CLINICAL VIGNETTE

Perioperative Management of a Transwoman with venous Thromboembolism

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Introduction

Cross-sex hormone therapy is the main medical treatment in transsexual patients. For male-to-female transsexuals (transwomen), estrogen is used to induce physical characteristics of the female gender. Estrogen treatment in transwomen is associated with a 20-fold increase in venous thrombosis[1]. The thrombogenic effect is considerably higher with oral ethinyl estradiol than with transdermal or oral 17-beta-estradiol[2]. The Endocrine Society recently published clinical practice guidelines on hormonal treatment of transsexual persons[3]. These guidelines recommend measuring serum testosterone and estradiol levels, and adjusting the dosage of estrogen such that it does not exceed the peak physiological range for young healthy females (<200 pg/ml). Nevertheless, there is a lack of guidance in managing of hormone therapy in transsexuals after development of serious adverse complication, such as venous thrombosis. We present the case of a transwoman on chronic hormone therapy who developed venous thromboembolic disease (VTE) in the setting of acute trauma and immobilization. This case raises questions regarding continuation and dosage of estrogen after a serious adverse complication, and the duration of anticoagulation in treatment of VTE in patients with continued estrogen therapy.

Case Report

A 66-year-old Caucasian transwoman was transferred to our facility from an outside emergency department to the hospital after a ground level fall during an assault, resulting in a displaced complex fracture of the left acetabulum. The patient had sex reassignment surgery and had been on hormone therapy (HT) for over 30 years. At the time of admission the patient had been taking oral conjugated estrogen 1.25mg daily. She was a nonsmoker for over 30 years and there was no personal or family history of clotting disorders. Examination was significant for an obese woman with decreased range of motion of the left hip due to pain. Dalteparin was initiated for VTE prophylaxis. Given her estrogen use and time spent at an outside facility, a screening duplex ultrasound of the legs was obtained which identified acute thrombus in the right peroneal and soleal veins. Estrogen was discontinued, and she underwent open reduction, internal fixation. Postoperative surveillance ultrasound revealed extension of the right-sided VTE and new left-sided VTE that extended above the knee. A vena caval filter was placed and dalteparin was increased to treatment doses postoperatively when bleeding risk was acceptable. She ultimately transitioned to warfarin. After transfer to her rehabilitation center, the patient became emotionally distressed, refused physical therapy, and demanded re-initiation of her HT. After in-depth discussion of risks and benefits, oral conjugated estrogen was resumed, though at a lower dose (0.9mg daily). Warfarin with an INR range of 2.0 to 3.0 was continued for one year given her estrogen use. Hypercoagulable work-up was unremarkable. Her subsequent ultrasound studies did not reveal any VTE.

Discussion

Cross-sex hormone therapy for transwomen includes antiandrogen therapy to reduce endogenous testosterone level, and estrogen to induce physical characteristics of the female gender. Major adverse effects of HT include venous thromboembolic disease, coronary artery disease, cerebrovascular disease, hyperprolactinemia, elevated liver enzymes, breast cancer, and severe migraine headaches[3]. The risk of venous thrombosis is correlated to the dose and type of estrogen. Studies on reproductive women have shown that estrogen dosage correlates to the development of venous thromboembolic disease, pulmonary embolism, myocardial infarction, and stroke[4-5]. The thrombogenic effect is considerably higher with oral ethinyl estradiol than transdermal or

oral 17-beta-estradiol. Oral ethinyl estradiol results in a significant increase of activated protein C resistance and decrease in plasma protein S level, compared to 17-beta-estradiol[2]. Based on clinical impressions and the studies mentioned above, the Endocrine Society's clinical guidelines emphasize the benefit of using transdermal 17-beta-estradiol in transwomen patients. The recommendations include measuring the serum estradiol level every 3 months and adjusting the dose of estrogen such that it does not exceed the peak physiological range for young healthy females (<200 pg/ml)[3].

There are no widely accepted guidelines regarding management of hormone replacement therapy (HRT) in postmenopausal women or HT in transwomen during the perioperative period. Some practitioners recommend patients on HRT and HT gradually discontinue the therapy three to four weeks before an elective surgery, although there is lack of data to support its benefit[6,7]. This practice may reduce the risk of venous thromboembolic events, while limiting the unpleasant side effects of abruptly discontinuing hormone therapy. When transwomen require an emergent surgical intervention, should the HT be discontinued abruptly? If so, when should it be restarted? The American Heart Association has recommended that if a woman is immobilized while taking estrogen, it should be discontinued, and prophylaxis against venous thromboembolism should be considered[8]. Other authors suggest continuing HRT in women during the perioperative period, especially if they have been on HRT for over a year, but strengthening the prophylaxis for venous thromboembolism[9,**10**]. In 2001, the New Zealand Guidelines Group recommended stopping HRT at least 30 days before an elective surgery and restarting it after 90 days. Subsequently, the Group's revised guidelines in 2004 only suggested that stopping HRT perioperatively should be considered, due to insufficient evidence that stopping HRT would reduce the risk for venous thrombosis[11]. Another recent manuscript highlights the lack of evidence in hormone administration before and after surgeries in transsexuals, especially in relation to gender reassignment surgery[7]. Transwomen may benefit from discontinuing HT when they are immobilized and initiating more aggressive thromboprophylaxis. However, this has not been proven and the timing of re-initiation of HT requires further investigation.

This patient was found to have a DVT several days after admission though she was on adequate thromboprophylaxis for hip fracture surgery per the 9th edition of the American College of Chest Physicians guidelines[12]. She was initiated on dalteparin 5000 units SC daily on the day of admission until the time of surgery. She had an IVC filter placed to prevent fatal emboli while recovering from surgery as her VTE had extended. The patient was anticoagulated with low molecular weight heparin while transitioning to warfarin for VTE treatment. The general guideline for duration of anticoagulation is three months in patients whose thrombosis is associated with a major transient risk factor[13]. Our patient's DVT was associated with immobilization and oral estrogen therapy. The hip fracture leading to immobilization was a transient risk factor, but the oral estrogen therapy was restarted two weeks after surgery. Given the prothrombotic effect of estrogen, the patient was continued on warfarin for one year, and the dose of oral conjugated estrogen was decreased by 28%.

According to the Endocrine Society clinical review, transwomen greater than 40 years of age should change from oral estrogen (ethinyl estradiol or conjugated estrogen) to transdermal 17-beta-estradiol[14]. Though the patient's oral conjugated estrogen dose (1.25 mg/d) was lower than the treatment dose (2.5 mg/d) for transwomen, her risk for thromboembolic events would likely have been reduced if she had been on the transdermal 17-beta-estradiol, since she was over 40 years of age. Prospective studies are necessary to determine the optimal duration of anticoagulant therapy in transwomen patients on chronic estrogen therapy after a first venous thromboembolic event. In particular, would patients like this benefit from life-long anticoagulation while on continued HT?

Hormone therapy is critically important for transsexual individuals, not only for its physiological effects, but also for its emotional and psychosocial impact. The patient described in this case demanded to continue on oral estrogen therapy despite understanding that she was at a higher risk of developing further venous thromboembolic or cardiovascular events. Our patient was in emotional distress because she had not been receiving her estrogen therapy at the rehabilitation center. She was unwilling to participate with physical therapy, which delayed her recovery. The emotional implication of discontinuing HT should not be neglected in the medical care of transsexual patients, while balancing the need to prevent adverse complications.

Conclusion

The use of HRT has been controversial in women due to its serious adverse complications, such as venous thrombosis and cardiovascular events. There is only a small amount of literature regarding HT in transwomen. The Endocrine Society recently published guidelines in the management of HT in transwomen; however, it is not clear what the optimal method is to prevent the adverse complications from HT, especially those related to the prothrombotic effect of estrogen. We present the case of a transwoman patient on chronic HT, who developed a VTE in the setting of acute trauma and immobilization. Our case is unusual in that she was an older patient on oral conjugated estrogen for over 30 years requiring an urgent orthopedic surgery for hip fracture, subsequently developing a VTE. This case highlights the importance of adequate management of HT in transwomen to minimize the risk factors for development of. Additionally, it underscores the need for further studies to determine the optimal duration of anticoagulation for VTE treatment and prevention in transwomen on continued HT.

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