

Are Some Types of Hormone Therapy Safer Than Others? Lessons From the Estrogen and Thromboembolism Risk Study

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Despite great strides in hormone therapy (HT) research, clinical trial data on the benefit-to-risk profile of different formulations, doses, and routes administration of HT remain lacking. Most of the large-scale clinical trials¹⁻³ have tested oral conjugated equine estrogens with or without medroxyprogesterone acetate, and data on nonoral routes and different types and doses of estrogens and progestogens have been limited. The evidence is mounting that route of delivery and possibly type and dose of HT are important factors, particularly for venous thromboembolism (VTE). Results of clinical trials^{4,5} and observational studies⁶ have been concordant in demonstrating an increased risk of VTE with oral exogenous HT. Recent studies suggest that VTE risk may be lower with transdermal than oral estrogen⁷ and with estrogen alone than with combined therapy.⁴ However, in the absence of rigorous evidence from large-scale clinical trials on differential effects by hormone formulation or route of delivery, should these findings influence clinical practice?

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The Estrogen and Thromboembolism Risk (ESTHER) study,⁷ published in the current issue of *Circulation*, adds important, relevant data to bolster the case that HT type and route of delivery do indeed make a difference. This well-designed, French, multicenter case-control study of VTE enrolled 271 consecutive cases of VTE in women (age, 45 to 70 years) and matched them to hospital and community controls. Current HT use was present in 46% of the VTE cases compared with 37% of controls. Oral HT users had 4-fold-increased odds of VTE; however, there was no increased risk among transdermal hormone users (odds ratio, 0.9). Previous randomized trials have suggested that the risk of VTE may be higher with combined oral estrogen and progestogen therapy than with estrogen alone.^{4,5} In ESTHER, type of progestogen also appeared to influence risk of VTE. Neither micronized progesterone nor pregnane derivatives (including medroxyprogesterone acetate) were associated with VTE, whereas norepregnane derivatives were associated with a 4-fold increase in odds of VTE.

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The present study has several important strengths, including a large number of carefully adjudicated cases, a population with a large percent of transdermal estrogen users, and a wide variety of progestogen types. Similar data on the relationship of clinical end points to route of estrogen and type of progestogen would not be readily obtainable in the United States, where transdermal preparations and alternate types of progestogens constitute a relatively small proportion of total HT use. Because of small numbers, cases and controls using nortestosterone derivatives were excluded from the main analyses, although a significantly increased risk also was observed in this group.

As for any observational or case-control study, selection and confounding biases must be considered. Reasons for choosing a particular progestogen in this population are unknown, so it is possible that clinical factors could have contributed to this choice and the observed risks. As the authors point out, norepregnane derivatives often are used for premenopausal women, those with hyperestrogenic symptoms, or those intolerant of estrogens; thus, prescription bias might partially explain the higher risk observed in this group because higher endogenous estrogens may be linked to VTE.⁸ Transdermal users in ESTHER also were older and had a longer duration of hormone use than oral users. Bias also could have arisen in the selection of controls.

No large-scale randomized trials of transdermal estrogens in relation to VTE have been conducted. Results of observational studies on this subject warrant consideration, however. In addition to an earlier report from ESTHER,⁹ 3 previous case-control studies with small numbers of cases using transdermal estrogen¹⁰⁻¹² found no significant differences between oral and transdermal preparations and odds ratios of ≈ 2 for transdermal users compared with HT nonusers with wide CIs that included null.¹³ The observed VTE risks for oral estrogen and progestogen in ESTHER were higher than for the Women's Health Initiative (WHI) randomized trial findings.^{4,5} Unlike the WHI, the ESTHER study examined only primary or idiopathic VTE; those with predisposing factors (including those with prior history of VTE; recent surgical intervention, immobilization, or bed rest for >8 days; or known cancer, thrombophilia, or systemic inflammatory disease) were excluded. If hormone use is a particularly strong risk factor for primary VTE, this might explain the higher risk observed for ESTHER, although selection biases are an alternate explanation and indicate the need for caution in interpreting the findings.

Route of Administration

The data from ESTHER lend additional support to the evidence that route of estrogen administration matters. Trans-

dermal preparations avoid the induction of hepatic protein synthesis associated with the first-pass effect of oral estrogens. Hypercoagulant effects (higher prothrombin fragment 1+2 and factor VII levels) and increased synthesis of C-reactive protein are observed after oral but not transdermal estrogen.¹⁴ Transdermal estradiol also avoids peaks and nadirs in circulating concentrations. Although the differences in rates of VTE with route of estrogen are intriguing, any extrapolation of these findings to other forms of cardiovascular disease should be undertaken with caution given the increased risk of cardiovascular disease events observed in the Papworth trial, a trial of transdermal estrogen for the secondary prevention of cardiovascular disease.¹⁵

Type of Progestogen

Why would the type of progestogen influence the risk of VTE? Although all progestogens share a protective effect on estrogen-primed endometrium, many other biological effects differ between formulations. The parent compounds differ for progestins and may determine many of the biological effects through differing activity on progesterone, androgen, glucocorticoid, and antimineralocorticoid receptors.¹⁶ Progestogen types may have different effects on lipids, markers of inflammation, coagulation, and thrombosis,¹⁶ but few direct comparisons exist. In a small study comparing medroxyprogesterone acetate and micronized progesterone, both significantly decreased tissue factor antigen and increased tissue factor activity, suggesting activation of coagulation pathways, and both lowered plasminogen activator-1 levels, demonstrating enhanced fibrinolysis.¹⁷ In the oral contraceptive literature, type of progestogen has been related to risk of VTE, with 19-nortestosterone derivatives particularly associated with higher risk of VTE.¹⁸ Thus, although not definitive, the ESTHER results should focus more attention on the particular properties of different progestogen formulations and their impact on clinical outcomes.

Dose

Although the authors did not specifically examine dose, this also should be considered in clinical practice. In observational studies, higher-dose oral contraceptives and higher-dose HT have been associated with significantly higher risk of VTE.¹⁸ Low-dose HT (0.3 mg conjugated equine estrogen) had significantly fewer effects on coagulation and inflammatory markers (prothrombin fragment 1+2, antithrombin III, and C-reactive protein) than conventional dose therapy.¹⁹ Thus, dose should remain a consideration when hormonal therapies are prescribed.

Clinical Implications and Avenues for Future Research

The ESTHER study suggests that, at least for risk of VTE, both the route of estrogen administration and the choice of progestogen make a difference. The lower risk of VTE associated with transdermal compared with oral estradiol for postmenopausal HT raises the question of whether transdermal routes for contraceptives might also minimize the excess risk of VTE, although estrogen dosing and progestogen formulation also would have to be considered.

For perimenopausal and postmenopausal HT, the present study suggests differences in VTE risk with route of estrogen administration and possibly progestogen type. Whether differences in other cardiovascular disease end points also might be affected by route of estrogen administration and type of progestogen should be tested in clinical trials, but such large-scale clinical trials are unlikely to be conducted in the near future. In the meantime, studies should look at biological intermediaries associated with different hormone regimens. The Kronos Early Estrogen Prevention Study (KEEPS) will offer one look at these differences. KEEPS is randomizing recently menopausal women to conjugated equine estrogens (0.45 mg) and micronized progesterone (200 mg) daily or to transdermal estradiol (50 μ g) and micronized progesterone (200 mg) daily and evaluating changes in carotid intimal medial thickness, coronary artery calcium, and thrombotic, inflammatory, and other biomarkers.²⁰ At present, the totality of evidence appears compelling enough to suggest that transdermal preparations be considered, among other factors relevant to decision making, when choosing an HT regimen. The findings from ESTHER remind us that HT is not a singular entity; we need to consider route, type, and dose of these complex agents in practice and in future research.

Disclosures

None.

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