LETTER TO THE EDITOR

To the Editor

Ischemic Stroke in a Transgender Woman Receiving Estrogen Therapy

Keywords: Stroke, Transgender health, Hormone replacement therapy

A 57-year-old male-to-female (MTF) transgender woman presented to the emergency department after a fall. She reported unsteadiness and vertigo for the past few days. Her past medical history included hypertension, hypercholesterolemia, smoking, and borderline insulin resistance. As part of her gender transition treatment, she had been on a combination of spironolactone and 17-beta estradiol for the past 10 years. Six months prior to presentation, she underwent sexual reassignment surgery and was now maintained on a low dose of 17-beta estradiol. On examination, she demonstrated both limb and gait ataxia, with past pointing on finger-to-nose testing and a wide-based gait. A head CT revealed a large subacute infarct in the left cerebellum. CT angiography revealed extensive atherosclerosis both intracranially and extracranially. The remainder of her workup, including transthoracic echocardiogram and a 48-hour Holter monitor, was normal.

She was started on aspirin and atorvastatin for secondary stroke prevention. At a follow-up visit, she had some residual ataxia but her gait had improved. In discussion with her endocrinologist, the decision was made to continue oral estrogen therapy at a lower dose.

Hormone therapy in transgender individuals is used both to reduce biological sexual characteristics and to induce secondary sexual characteristics of the opposite gender. In MTF transgender patients, hormone therapy may consist of both anti-androgen therapy and estrogen therapy. A variety of estrogens are available in oral, intramuscular and transdermal forms. In general, these regimens use higher doses than are used for the treatment of vasomotor symptoms in post-menopausal women.[1]

Complications of estrogen therapy include venous thromboembolism (VTE), cardiovascular disease, cerebrovascular disease, hematologic complications, and malignancy. Much of the current understanding of these risks come from studying post-menopausal women on hormone replacement therapy (HRT), with evidence suggesting that oral estrogen therapy increases the risk of VTE and stroke in post-menopausal women.[2,3] There is somewhat divergent data on the effect of estrogen on cardiovascular events, with older women carrying a higher cardiovascular risk compared to younger women.[3] According to the 2013 Endocrine Society guidelines for treatment of menopausal symptoms in women, HRT is contraindicated in women with a history of VTE, coronary artery disease, or previous stroke/transient ischemic attack (TIA).[4]

The literature on estrogen therapy in transgender populations is less robust. Several retrospective series have reported a higher risk of VTE in transgender women on certain estrogen therapies, particularly oral ethinylestradiol. Of the various estrogen formulations, transdermal estrogen was associated with the lowest rates of VTE.[5] A retrospective study in a Belgian population of MTF transgender women on estrogen therapy found that nearly all patients who experienced VTE had additional risk factors for thromboembolism including smoking, immobilization, or a clotting disorder. Similarly, all patients who experienced TIA or stroke had existing vascular risk factors such as hypertension, hypercholesterolemia, smoking, or diabetes.[6] This raises the question of how baseline risk factors and exogenous estrogen interact to affect the risk of complications. In the case of our patient above, a prior history of hypertension, smoking, and hypercholesterolemia were likely significant contributors to her stroke.

A Dutch retrospective study of a large cohort of transgender patients reported on long-term mortality in both female-to-male and MTF transgender populations. The overall mortality in MTF transgender women was found to be 51% higher compared to the general population. The risk of cardiovascular death (defined as death due to myocardial infarction or stroke) in this population was also higher.[7] The study did not control for risk factors such as smoking or hypercholesterolemia, both of which had a higher incidence in the transgender population compared to the male general population. Interestingly, cardiovascular death was independently associated with the use of oral ethinylestradiol but not with other formulations of estrogen.

It has been hypothesized that estrogen may be protective in younger patients but exacerbate or accelerate existing cardiovascular risk in older patients. The patient in our case was started on estrogen at age 47, at which point she likely had already developed vascular risk factors. Given the comparatively younger age at which hormone therapy is initiated in transgender patients (average age at onset of therapy was 39 in the MTF population of the Dutch study, with 79% of patients under the age of 40), estrogen may in fact be safer in this population compared with post-menopausal women. However, more robust studies are needed to examine the effect of vascular risk factors in these populations compared to general populations.

Management of complications in the transgender patient population requires careful consideration, given the fact that hormone therapy is essential to the gender transition process and may need to be continued long-term. Current practice guidelines suggest changing from oral to transdermal estrogen for women who experience a VTE while on estrogen therapy. Treatment with anticoagulation may have to be continued indefinitely in patients on continuous hormone therapy.

Prevention is of key importance in the management of cardiovascular and cerebrovascular complications related to hormone therapy. Current practice guidelines recommend excellent control of risk factors in transgender patients prior to initiating hormone therapy. For transgender women with existing risk factors or established cardiovascular/cerebrovascular disease, transdermal estrogen is recommended as the first-line therapy over oral estrogen formulations.[8]

Our current understanding of estrogen therapy and stroke risk is extrapolated from studies of post-menopausal women and cannot necessarily be generalized to an MTF transgender population. There may be an increased risk of TIA or stroke in transgender patients who already have vascular disease risk factors. How that

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risk compares to biological women (or men) with similar risk factors, as well as the difference across various regimens and formulations of estrogen therapy, remain unclear. There is a need for more comprehensive, larger-scale studies of transgender populations, particularly in North American populations.

Author Contributions

PK was involved with the study concept and design, analysis of data, and literature review. AP was involved with the study supervision and critical revision of manuscript.

Disclosure Information

Priscilla Kwan and Aleksandra Pikula have nothing to disclose.

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References

1. Shatze JJ, Connelly KH, DeLoughery TG. Thrombotic issues in transgender medicine: a review. Am J Hematol. 2017;92 (2):204-8.
2. Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med. 2001;345:1243.
3. Simon JA, Hsia J, Cauley JA, et al. Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-progestin Replacement Study (HERS). Circulation. 2001; 103:638.
4. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100:3975.
5. Mohammed K, Abu Dabrh AM, Benkhadra K, Al Nofal A, Carranza Leon BG, et al. Oral vs Transdermal Estrogen Therapy and Vascular Events: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2015;100(11):4012-20.
6. Wierckx K, Van Caenegem E, Schreiber T, Haraldsen I, Fisher A, Toye K, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case–control study. Eur J Endocrinol. 2013;169(4):471-8, https://doi.org/10.1530/EJE-13-0493.
7. Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011;164(4):635-42.
8. Radix A, Deutsch MB. Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People. Center of Excellence for Transgender Health, Department of Family and Community Medicine, University of California San Francisco. 2nd edition. ed. 2016.

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