The Effects of Hormone Replacement Therapy (HRT) on Hemostatic Variables in Women with Previous Venous Thromboembolism – Results from a Randomized, Double-Blind, Clinical Trial

Else Høibraaten, Erik Qvigstad, Trine Opstad Andersen, Marie-Christine Mowinckel, Per Morten Sandset

Department of Hematology, Hematological Research Laboratory, and 1Department of Gynecology, Ullevål University Hospital, Oslo, Norway

Key words
Hormone replacement therapy, venous thromboembolism, coagulation factors, coagulation inhibitors, activated coagulation

Summary
In a recent randomized, double-blind, placebo-controlled trial of women with a history of venous thromboembolism (VTE), we found that hormone replacement therapy (HRT) was associated with an early excess risk of recurrent thrombosis. The aims of the present study were to elucidate the mechanism(s) by which HRT increases the risk of thrombosis. The study comprised 140 women who were randomized to receive continuous treatment for 24 months with once daily 2 mg 17β-estradiol plus 1 mg norethisterone acetate (n = 71) or placebo (n = 69). HRT caused significant increases in prothrombin fragments 1+2, thrombin-antithrombin complex, and D-Dimer after 3 months, but these changes were less pronounced on prolonged treatment. The increases in markers of activated coagulation were higher in those women who subsequently developed recurrent thrombosis, but was similar in carriers and non-carriers of the factor V Leiden mutation. HRT had no effects on fibrinogen and factor VIII. Activated factor VII, but not factor VII antigen, decreased significantly on HRT as compared with placebo. The coagulation inhibitors antithrombin, protein C, and TFPI, but not protein S, all showed significant sustained decreases in the HRT group as compared with placebo. Antithrombin and protein C decreased by 8-12% on HRT, whereas TFPI activity decreased by 12-17% and TFPI free antigen by 29-30%. In multivariate analysis, only TFPI activity was a significant predictor for the increased activation of coagulation. We conclude that HRT was associated with early activation of coagulation, which corroborates the finding of an early risk of recurrent VTE. This activation may in part be explained by reduction in circulating anticoagulants.

Introduction
During the last decade, several epidemiological studies (1-6) have found an increased risk of venous thromboembolism (VTE) among current users of hormone replacement therapy (HRT). The risk of VTE was highest during the first year of treatment, but relationships with estrogen dose, HRT formulation, and route of administration were not identified. The results of these studies have now been confirmed in two randomized, placebo-controlled trials of women at high risk of thrombosis, i.e., in women with established coronary heart disease (7) and in women with previous venous thrombosis (8).

No single or combined effects on hemostatic variables may so far explain the increased risk of VTE associated with HRT. Several studies have investigated the effect of HRT on coagulation, but the absolute changes detected have been small and have usually stayed within the normal ranges (9). The results in different studies have been inconsistent, which may be explained by different HRT regimens, relatively small sample sizes, and also poorly defined susceptibility for thrombosis in participating women.

In our own randomized, double-blind, clinical trial we found an increased risk of recurrent VTE associated with HRT (8). The influence of HRT on coagulation in women with previous thrombosis may be stronger and more easily detected than in other studies. In the present study, we have investigated the effect of HRT on coagulation in these women, and the effects of HRT have been related to the risk of recurrent thrombosis.

Materials and Methods
Subjects
The participants were randomized in the Estrogen in Venous Thromboembolism Trial (EVTET). The study design and main results of the study have been reported earlier (8). All participants gave written informed consent to participate. The protocol was approved by the Regional Ethical Committee of Health Region I and by the Norwegian Medicines Control Authority.

Altogether 140 postmenopausal women younger than 70 years, who had suffered previous deep venous thrombosis (DVT) or pulmonary embolism (PE), were randomized. Postmenopausal was defined as no natural menses for at least one year. Women were excluded for the following reasons: current use or use of anticoagulants within the last three months, familial antithrombin deficiency, any type of malignant diseases, acute or chronic liver disease or history of liver disease, porphyria, known drug abuse or alcoholism, life expectancy less than two years or patients who had taken part in other clinical drug trials within 12 weeks before the study entry.

Correspondence to: Else Høibraaten, MD, Ullevål University Hospital, Department of Hematology, Hematological Research Laboratory, N-0407 Oslo, Norway – Tel.: +47 22118280; Fax: +47 22117533, E-mail: else.hoibraaten@ioks.uio.no
Study Design

The study was a randomized, double-blind, placebo-controlled trial. The participants were allocated to treatment with HRT tablets (n = 71) containing 2 mg 17-β-estradiol and 1 mg norethisterone acetate (Kliogest®, Novo Nordisk, Gentofte, Denmark) or to equal-looking placebo tablets (n = 69). Major outcome parameter was recurrent VTE, and occurred in 8 women in the HRT group and 1 woman in the placebo group (8). The study was terminated prematurely due to results of new studies published during the execution of the trial showing an excess risk of VTE associated with use of HRT, and because of clustering of VTEs in one study group. Scheduled follow-up visits with venipuncture occurred before randomization (baseline), and after 3, 12, and 24 months of treatment. Participants who ended the study prematurely due to premature termination met for a final visit with blood sampling before discontinuation of trial medication and the results for this visit was carried forward to the next scheduled visit. Safety parameters, including standard hematological and biochemical tests, were assessed at each visit.

Blood Collection

Venous blood samples were collected between 8 and 10 am after overnight fasting and after 10 min rest. Blood was collected in 5 ml Vacutainer® tubes (Becton-Dickinson, Meylan-Cedex, France) containing 0.5 ml buffered citrate (0.129 mol/L). The tubes were kept at ambient room temperature to avoid cold activation, and were centrifuged at 2000 g for 20 min within 1 h. Plasma aliquots were frozen and kept at -70°C until assay.

Assays

All assays were performed examiner blind in batch by the end of the study using a balanced set-up with equal number of samples from placebo and HRT allocated women and with all samples for the same individual in each run. Commercial kits were used and run essentially as described by the manufacturer. Fibrinogen and factor VIII clotting activity were assayed on an ACL Futura coagulometer (Instrumentation Laboratories, Milan, Italy) with reagents from Instrumentation Laboratories. Prothrombin fragments 1+2 (F1+2) and thrombin-antithrombin complex (TAT) were assayed with kits, Enzygnost® F1+2 and Enzygnost® TAT, respectively, from Dade-Behring (Marburg, Germany). Factor VII antigen, activated factor VII (factor VIIa), free protein S antigen, and D-Dimer were assayed with kits, Asserachrom® VII:Ag, Staclot® VIIa-rTF, Asserachrom® Free Protein S antigen, and Asserachrom® D-Di, respectively, from Stago (Asnière, France). Staclot VIIa-rTF was adapted for automated use on the ACL Futura. Antithrombin activity and protein C activity were assayed with chromogenic assay kits, Coamatic® Antithrombin and Coamatic® Protein C, respectively, from Chromogenix AB (Möln达尔, Sweden). Tissue factor pathway inhibitor (TFPI) activity and TFPI free antigen were assayed with in-house methods as described earlier (10, 11).

Statistics

Initial graphs revealed that the distribution of F1+2, TAT, and D-Dimer were not normally distributed. The data are therefore presented as medians with 25 and 75 percentiles unless otherwise stated, and all statistical comparisons were performed using non-parametric tests. Treatment effects were calculated as the change, i.e., difference from baseline to 3, 12, and 24 months, relative to the baseline value. The primary analysis involved comparison of treatment effects between the two treatment groups using Mann-Whitney rank-sum test. The Wilcoxon’s signed-rank test was used to test for changes within treatment groups. Multiple linear regression was used to identify hemostatic changes of potential explanatory importance for the changes in F1+2, TAT, and D-Dimer. The regression was performed backwards for each dependent variable (F1+2, TAT, and D-Dimer). A two sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using the computer program SPSS statistical software version 9.0.

Results

Baseline characteristics were similar for HRT allocated females and controls with regard to previous diseases (coronary heart disease, hypertension, stroke, diabetes), smoking habits, and serum lipids (8). All women had previously suffered at least one VTE, and the total numbers of previous VTEs were 75 in the placebo group and 77 in the HRT group. Mean age (SD) was 55.7 (6) years in the placebo group and 55.8 (7) years in the HRT group (ns), whereas mean body mass index was 27.4 (4) kg/m² and 26.8 (4) kg/m², respectively (ns).

Table 1  Effect of HRT on coagulation factors and markers of thrombin generation. Results are given as medians (25%, 75%iles).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>12 months</th>
<th>24 months</th>
<th>Baseline</th>
<th>3 months</th>
<th>12 months</th>
<th>24 months</th>
<th>Δ0-3 months</th>
<th>Δ0-12 months</th>
<th>Δ0-24 months</th>
</tr>
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<tbody>
<tr>
<td>F1+2 (nmol/l)</td>
<td>1.2 (1.0, 1.6)</td>
<td>1.5* (1.0, 2.2)</td>
<td>1.4* (1.0, 2.3)</td>
<td>1.3* (1.0, 2.2)</td>
<td>1.1 (0.9, 1.5)</td>
<td>1.1 (0.8, 1.5)</td>
<td>1.1 (0.8, 1.5)</td>
<td>1.1 (0.8, 1.5)</td>
<td>0.001</td>
<td>0.187</td>
<td>0.101</td>
</tr>
<tr>
<td>TAT (ng/ml)</td>
<td>2.9 (2.3, 4.2)</td>
<td>3.4 (2.6, 5.5)</td>
<td>3.8* (2.6, 6.2)</td>
<td>3.0 (2.4, 5.2)</td>
<td>3.2 (2.1, 5.6)</td>
<td>2.8* (1.8, 4.2)</td>
<td>2.7 (2.3, 6.8)</td>
<td>2.9 (2.1, 4.2)</td>
<td>0.011</td>
<td>0.118</td>
<td>0.417</td>
</tr>
<tr>
<td>D-Dimer (ng/ml)</td>
<td>310 (228, 428)</td>
<td>457* (285, 873)</td>
<td>297* (279, 615)</td>
<td>424* (303, 633)</td>
<td>301 (226, 441)</td>
<td>282 (210, 455)</td>
<td>305 (247, 439)</td>
<td>343 (232, 558)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.7 (3.3, 4.1)</td>
<td>3.7 (3.3, 4.4)</td>
<td>3.6 (3.3, 4.1)</td>
<td>3.9 (3.3, 4.3)</td>
<td>3.7 (3.3, 4.1)</td>
<td>3.7 (3.4, 4.0)</td>
<td>3.7 (3.4, 4.1)</td>
<td>3.9 (3.4, 4.3)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Factor VII antigen (%)</td>
<td>99 (84, 117)</td>
<td>98* (86, 109)</td>
<td>100* (85, 113)</td>
<td>100 (81, 112)</td>
<td>106 (91, 119)</td>
<td>112 (99, 121)</td>
<td>106 (93, 116)</td>
<td>107 (94, 118)</td>
<td>0.003</td>
<td>0.062</td>
<td></td>
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<tr>
<td>Factor VIIa (nM/U/ml)</td>
<td>100 (68, 109)</td>
<td>75* (49, 94)</td>
<td>77* (60, 92)</td>
<td>75* (57, 89)</td>
<td>88 (64, 107)</td>
<td>93 (61, 118)</td>
<td>87 (58, 123)</td>
<td>81 (59, 103)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Factor VIII</td>
<td>143 (115, 171)</td>
<td>151* (123, 171)</td>
<td>150 (126, 166)</td>
<td>ND</td>
<td>150 (129, 174)</td>
<td>147 (129, 172)</td>
<td>161* (138, 173)</td>
<td>ND</td>
<td>ns</td>
<td>ns</td>
<td></td>
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*P < 0.05, Wilcoxon Rank sum test, versus baseline value

** Mann-Whitney rank-sum test, comparison of relative changes from baseline after 3, 12, and 24 months between the two groups.
Six women, 3 in each treatment group, did not have adequate blood samples taken for sequential coagulation analyses since they were randomized at external sites. At follow-up visits, blood samples were missing for women suffering end-points and in women who withdrew consent since the former visit. The numbers of women with blood samples at each visit are indicated in Tables 1 and 2.

**Effects on Coagulation Factors**

No significant differences were detected in baseline levels of the coagulation factors between HRT and placebo allocated women (Table 1). Fibrinogen and factor VIII were not influenced by HRT (Table 1). Factor VIIa decreased significantly during HRT by median 17-23% (p < 0.001), but was not associated with a similar decrease in factor VII antigen (Fig. 1). Compared with placebo allocated women, the changes in factor VIIa were statistically highly significant after 3, 12, and 24 months (p < 0.001), whereas changes in factor VII antigen were statistically significant only after 3 months (p = 0.003).

**Effects on Coagulation Inhibitors**

No significant differences in baseline levels of coagulation inhibitors were detected between the two groups (Table 2). In the HRT group, all coagulation inhibitors, except free protein S, decreased highly significant during follow-up visits.

\[
\begin{array}{|c|c|c|c|c|c|c|c|c|c|c|c|c|c|}
\hline
\text{Inhibitor} & \text{HRT} & \text{Placebo} & \text{P-value}\text{*} & \text{P-value}\text{**} \\
& \text{Baseline} & \text{3 months} & \text{12 months} & \text{24 months} & \text{Baseline} & \text{3 months} & \text{12 months} & \text{24 months} & \text{3 months} & \text{12 months} & \text{24 months} & \text{3 months} & \text{12 months} & \text{24 months} \\
& n=68 & n=63 & n=52 & n=41 & n=66 & n=59 & n=50 & n=38 & & & & & & \\
\hline
\text{Antithrombin (\%)} & 119 & 108* & 110* & 107* & 107 & 106 & 115 & 117 & 118 & 0.001 & 0.001 & 0.001 \\
& (113, 125) & (102, 114) & (102, 117) & (103, 119) & (107, 123) & (109, 124) & (109, 124) & (109, 127) & & & & & & \\
\hline
\text{Protein C (\%)} & 124 & 108* & 112* & 111* & 132 & 135 & 136 & 131 & <0.001 & 0.001 & 0.003 \\
& (109, 136) & (95, 120) & (103, 122) & (102, 123) & (116, 145) & (117, 146) & (120, 148) & (117, 144) & & & & & & \\
\hline
\text{Free protein S antigen (\%)} & 86 & 86 & 88 & 88.0 & 93 & 92 & 94 & 93 & 0.039 & 0.071 & 0.237 \\
& (81, 98) & (80, 94) & (81, 93) & (81, 95) & (84, 98) & (86, 98) & (85, 100) & (89, 99) & & & & & & \\
\hline
\text{TFPI activity (\%)} & 134 & 118* & 114* & 118* & 129 & 132 & 134 & 130 & <0.001 & <0.001 & <0.001 \\
& (117, 152) & (94, 139) & (90, 132) & (94, 131) & (111, 151) & (110, 146) & (114, 148) & (110, 149) & & & & & & \\
\hline
\text{FtFPI antigen (ng/ml)} & 27.8 & 21.1* & 20.0* & 19.5* & 27.3 & 27.3 & 28.1 & 27.0 & <0.001 & <0.001 & <0.001 \\
& (23.0, 33.4) & (18.1, 23.3) & (17.2, 24.4) & (15.6, 23.7) & (24.1, 32.2) & (23.6, 31.2) & (25.2, 31.4) & (23.9, 30.1) & & & & & & \\
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\end{array}
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*P<0.05, Wilcoxon Rank sum test, versus baseline value
**Mann-Whitney rank-sum test, comparison of relative changes from baseline after 3, 12, and 24 months between the two groups.

Figs. 1 Median per cent changes in the levels of coagulation factors, i.e., fibrinogen, factor VIII clot, factor VII antigen, and factor VIIa, after 3, 12, and 24 months. Open bars: placebo, filled bars: Hormone replacement therapy (HRT). Group comparisons with Mann-Whitney Rank Sum test.
icantly compared with baseline (Fig. 2). Antithrombin decreased by median 8-9% (p < 0.001), protein C by 9-12% (p < 0.001), TFPI activity by 12-17% (p < 0.001), and TFPI antigen by 29-30% (p < 0.001). Compared with the placebo group, these changes were statistically highly significant at all time points. Free protein S also decreased during HRT, but the effect was less pronounced (median reduction 2-10%, ns) and the differences compared with placebo were only marginally statistically significant.

**Effects on Markers of Activated Coagulation**

Baseline levels of F$_{1+2}$, TAT, and D-Dimer were equal in placebo and HRT allocated females (Table 1). F$_{1+2}$ and D-Dimer, but not TAT, increased significantly in the HRT group after 3, 12, and 24 months as compared with baseline. F$_{1+2}$ increased by median 10-19%, TAT by 15 to 35%, and D-Dimer by 30-49% (Fig. 3). Compared with placebo allocated women, the changes in D-Dimer were statistically highly significant after 3, 12, and 24 months, whereas changes in F$_{1+2}$ and TAT were only significant after 3 months.

Multivariate analysis of the relative changes from baseline to 3 months revealed that only TFPI activity was a significant predictor for the increase in F$_{1+2}$ (p = 0.003, $R^2 = 0.14$) and that TFPI activity and TFPI antigen each were predictors for the increase in D-Dimer (p < 0.001, $R^2 = 0.23$, p = 0.004, $R^2 = 0.13$, respectively) associated with the use of HRT. Important factors for the change in TAT were not identified, although change in factor VIII was borderline significant.

**Effects of HRT in Women with Factor V Leiden Mutation and Recurrent VTE**

An analysis was carried out to determine the influence of HRT on the coagulation parameters in the absence and in the presence of the factor V Leiden mutation. Ten of the 59 women allocated placebo and 11 of the 63 women allocated HRT remaining in the study after 3 months of treatment were heterozygous carriers of the factor V Leiden mutation. In addition, one woman in each group was homozygous carrier. In the HRT group, statistical comparison of the relative changes in thrombin generation or any other parameter measured from baseline to

![Fig. 2](image-url) Median per cent changes in the levels of coagulation inhibitors, i.e., antithrombin activity, protein C activity, free protein S antigen, TFPI activity, and TFPI free antigen, after 3, 12, and 24 months. Open bars: placebo, filled bars: Hormone replacement therapy (HRT). Group comparisons with Mann-Whitney Rank Sum test.
3 months did not reveal any significant differences between the 12 carriers and the 51 non-carriers of the factor V Leiden mutation (Table 3).

An analysis was also performed to discriminate the effect of HRT in women with or without recurrent VTE. In the HRT group, 8 women suffered recurrent VTE, but three of these, all with the factor V Leiden mutation, occurred before 3 months of treatment (8). Consequently, five of the 63 women remaining in the study after 3 months later suffered VTE. These women showed higher increases in $F_{1+2}$ ($p = 0.019$) and D-Dimer ($p = 0.09$) from baseline to 3 months compared with those who did not suffer recurrent VTE.

**Discussion**

In the present study, we have investigated the effects of oral HRT on coagulation in postmenopausal women with a history of VTE, who were randomized in our double-blind, placebo-controlled trial (8). We have found that HRT was accompanied by significant early activation of coagulation with increased levels of $F_{1+2}$, TAT, and D-Dimer after 3 months of treatment, which corroborates the finding of an early excess risk of recurrent VTE in this study (8) and with the early excess risk observed in recent epidemiological studies (1–6). Our data are therefore consistent with HRT acting as an additional pro-thrombotic risk factor in these women.

Activation of coagulation seemed to be less pronounced after 12 and 24 months of therapy. Only D-Dimer remained statistically significantly higher in the HRT group, which may suggest that activation of coagulation was attenuated over time by compensatory mechanism(s). Another possibility is that high-responders to the effect of HRT were selectively lost to follow-up after 3 months. In fact, all eight recurrences in the HRT group developed within 9 months of therapy, i.e., three within 3 months and five additional within 9 months, and they were consequently lost for follow-up on the effect of HRT on coagulation (8). Our data indicate that women with recurrent VTE had a markedly stronger effect of HRT on coagulation than women who did not develop recurrent thrombosis, although the power of this analysis was limited by the small sample size. Some women may therefore be more sensitive or high-responders to the effect of HRT to develop a pro-thrombotic state.

Previous studies on activation of coagulation have reported contradictory results for the effects of HRT on $F_{1+2}$ (12–18), TAT (13, 14, 17–19), and D-dimer (15, 17, 20–22). The results of these studies are generally difficult to interpret, since many different HRT formulations have been tested. Selection of participating women and their risk for thrombosis have often been poorly defined. Many studies have recruit-

![Prothrombin Complex F1+2](image)

![Thrombin-Antithrombin Complex](image)

![D-Dimer](image)

**Fig. 3** Median per cent changes in the levels of prothrombin fragment 1+2, thrombin-antithrombin complexes, and D-dimer after 3, 12, and 24 months. Open bars: placebo, filled bars: Hormone replacement therapy (HRT). Group comparisons with Mann-Whitney Rank Sum test.

**Table 3** Per cent changes after 3 months of treatment relative to baseline values in HRT allocated women in carriers and non-carriers of the factor V Leiden mutation and in women with or without recurrent VTE in HRT allocated women. Results are given as medians (25%, 75%iles).

<table>
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<tr>
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<th>Factor V Leiden</th>
<th>Recurrent VTE</th>
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<tbody>
<tr>
<td></td>
<td>$+$ $n=12$</td>
<td>$-$ $n=51$</td>
</tr>
<tr>
<td>$F_{1+2}$</td>
<td>22 (-4 , 61)</td>
<td>13 (-7 , 41)</td>
</tr>
<tr>
<td>TAT</td>
<td>14 (-34 , 223)</td>
<td>15 (-31 , 106)</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>31 (2 , 112)</td>
<td>52 (6 , 112)</td>
</tr>
</tbody>
</table>
ed small numbers of women and may thus have been deficient of power to detect significant effects of HRT either way on thrombin generation. The present randomized study was sized to detect a difference in clinical end-points. All participating women had previously suffered at least one VTE, and the effects of HRT in such women may be stronger and more easily detectable than in former studies.

Coagulation activation is delicately balanced by procoagulant and anticoagulant factors. It has been shown in vitro that even minor relative changes in the concentration of procoagulants and anticoagulants by approximately 10% may significantly alter the rate of thrombin generation (23). In the present study, we found marked and persistent reductions in the levels of the coagulation inhibitors antithrombin, protein C, and TFPI, but not protein S, which may have contributed to activation of coagulation. The importance of TFPI for activation of coagulation was confirmed in the multivariate analysis. Other studies have detected no or minor reductions in the levels of antithrombin (12, 14, 17–19, 24, 25), protein C (12, 14, 17–19, 25), and protein S (12, 14, 17, 18, 22). Our findings on TFPI confirm and extend previous observations with transdermal HRT (17) and with oral contraceptives (26).

The mechanism for the reduction in TFPI activity and antigen is not clear. One possibility is that TFPI activity was reduced as an effect secondary to the effect of HRT on plasma lipoproteins, as has previously been shown with statins (27). In the present study, total cholesterol and LDL cholesterol decreased by 10-20%, but multivariate analysis failed to show that the reduction in TFPI activity was due to an effect on blood lipids (data not shown). This is consistent with the even stronger reduction in TFPI free antigen, which is not associated with plasma lipoproteins. Alternatively, the reduction in TFPI could be an effect of HRT on TFPI synthesis and release, as was recently suggested in a study of human umbilical vein endothelial cells in culture (28).

The reduction in TFPI was followed by a rather similar reduction in activated factor VII, which was assayed with a specific method (29). The effect on factor VII concentration was much less, which suggests a down-regulation of the activity state of factor VII and a protective effect of HRT on factor VII. The mechanism(s) involved are not clear, but could be an effect secondary to reduced reactivity of monocytes and platelets in whole blood after HRT exposure, which has been observed in one study (30). Our findings on factor VII are in accordance with a study on presumed healthy women randomized to the same HRT regimen (25), and also with one cross-sectional study suggesting that HRT may lower activated factor VII (16). Other studies on factor VII have yielded conflicting results (14, 22, 31–33), which may have been due to inadequate assay methodology to detect activated factor VII. In the present study, HRT had no significant effects on fibrinogen or factor VIII. Similar results with fibrinogen have been reported in one study (17), but other studies have found a reduction in fibrinogen (31, 33).

Our study recruited a significant number of women with the factor V Leiden mutation. This allowed us to investigate the potential role of the factor V Leiden mutation for the pro-thrombotic effect of HRT. This analysis revealed no difference in the effects of HRT on activation of coagulation or any other parameter measured between carriers and non-carriers of the factor V Leiden mutation. Although the sample size of this analysis was limited, these data may indicate that the pro-thrombotic effects of the factor V Leiden mutation and HRT is additive rather than multiplicative. These results could therefore be of importance for advising women carrying the factor V Leiden mutation on the risk of VTE associated with HRT, especially in asymptomatic women without a family history of thrombosis.

Finally, it should be emphasized that the results of our study are limited to continuous oral treatment with natural estrogen (17-β-estradiol) in combination with norethisterone acetate and given to women at high risk of VTE. However, our results of early increased activation of coagulation are consistent with clinical end-points in our study, and also with the consistently early increased risk of VTE detected in many recent studies using different HRT regimens (1–7). We therefore find it highly probable that properly sized studies using another dose or type of estrogen would have yielded similar effects on coagulation.

Acknowledgements

We wish to express our gratitude to all the women who contributed enthusiastically to the execution of this trial. We also wish to thank Dr. Ingebjorg Seljeflot and Gro Gjønnes for technical assistance. The study was supported by grants from Novo-Nordisk Pharma, Oslo, Norway, and Research Forum, Ullevål University Hospital.

References


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