Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women

Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study

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Background—Oral estrogen therapy increases the risk of venous thromboembolism (VTE) in postmenopausal women. Transdermal estrogen may be safer. However, currently available data have limited the ability to investigate the wide variety of types of progestogen.

Methods and Results—We performed a multicenter case–control study of VTE among postmenopausal women 45 to 70 years of age between 1999 and 2005 in France. We recruited 271 consecutive cases with a first documented episode of idiopathic VTE (208 hospital cases, 63 outpatient cases) and 610 controls (426 hospital controls, 184 community controls) matched for center, age, and admission date. After adjustment for potential confounding factors, odds ratios (ORs) for VTE in current users of oral and transdermal estrogen compared with nonusers were 4.2 (95% CI, 1.5 to 11.6) and 0.9 (95% CI, 0.4 to 2.1), respectively. There was no significant association of VTE with micronized progesterone and pregnane derivatives (OR, 0.7; 95% CI, 0.3 to 1.9 and OR, 0.9; 95% CI, 0.4 to 2.3, respectively). In contrast, norpregnane derivatives were associated with a 4-fold-increased VTE risk (OR, 3.9; 95% CI, 1.5 to 10.0).

Conclusions—Oral but not transdermal estrogen is associated with an increased VTE risk. In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk. If confirmed, these findings could benefit women in the management of their menopausal symptoms with respect to the VTE risk associated with oral estrogen and use of progestogens. (Circulation. 2007;115:840-845.)

Key Words: embolism ■ epidemiology ■ estrogens ■ progestogens ■ thrombosis

Since the publication of the Women Health Initiative (WHI) results,1 medical practices of hormone therapy have been dramatically altered.2 Despite a striking decrease in hormone therapy use, many women remain eligible for this treatment to correct postmenopausal climacteric symptoms and to prevent osteoporosis. Cardiovascular disease, including venous thromboembolism (VTE), is an important determinant of the benefit-to-risk profile of hormone therapy.3 Both observational studies4–13 and clinical trials13,14,15 have shown a significant increase in VTE risk among postmenopausal women using hormone therapy. However, most of these studies were done in women using preferentially oral estrogen alone or combined with a specific pregnane derivative (medroxyprogesterone acetate), and these results are not necessary relevant to other hormone regimens. In European countries, especially in France, the transdermal route of estrogen administration is used most often. In addition, many progestogen derivatives are available, and the impact of the different types of progestogens on the VTE risk has not been investigated. Therefore, we designed the Estrogen and Thromboembolism Risk (ESTHER) study, a multicenter case–control study performed in...
France, to investigate the impact of the route of estrogen administration on VTE risk among postmenopausal women. Early results of our study have shown that oral but not transdermal estrogen increases VTE risk. Final analysis of the ESTHER study, based on a more important pool of cases and controls, focuses on the impact of the progestogens on VTE risk.

Methods
The ESTHER study is a multicenter case–control study. It was done in France in 8 hospitals and in the general population between 1999 and 2006. Details of the study design have been described. Selection of Cases and Controls
We included consecutively 208 hospital cases with a first documented episode of idiopathic VTE and 426 hospital controls. Controls had to have been admitted to the hospital with an a priori diagnosis unrelated to estrogen use. These diagnoses included diseases of eye, ear, skin, respiratory and alimentary tracts, bones and joints, and kidneys; infectious diseases; and diabetes. In addition, we included consecutively 63 outpatient cases from 3 hematology centers matched with 184 community controls selected at random from electoral rolls. About 5% of hospital controls and 10% of community controls refused to participate in this study. Cases and controls were matched for center, 2-year age band, admission date, and area of residence. Each case was matched with 1 to 3 controls.

Both hospital and outpatient cases were excluded if they reported a personal history of VTE, had a contraindication for hormone therapy (breast cancer, endometrial cancer, and cardiovascular disease), or had a predisposing factor for VTE (history within the previous month of surgical intervention, trauma with immobilization for >8 days, illness necessitating bed rest for >8 days, known cancer, systemic inflammatory disease). Outpatient cases also were excluded if they were referred to clinical centers for estrogen advice or known thrombophilia. Controls were subjected to the same exclusion criteria as cases.

Ascertainment of Cases
Clinical events had to be diagnosed with an imaging procedure. Pulmonary embolism was defined as the presence of either helicoidal computed tomography showing at least 1 intraluminal defect in 1 segmental pulmonary artery, high-probability ventilation/perfusion scan according to criteria from the Prospective Investigation of Pulmonary Embolism Diagnosis, or pulmonary angiography showing a clot. Deep venous thrombosis was diagnosed by use of compression ultrasonography. Events were adjudicated within each center but also centrally for outpatient cases. Events were validated by investigators blinded to estrogen use.

Data Collection
Cases and controls were identified without knowledge of estrogen use, and they were interviewed at hospital in a standard way with the same questionnaire. Menopause was defined by amenorrhea for >12 months or bilateral ovariectomy or hysterectomy together with an age questionnaire included details of type, dose, and duration of treatment. Identification of hormone therapy was assisted by showing the participants pictures of both available estrogens and progestogens. The questionnaire included details of type, dose, and duration of treatment.

Current users of hormone therapy were classified according to both the route of estrogen administration and the type of progestogens. First, treated women were classified as either oral estrogen users or transdermal estrogen (patch or gel) users. Second, current users of hormone therapy also were categorized according to the progestogen North American Menopause Society classification. Women were classified as users of micronized progesterone or progestin derivatives, norprogesterin derivatives, or nortestosterone derivatives. Progesterin derivatives included dydrogesterone or medrogestone, chlormadinone acetate, cyproterone acetate, or medroxypregesterone acetate. Norprogesterin derivatives included either norgestrel acetate or promegestone.

Statistical Analysis
Continuous data are expressed as mean and SD; categorical variables are given as absolute values and percentages.

We estimated the odds ratios (ORs) and 95% CIs from conditional logistic regressions. Data were analyzed by classifying the cases and controls according to hormone therapy. Current users were compared with nonusers in a joint model of both route of estrogen administration (either oral or transdermal) and type of progestogens (either micronized progesterone or progestin or norprogesterin derivatives). We excluded the users of oral estrogen combined with nortestosterone derivatives (12 cases, 7 controls), and VTE odds ratio associated with this type of hormone therapy was estimated separately with nonusers as the reference group. ORs were adjusted for obesity status, familial history of VTE, and varicose veins (adjustment 1) and further adjusted for education, age at menopause, hysterectomy, and cigarette smoking (adjustment 2). Interactions between estrogens and progestogens effect were tested by using a multiplicative OR model. Stratified analyses were done to investigate the impact of estrogen dose and duration of treatment on the main findings. Statistical analyses were performed with SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC).

Results
General characteristics of cases and controls are given in Table 1. As expected, the mean age of cases and controls was similar. Mean body mass index and age at menopause were significantly higher among cases than controls. Cases were more likely than controls to have reported familial history of VTE and varicose veins. No significant differences in current smoking, education level, type of menopause, and hysterectomy were found between cases and controls. There was no association between past use of estrogen and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7). In addition, because recency of treatment was not associated with VTE risk, past users and never users were pooled as nonusers.

Overall, 26.0% of cases and 29.9% of controls used transdermal estrogen therapy (OR, 0.9; 95% CI, 0.4 to 2.1), and 17.4% of cases and 6.5% of controls were treated by oral estrogen therapy (OR, 4.0; 95% CI, 1.4 to 11.4) (Table 2). Adjustment for potential confounding factors made little changes to the results. Most current users of estrogen therapy received 17β-estradiol. No controls and only 2 cases used conjugated equine estrogens. The most common dose for transdermal estrogen use was ≤50 μg/d. Approximately 15% of transdermal estrogen users received preparations delivering >50 μg/d. In current users of oral estrogen therapy, the mean dose of estradiol was 1.5 mg/d, ranging from 0.5 to 2 mg daily.

Table 2 gives the VTE OR associated with the types of progestogen after exclusion of 12 cases and 7 controls who used oral estrogen combined with nortestosterone derivatives (OR, 6.7; 95% CI, 2.1 to 21.9). There was no significant interaction between estrogens by route of administration and progestogens.
Overall, only 5.4% of cases and 6.7% of controls were treated by estrogen alone. Micronized progesterone was used by 7.4% of cases and 10.4% of controls (OR, 0.7; 95% CI, 0.3 to 2.0). Mean dose of micronized progesterone was 100 mg/d. Pregnanes were used by 15.1% of cases and 13.1% of controls (OR, 0.9; 95% CI, 0.4 to 2.4). Pregnane derivatives included dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, and medroxyprogesterone acetate. Finally, norpregnane derivatives, either nomegestrol acetate or promegestone, were used by 15.5% of cases and 6.1% of controls. Twenty-two cases received nomegestrol acetate; 18 received promegestone. The usual daily dose of nomegestrol acetate was 5 mg and of promegestone was 0.250 mg. The risk of VTE increased significantly (3 times) among users of norpregnane derivatives compared with nonusers (OR, 3.9; 95% CI, 1.5 to 10.2). In addition, ORs of VTE in current users of nomegestrol acetate and current users of promegestone were similar and significantly differed from 1 (data not shown).

### TABLE 1. Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n=271)</th>
<th>Controls (n=610)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.6±6.7</td>
<td>61.5±6.6</td>
<td>0.33</td>
</tr>
<tr>
<td>Body mass index,† kg/m²</td>
<td>27.0±5.7</td>
<td>24.5±4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obesity (body mass index &gt;30 kg/m²),† n (%)</td>
<td>56 (20.7)</td>
<td>75 (12.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Familial history of VTE, n (%)</td>
<td>83 (30.6)</td>
<td>125 (20.5)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Personal history of varicose veins, n (%)</td>
<td>149 (55.8)</td>
<td>273 (44.8)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Current smokers,‡ n (%)</td>
<td>33 (12.4)</td>
<td>78 (12.8)</td>
<td>0.773</td>
</tr>
<tr>
<td>Education level beyond secondary, n (%)</td>
<td>44 (17.1)</td>
<td>119 (19.8)</td>
<td>0.385</td>
</tr>
<tr>
<td>Age at menopause,§ y</td>
<td>49.6±4.6</td>
<td>48.6±5.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Hysterectomy,∥ n (%)</td>
<td>42 (17.1)</td>
<td>113 (19.2)</td>
<td>0.6302</td>
</tr>
<tr>
<td>Type of menopause,∥∥ n (%)</td>
<td></td>
<td></td>
<td>0.6074</td>
</tr>
<tr>
<td>Natural</td>
<td>203 (82.5)</td>
<td>474 (80.6)</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>43 (17.5)</td>
<td>114 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Estrogen therapy use,¶ n (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Never use</td>
<td>106 (39.3)</td>
<td>286 (46.9)</td>
<td></td>
</tr>
<tr>
<td>Past use</td>
<td>40 (14.8)</td>
<td>98 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Current use of transdermal estrogen</td>
<td>67 (24.8)</td>
<td>180 (29.5)</td>
<td></td>
</tr>
<tr>
<td>Current use of oral estrogen</td>
<td>57 (21.1)</td>
<td>46 (7.5)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±SD when appropriate.
*Probability values are derived from conditional logistic regression.
†Data for 1 case and 1 control are missing.
‡Data for 4 cases are missing.
§Data for 22 cases and 19 controls are missing.
∥Data for 25 cases and 22 controls are missing.
¶Data for 1 case are missing.

### TABLE 2. Impact of Hormone Therapy on VTE Risk by Route of Estrogen Administration and Type of Progestogens

<table>
<thead>
<tr>
<th>Matched OR (95% CI)</th>
<th>Cases (n=259)</th>
<th>Controls (n=603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse</td>
<td>146</td>
<td>384</td>
</tr>
<tr>
<td>Oral estrogen use</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>Transdermal estrogen use</td>
<td>67</td>
<td>180</td>
</tr>
<tr>
<td>No progestogens</td>
<td>14</td>
<td>40</td>
</tr>
<tr>
<td>Micronized progesterone</td>
<td>19</td>
<td>63</td>
</tr>
<tr>
<td>Pregnane derivatives</td>
<td>39</td>
<td>79</td>
</tr>
<tr>
<td>Norpregnane derivatives</td>
<td>40*</td>
<td>37†</td>
</tr>
</tbody>
</table>

Users of oral estrogen combined with nortestosterone derivatives (12 cases, 7 controls) were excluded (OR, 6.7; 95% CI, 2.1 to 21.9 vs nonusers). Estrogen-by-progestogen interaction terms were not significant. Adjustment 1: adjustment for obesity status, familial history of VTE, and history of varicose veins. Adjustment 2: adjustment for obesity status, familial history of VTE, history of varicose veins, education, age at menopause, hysterectomy, and cigarette smoking.

*Twenty-two cases received nomegestrol acetate, and 18 cases received promegestone.
†Nineteen controls received nomegestrol acetate, and 18 controls received promegestone.
To ensure that our findings were not influenced by estrogen dose and time of hormone exposure, stratified analyses were done. Using the median of the distribution of exposure time (5 years) as a cutoff point, we obtained consistent results in the corresponding subgroups. When the analysis was restricted to women using the more common doses of estrogens (≤50 μg/d for transdermal estrogen and ≤1.5 mg/d for oral estrogen), risk estimates were similar to those observed in the whole population.

With regard to the potential determinants of the route of estrogen administration and type of progestogens, transdermal estrogen users were older and used estrogen longer than oral estrogen users. There was no significant difference in other characteristics between oral and transdermal estrogen users. No significant correlates of type of progestogens were found, except for the estrogen dose. The proportion of women using high- or low-dose estrogen was lower in the pregnane subgroup without any change in the mean dosage.

Discussion

Our data confirm that oral but not transdermal estrogen increases VTE risk among postmenopausal women. In addition, these data show that micronized progesterone and pregnane derivatives may be safe with respect to thrombotic risk. Furthermore, our results suggest that norpregnane derivatives are thrombogenic.

Progestagen is added to estrogen therapy among postmenopausal women with an intact uterus to prevent the elevated risk of estrogen-induced endometrial hyperplasia and adenocarcinoma. Unlike medical practices in the United States where medroxyprogesterone acetate is the almost exclusively prescribed progestogen among postmenopausal women, a wide variety of progestogens is used in European countries, especially in France. Progestogens include both progesterone and synthetic progestins derived from progesterone (pregnanes and 19-norpregnanes) or from testosterone (19-nortestosterones). Progestins have different pharmacological properties depending on the parent molecule from which they are derived. Very small structural changes in the parent molecule may induce considerable differences in the progestin activity.19 The effects of progestins are related to interactions not only with progesterone receptors but also with other steroid hormone receptors. Norpregnane derivatives, including nomegestrol acetate and promegestone, appear to have a very high progestational activity.19 Some data on the effect of progestogens by route of estrogen administration on VTE risk have been published.32,33 Few data on the effect of progestogens by route of estrogen administration on hemostatic variables have been reported. However, we have previously reported that transdermal estrogen combined with micronized progesterone had little or no effect on blood coagulation activation as shown by the absence of significant variation in plasma concentration of prothrombin fragment 1+2.29 In addition, 2 randomized controlled trials have shown that oral but not transdermal estrogen, both combined with micronized progesterone, induced an activated protein C resistance.35,36 Thus, hemostatic data, together with the results of the ESTHER study, suggest that transdermal estrogen combined with micronized progesterone is safe with respect to VTE risk. Similarly, recent data showing that chlormadinone acetate, a progestin derivative, has little or no effect on blood coagulation and fibrinolysis are consistent with the absence of increased VTE risk among postmenopausal women using transdermal estrogen combined with progesterone derivatives. With regard to the
norpregnane derivatives, one randomized trial failed to show any changes in hemostatic variables among women receiving oral estrogen combined with nomegestrol acetate. Among women recruited from the Project Aging Women, van Baal et al and Post et al have studied the effect of trimegestone (a norpregnane derivative), dydrogesterone, or both combined with oral estrogen therapy on hemostatic variables. Deleterious effects of oral estrogen therapy on coagulation without significant differences between all progestogen subgroups were found. These results are consistent with our clinical findings about oral estrogen use but are not relevant to transdermal estrogen therapy. Thus, whether norpregnane derivatives have prothrombotic effects among postmenopausal women requires further investigation.

Elevated VTE risk among postmenopausal women using some hormone regimens also could be mediated through changes in venous structure and function. The occurrence of venous stasis during luteal phase or pregnancy, together with the presence of estrogen and progesterone receptors in the venous wall, suggests that venous blood flow may be directly modulated by steroid hormones. Therefore, norpregnane derivatives, which have a high progestational activity, might increase the VTE risk through venous stasis via a progestrogen receptor-mediated pathway. The role of progestogens in the alteration of vessels blood flow and in the development of varicose veins warrants further study.

One potential limitation of our study is that observational studies are subject to bias. The validity of the ESTHER study has been discussed. To minimize the effects of bias on interpretation, both cases and controls were recruited using a number of selection criteria. Elevated levels of VTE risk factors, including age, obesity, familial history of VTE, varicose veins, and prothrombotic mutations, could explain our findings related to the route of estrogen administration and progestogens. However, the proportion of women at high risk for VTE was similar across all the estrogen and progestogen subgroups. In addition, adjustment for these potential confounders and other relevant covariates made few changes to the results. On the other hand, stratified analyses by characteristics of hormone therapy, including estrogen dose and duration of treatment, showed consistent results. Another selection bias could be related to the differential prescription of progestogens according to the estrogen status of women using hormone therapy. Norpregnane derivatives are more likely to be prescribed to women with hyperestrogenic symptoms. Because there is evidence that lifetime estrogen exposure is positively related to VTE risk in postmenopausal women, such prescription bias could explain in part the high VTE risk among women using transdermal estrogen combined with norpregnane derivatives. Another limitation of our study is related to the small number of subjects within progestogen subgroups, especially among users of oral estrogen. Among transdermal estrogen users, the upper 95% confidence bounds for the adjusted odds ratios show that the data only rule out increases in the odds ratios of VTE >80%, 20%, and 60% for estrogen alone, estrogen combined with micronized progesterone, and estrogen combined with pregnane derivatives, respectively.

In the WHI trials, pulmonary embolism accounts for about one third of the excess incidence of potentially fatal events resulting from oral estrogen. Therefore, our findings may be of great clinical relevance in minimizing the VTE risk among women who require hormone therapy. Our data emphasize the importance of the route of estrogen administration and the choice of progestogen in determining of the benefit-to-risk profile of hormone therapy. The effect of transdermal estrogen combined with different progestogen types on health outcomes should be investigated in randomized trials.

Acknowledgments

Sources of Funding
The study was supported by the Fondation de France, by the Fondation pour la Recherche Médicale and Institut National de la Santé et de la Recherche Médicale (Inserm), and by grants from Aventis, Besins International, Sanofi, and Servier Institute.

Disclosures
None.

References


19. Kumar N, Koide SS, Tsong Y, Sundaram K. Nestorone: a progestin with a side effect of hormone therapy, and pulmonary embolism accounts for about one third of the excess incidence of potentially fatal events resulting from hormone therapy. So far, most studies assessing the effect of hormone therapy on clinical outcomes have been done in women using preferentially oral estrogen, alone or combined with medroxyprogesterone acetate. In European countries, many women use transdermal estrogen, alone or combined with a large variety of progestogens. The Estrogen and Thrombosis Risk study, a French case–control study, was the first to provide evidence for a differential association of oral and transdermal estrogen with venous thromboembolism risk. Final analysis of this study confirms that oral but not transdermal estrogen increases venous thromboembolism risk. In addition, these data suggest that nonpregnane derivatives may be thrombogenic, whereas micronized progesterone and progestagens derivatives appear safe with respect to thrombotic risk. Although these findings have to be confirmed by randomized clinical trials, they suggest that the route of estrogen administration and the type of progestogen may be important determinants of the benefit–risk profile of hormone therapy, especially in women at high venous thromboembolism risk.

**CLINICAL PERSPECTIVE**

Since the results of the Women’s Health Initiative trials, hormone therapy use dramatically decreased among postmenopausal women. However, many women remain eligible for this treatment. Venous thromboembolism is a serious side effect of hormone therapy, and pulmonary embolism accounts for about one third of the excess incidence of potentially fatal events resulting from hormone therapy. So far, most studies assessing the effect of hormone therapy on clinical outcomes have been done in women using preferentially oral estrogen, alone or combined with medroxyprogesterone acetate. In European countries, many women use transdermal estrogen, alone or combined with a large variety of progestogens. The Estrogen and Thrombosis Risk study, a French case–control study, was the first to provide evidence for a differential association of oral and transdermal estrogen with venous thromboembolism risk. Final analysis of this study confirms that oral but not transdermal estrogen increases venous thromboembolism risk. In addition, these data suggest that nonpregnane derivatives may be thrombogenic, whereas micronized progesterone and progestagens derivatives appear safe with respect to thrombotic risk. Although these findings have to be confirmed by randomized clinical trials, they suggest that the route of estrogen administration and the type of progestogen may be important determinants of the benefit–risk profile of hormone therapy, especially in women at high venous thromboembolism risk.
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_Circulation_. 2007;115:840-845
doi: 10.1161/CIRCULATIONAHA.106.642280
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
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