

Patch Instead of Pill A Safer Menopausal Estrogen?

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Large clinical trials have shown that oral postmenopausal estrogen treatment does not provide overall clinical benefit in chronic disease prevention,^{1,2} and current recommendations suggest that it be prescribed for only short durations for relief of menopausal symptoms. Because these drugs provide effective relief of menopausal symptoms, and venous thrombosis is the most common adverse vascular outcome of treatment, a better understanding of the venous safety of alternative forms of hormones than those widely studied is needed. In this issue of *Atherosclerosis, Thrombosis, and Vascular Biology*, results from the E3N cohort study relating route of administration of postmenopausal hormones to the risk of idiopathic venous thrombosis are presented.³ The investigators ascertained use of postmenopausal hormone treatment at 2-year intervals in 80 308 postmenopausal women without a history of cancer or prior thrombosis. Women were followed on average for 10.1 years, between 1992 and 2005. Participants were primarily teachers living in France. Hormone use status was evaluated in relation to the risk of developing venous thrombosis. During follow up, 549 women experienced idiopathic venous thrombosis, 415 with deep vein thrombosis and 134 with pulmonary embolism. The 329 women who experienced a provoked venous thrombosis were censored from the analysis at the time of their event. The rationale for this was to avoid “diluting” the impact of hormone treatment on thrombosis risk. Women experiencing other types of venous thrombosis, such as upper extremity, superficial thrombophlebitis, or retinal vein thrombosis were not considered cases. The major finding of this study was that oral, but not transdermal estradiol, was associated with risk of venous thrombosis. Adjusting for other risk factors, use of oral estradiol was associated with a 1.7-fold increased risk of venous thrombosis (95% confidence interval [CI], 1.1 to 2.8), whereas the risk estimate for transdermal estradiol was 1.1 (95% CI, 0.8 to 1.8). The authors further assessed the progestagen type used in relation to venous thrombosis risk. Among micronized progesterone, pregnane derivatives, norpregnane derivatives, and nortestosterone derivatives, only the use of norpregnane derivatives (norgestrel acetate and promegestone), compared to no progestagen, was associated with increased risk of venous thrombosis when used with transdermal estrogen. The authors con-

clude that transdermal estrogen may be safe from the standpoint of venous thrombosis unless administered with norpregnane progestagens, agents used in Europe and not the United States.

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Other observational studies have evaluated the relationship of transdermal estrogen with risk of venous thrombosis. In the most recent data from the Estrogen and Thromboembolism Risk (ESTHER) study in France, Canonico et al reported no increased risk of venous thrombosis with transdermal estradiol (odds ratio [OR], 0.9; 95% CI, 0.4 to 2.1), whereas the oral route was associated with a 4.0-fold increased risk (95% CI, 1.4 to 11.4).⁴ Before the present report, this study had evaluated the largest number of women using transdermal estrogen (67 cases, 180 controls). The norpregnane derivatives were also associated with increased thrombosis risk in this study (OR 3.9 (95% CI, 1.5 to 10.2), whereas other progestagens were not. Daly et al reported a case-control study of postmenopausal hormones and risk of venous thrombosis involving 108 cases and 232 controls. The overall adjusted OR of thrombosis with current hormone use was 3.5 (95% CI, 1.8 to 7.0) and although power was limited, the transdermal route doubled the risk of thrombosis (OR, 2.0; 95% CI, 0.5 to 7.6).⁵ Similarly, in the United Kingdom General Practice Research Database, evaluating 243 thrombosis cases and 8446 noncases, Pérez-Gutthann et al reported a 2.1-fold increased risk of venous thrombosis with hormone therapy (95% CI, 1.4 to 3.2), with a 2.1-fold increased risk (95% CI, 0.9 to 4.6) with the transdermal route.⁶ Only 7 cases used transdermal hormones. In a metaanalysis of observational studies and clinical trials not including the current study, oral administration of estrogen was associated with a 2.5-fold increased risk (95% CI, 1.9 to 3.4), whereas the transdermal route was associated with a 1.2-fold increased risk (95% CI, 0.9 to 1.7).⁷

A few criticisms of the present study by Canonico et al³ should be considered. First, as the authors point out, this is an observational study, so we cannot be certain that results reflect what would be observed in a randomized clinical trial. This is because there might be unmeasured confounders or biases that explain the observed findings. Second, the authors only considered idiopathic venous thrombosis as an end point. Venous thrombosis is a multicausal disease that, to manifest, often requires the presence of several risk factors at the same time. Along with the knowledge that approximately half of all venous thrombosis are provoked events, the present study may not capture the full picture of the association of transdermal hormones and venous thrombosis. It is possible that transdermal

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Arterioscler Thromb Vasc Biol is available at <http://atvb.ahajournals.org>
DOI: 10.1161/ATVBAHA.109.199083

hormones only increase thrombosis risk when other factors are present. Third, the authors did not consider upper-extremity or unusual-site thrombosis, entities with similar risk factors as lower-extremity deep vein thrombosis and pulmonary embolus. Further analyses including provoked thrombosis and thrombosis at these sites are needed to support their hypothesis.

Results must be carefully considered before allowing translation of these new findings to clinical practice. Because of the biases inherent in observational data and the fact that most pertinent data have come from 2 studies in 1 country (France), where the studied women have different characteristics from those in other countries (less obesity, for example), more data are needed before we can recommend that transdermal estrogen is safer than oral. Optimally, a large randomized controlled trial is needed to study clinical outcomes of women randomly assigned to the patch or placebo. The Kronos Early Estrogen Prevention Study (KEEPS) is an ongoing randomized placebo-controlled double-blind trial evaluating the effects of menopausal hormone therapy on atherosclerosis progression, as measured by the carotid intima-media thickness and coronary artery calcification, in 728 early postmenopausal women free of cardiovascular disease, coronary artery calcification, venous thrombosis, and severe major cardiovascular risk factors.⁸ Participants were randomly assigned to daily placebo, oral conjugated equine estrogen, or transdermal estradiol. Unfortunately, although this study addresses an issue of importance for atherosclerotic disease, it will be underpowered to address venous thrombosis end points.

Other study designs that could help inform this question are studies of surrogate end points, such as circulating biomarkers of venous thrombosis risk with hormones. As recently reviewed,⁹ compared to oral estrogen, transdermal treatment induces no or lesser effects on key variables related to thrombosis with hormones, such as activated protein C resistance. However, results have not been consistent in trials to date for some biomarkers such as anticoagulant protein levels, which seem to be similarly lowered with transdermal and oral estradiol. The dosing and formulation of the patch medication is also important, as recently demonstrated for a contraceptive patch.¹⁰ At this time, surrogate end point data, when taken together with the observational data available, is not sufficient to support safety from the venous thrombosis perspective. A large clinical trial or further observational studies supporting this hypothesis are needed.

Sources of Funding

None.

Disclosures

None.

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