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Postmenopausal Estrogen Therapy: Route of Administration and Risk of Venous Thromboembolism

ABSTRACT: The development of menopausal symptoms and related disorders, which lead women to seek prescriptions for postmenopausal estrogen therapy and hormone therapy, is a common reason for a patient to visit her gynecologist, but these therapies are associated with an increased risk of venous thromboembolism. The relative risk seems to be even greater if the treated population has preexisting risk factors for venous thromboembolism, such as obesity, immobilization, and fracture. Recent studies suggest that orally administered estrogen may exert a prothrombotic effect, whereas transdermally administered estrogen has little or no effect in elevating prothrombotic substances and may have beneficial effects on proinflammatory markers. When prescribing estrogen therapy, the gynecologist should take into consideration the possible thrombosis-sparing properties of transdermal forms of estrogen therapy. As part of the shared decision-making process, the gynecologist should weigh the risks against the benefits when prescribing combination estrogen plus progestin hormone therapy or estrogen therapy and counsel the patient accordingly.

The purpose of this Committee Opinion is to review evidence on the safety of postmenopausal estrogen therapy. Noting that the gynecologist may prescribe either synthetic progestins or natural progesterone in conjunction with estrogen, this Committee Opinion will address estrogen-related risks only. The absolute risk of venous thromboembolism is age dependent. The incidence is estimated to be approximately 54/100,000 per year in women in their 40s, increasing to 62–122/100,000 per year in women in their 50s, and is approximately 300–400/100,000 per year in women aged 70–80 years. For women in their 80s, the estimated annual risk is approximately 700/100,000 (1–4). Combination estrogen plus progestin hormone therapy (HT) or estrogen therapy (ET) for the management of menopausal symptoms and related disorders is associated with an increased risk of venous thromboembolism. Commonly, a relative increase in risk of twofold to fivefold is cited for HT users (5–9). There is adequate evidence in the medical literature that natural progesterone is not associated with an increased risk of venous thromboembolism (10). Conversely, there is evidence that by comparison, synthetic progestins (eg, medroxyprogesterone acetate) do increase the risk of venous thromboembolism (10–12). The use of estrogen alone has been associated with a 1.2–1.5-fold relative risk compared with that of nonusers (13–18).

The relative risk of venous thromboembolism in women who take ET seems to be even greater if the treated population has preexisting risk factors for venous thromboembolism, such as obesity, immobilization, and fracture. As observed in the Heart and Estrogen/progestin Replacement Study, increased age and underlying coronary vascular disease are also risk factors for venous thromboembolism (16). Women with prothrombotic mutations, such as Leiden factor V, *G20210A* prothrombin mutation, protein C and protein S deficiencies, and other congenital thrombophilic disorders, are also especially at risk, as are women with acquired thrombophilic conditions (17). A number of substances, such as factor VII, factor VIIIc, factor IX, protein C, and C-reactive protein, are linked to an increased risk of venous thromboembolism (16, 17).

In most investigations of the relationship of venous thromboembolism and menopausal HT, the route of hormone administration has been primarily oral. It has been proposed that orally administered estrogen may exert a

prothrombotic effect through the hepatic induction of some of these substances (18–23). The prothrombotic effect is possibly related to high concentrations of estrogen in the liver due to the "first-pass" effect. Studies that compared oral and transdermal ET have demonstrated that transdermally administered estrogen has little or no effect in elevating prothrombotic substances and may have beneficial effects on proinflammatory markers, including C-reactive protein, prothrombin activation peptide, and antithrombin activity. Also, in contrast to oral ET, transdermal ET also may have a suppressive effect on tissue plasminogen activator antigen and plasminogen activator inhibitor activity (23–29).

The Estrogen and Thromboembolism Risk study, a multicenter case–control study of thromboembolism among postmenopausal women aged 45–70 years, demonstrated an odds ratio for venous thromboembolism in users of oral and transdermal estrogen to be 4.2 (95% CI, 1.5–11.6) and 0.9 (95% CI,0.4–2.1), respectively, when compared with nonusers (10). Transdermal estrogen had no increased risk compared with nonusers. Similar results were reported elsewhere (30–35) and of particular importance, in women who were stratified for weight (36) and the presence of prothrombotic mutations (37).

Several nonoral delivery systems presently are available for the administration of estradiol. These include transdermal estradiol patches, ethanolic estradiol-containing gels and sprays, and the vaginal (ring) delivery system. Topical vaginal creams and tablets prescribed for treatment of local urogenital atrophic changes have low levels of systemic absorption but have no detectable effect on coagulation proteins or incidence of venous thromboembolism. Both transdermal (patches or gels) and vaginal (ring) delivery bypass the gastrointestinal conversion of estradiol to estrone with less increase of triglyceride levels, clotting factors, and globulins (38). The vaginal ring containing estradiol acetate for systemic treatment, shown to be effective in the management of vasomotor symptoms, is not associated with an increased risk of venous thromboembolism (38–40). The practicing gynecologist should be aware that other less mainstream estrogen delivery methods, including transbuccal lozenges and troches, are widely used throughout the United States. These alternatives, which are meant to dissolve in the mouth and bypass the enterohepatic circulation, are available as single agents or in combination with other hormones and are fashioned by compounding pharmacies. Data on the safety and efficacy of compounded troches and lozenges are limited. Although widely prescribed, these less mainstream estrogen delivery methods have not been subjected to significant scientific scrutiny.

Conclusion

The development of menopausal symptoms and related disorders, which lead women to seek prescriptions for postmenopausal ET and HT, is a very common reason for a patient to visit her gynecologist. In healthy women with a negative risk history, the probability of venous thromboembolism is generally low. This risk increases with age and the presence of additional risk factors, including the presence of cardiovascular disease, obesity, fracture, renal disease, and both congenital and acquired thrombophilic disorders. These risk factors are not rare. Therefore, it is prudent for the prescriber to carefully assess the personal and family history of patients before prescribing HT or ET. When prescribing ET, the gynecologist should take into consideration the possible thrombosis-sparing properties of transdermal forms of ET. As part of the shared decision-making process, the gynecologist should weigh the risks against the benefits when prescribing HT or ET, and counsel the patient accordingly.

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