

Effects of Hormone Replacement Therapy on Coagulation and Fibrinolysis in Postmenopausal Women

Kwang Kon Koh

Cardiology, Gil Heart Center, Gachon Medical School, Incheon, Korea

Abstract

It has been speculated that hormone replacement therapy (HRT) containing relatively low dose of estrogen would be different from oral contraceptive pills in causing thromboembolism because activation of coagulation depends on the amount of estrogen. In contrast to this knowledge, activation of coagulation pathways has been detected in postmenopausal women treated with HRT in the observational and clinical studies. In this regard, recent studies have reported a 2~4 fold risk of venous thromboembolism or pulmonary embolism in postmenopausal women receiving HRT than in non-users of estrogen. On the other hands, HRT has shown to enhance systemic fibrinolysis with decreased plasma plasminogen activator inhibitor-1 (PAI-1) levels. In addition, levels of D-dimer exhibited a significant inverse correlation with PAI-1 levels, suggesting enhanced fibrinolysis potential. However, small doses of estrogen/progestogen induce increases in fibrinolytic capacity via a marked reduction of PAI-1. In other words, HRT at conventional dosages may affect fibrinolytic activity to a greater extent than coagulation activity, whereas the converse trend holds at higher estrogen doses. The increase in fibrinolytic potential was independent of any effect on coagulation of CEE at conventional dosages. However, in contrast to healthy postmenopausal women, we recently reported that HRT did not significantly decrease PAI-1 antigen levels and rather, increased tissue factor activity and prothrombin fragment F₁₊₂ levels from baseline in hypertensive and/or overweight postmenopausal women. Activation of coagulation following HRT may not be balanced by activation of fibrinolysis in some postmenopausal women. Thrombogenic events are considered more likely in patients with certain heritable conditions, such as platelet antigen-2 (PIA-2) polymorphisms. Further, Factor V Leiden mutation increases the risk of primary and recurrent venous thromboembolic events by three to sixfold and the risk of myocardial infarction. Indeed, HRT may decrease or increase atherothrombosis risk depending on the presence of Factor V Leiden mutation. Thus, HRT should not be initiated in women with established coronary artery disease or the coexistence of other risk factors for hypercoagulability-malignancy, immobility, obesity, diabetes, advanced age, or inherited traits. However, HRT at conventional dosages improves fibrinolysis potential in healthy postmenopausal women.

We reviewed the effects of hormone replacement therapy (HRT) on hemostasis in postmenopausal women [1].

1. Hormone Replacement Therapy and Coagulation System

It has been speculated that estrogen replacement therapy (ERT) containing relatively low dose of estrogen would be different from oral contraceptive pills in causing thromboembolism because activation of coagulation

depends on the amount of estrogen [2]. In contrast to these knowledge, activation of coagulation pathways has been detected in postmenopausal women treated with conjugated equine estrogen (CEE) in the United States [3]. Further, four recent studies and a randomized clinical trial (HERS) have reported a 2~4 fold risk of venous thromboembolism or pulmonary embolism in postmenopausal women receiving HRT than in non-users of estrogen [4-8]. In a prospective cohort study (Nurses' Health Study), Grodstein et al [4] documented 123 cases

of idiopathic pulmonary emboli, and observed that current users of hormone therapy had a relative risk of 2.1 after adjustment for multiple cardiovascular risk factors, compared with women who had never used hormone therapy. In another paper, these investigators reported that the apparent protective effect of CEE in the Nurses' Health Study was noted only at the 0.3 mg and 0.625 mg doses; 1.25 mg and higher doses were not cardioprotective regarding cardiovascular events potentially due to coronary thrombosis [9]. In HERS, more women in the hormone-treated group experienced deep vein thromboses (25 versus 8; $P=0.004$) and pulmonary emboli (11 versus 4; $P=0.08$), with both of the 2 fatal pulmonary emboli occurring in hormone-treated women [8].

Scarabin et al [10] reported the effects of oral and transdermal estradiol/progesterone replacement therapy on hemostatic variables on forty-five healthy postmenopausal women. They observed that oral estradiol valerate 2 mg daily, but not transdermal estradiol regimen significantly increased the mean value of prothrombin fragment 1+2 (F_{1+2}) and decreased mean antithrombin activity compared with no treatment. On the other hands, several different groups [11,12] conducted a prospective study to investigate the effect of oral CEE 0.625 mg with or without medroxyprogesterone acetate (MPA) in postmenopausal women. Oral estrogen resulted in a significant reduction in fibrinogen, factor VII, von Willebrand factor, soluble thrombomodulin, and tissue plasminogen activator (t-PA) levels, suggesting beneficial effects on endothelial function and atherogenesis. In this regard, Bellinger et al [13] reported an experimental study examining the effects of current low-dose oral contraceptive pill, CEE and MPA at a dose equivalent to that currently given to women on arterial thrombosis in premenopausal and surgically postmenopausal cynomolgus monkeys. They found that the current oral contraceptive pill and CEE regimens did not increase the susceptibility of the artery wall to develop and occlusive thrombus following injury and stenosis.

2. Hormone Replacement Therapy and Fibrinolysis

Significantly enhanced systemic fibrinolysis resulted from 1 month of treatment with oral CEE, either alone or combined with MPA, in 30 postmenopausal women in a randomized crossover trial [14]. Both CEE and CEE/MPA decreased plasma plasminogen activator inhibitor-1 (PAI-1) levels from baseline by more than 50%. These effects were more pronounced in women with higher levels of PAI-1 at baseline. In addition, levels of D-dimer exhibited a significant inverse correlation with PAI-1 levels, suggesting enhanced fibrinolysis potential. Six months of HRT with oral cyclic 17 β -estradiol combined with micronized progesterone (MP) also increased global fibrinolytic capacity by 63% vs. baseline ($P=.001$) and reduced both PAI-1 antigen (24%; $P=0.02$) and PAI activity (54%; $P=0.004$) in 45 healthy postmenopausal women [10]. However, such treatment

was also associated with an activation of coagulation system.

3. Relation of Fibrinolytic Potentiation to Coagulation Activation

Because activation of coagulation system has been detected dose-dependently in postmenopausal women treated with CEE 0.625 and 1.25 mg [3], potentiation of fibrinolysis could be a consequence of activation of coagulation system as a primary response to estrogen administration. However, Winkler et al [15] speculated that small doses of estrogen/progestogen induce increases in fibrinolytic capacity via a marked reduction of PAI-1. In other words, HRT at conventional dosages may affect fibrinolytic activity to a greater extent than coagulation activity, whereas the converse trend holds at higher estrogen doses. To evaluate this hypothesis, Koh and co-workers [16] measured indicators of coagulation system activation and fibrinolysis before and after 1 month of CEE (0.625 mg/day). After CEE treatment, the t-PA activity: PAI-1 activity ratio (t-PA:PAI-1), which is more reflective of fibrinolytic potential than either activity individually, increased by approximately fivefold ($P=0.008$ vs baseline). These increases correlated with *in vitro* evidence of heightened fibrinolytic activity: D-dimer concentrations in clotted blood incubation for 4 hours. Consistent with our previous study [14], D-dimer concentrations were significantly correlated (positively) with an increase in the t-PA:PAI-1 ratio [16]. However, the increases in fibrinolytic potential (t-PA:PAI-1) did not correlate with the minimal changes observed in F_{1+2} or thrombin-antithrombin levels after CEE. The increase in fibrinolytic potential was independent of any effect on coagulation of CEE at conventional dosages. Scarabin et al [10] also reported no correlation between fibrinolytic potential and coagulation activation using ERT regimens. Cushman and colleagues [17] found that hemostasis markers and evidence of procoagulation were not associated and fibrinolytic potential increased. However, in contrast to healthy postmenopausal women [10,14,16], we recently reported that HRT did not significantly decrease PAI-1 antigen levels and rather, tended to increase F_{1+2} levels from baseline in hypertensive and/or overweight postmenopausal women [18], consistent with the HERS.

4. Clinical Implications

Activation of coagulation following ERT or HRT may not be balanced by activation of fibrinolysis in some postmenopausal women [1,14]. Thrombogenic events are considered more likely in patients with certain heritable conditions, such as platelet antigen-2 (PIA-2) polymorphisms [19]. Further, Factor V Leiden mutation increases the risk of primary and recurrent venous thromboembolic events by three to sixfold [20] and the risk of myocardial infarction [21]. Indeed, HRT may decrease or increase atherothrombosis risk depending on the presence of Factor V Leiden mutation. [22] Thus,

ERT or HRT should not be initiated in women with established coronary artery disease or the coexistence of other risk factors for hypercoagulability- malignancy, immobility, obesity, diabetes, advanced age, or inherited traits.

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