was also taking daily progesterone. Progestins may have a role in developing breast tissue. Evidence for use of progestin in transgender women, and no benefits are currently proven, although increased risk of breast cancer and cardiovascular disease have been reported.⁹

Box 2 outlines some resources for the care of transgender patients.

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9. Meriggola MC, Berra M. Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes* 2013;20:565-9.

The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at www.cmaj.ca.

Competing interests: None declared.

This article has been peer reviewed.

The authors have obtained patient consent.

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Contributors: All of the authors wrote and revised the article, gave final approval of the version to be published and agreed to act as guarantors of the work

Acknowledgements: The authors thank Drs. Bernie Corenblum and Lynn Savoie, University of Calgary.

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