Hormone Replacement Therapy and the Factor V Leiden Mutation

Kenneth A. Bauer

The mechanism by which oral contraceptives are prothrombotic is complex. Prothrombotic effects include modest increases in the levels of procoagulant factors (factor VII, factor VIII, factor X, prothrombin, fibrinogen) and decreases in the levels of anticoagulant proteins (antithrombin, protein S). With a thrombin generation assay, it has been shown that women taking oral contraceptives develop acquired APC resistance. Though the molecular basis for this phenomenon is unknown, it provides a plausible explanation for the greatly increased thrombotic risk among oral contraceptive users who are carriers of the factor V Leiden mutation (reviewed by Vandenbroucke et al.6).

The thrombogenicity of oral contraceptives was recognized shortly after their introduction in the 1960s,6 but convincing evidence that the lower estrogen dose used for hormone replacement therapy is associated with an increased risk of venous thromboembolism was only conclusively reported in 1996.8 The estrogens commonly prescribed for hormone replacement are chemically different from those in oral contraceptives, but they are considered to have substantially lower biologic potency. Venous thrombotic risk associated with hormone replacement therapy is increased 2- to 4-fold, an effect that is similar in magnitude to oral contraceptives. However the use of hormone replacement therapy leads to a considerably larger number of excess cases as the result of an overall age-related increase in the incidence of thrombosis. Based on the interactions between oral contraceptives and factor V Leiden, it was anticipated that carriers of the mutation receiving hormone replacement therapy would have a significantly increased risk of venous thromboembolism. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Herrington et al.8 report on a nested case-control study of women enrolled in the Heart and Estrogen Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis Trial. Both were randomized trials of hormone replacement therapy versus placebo in women with clinical evidence of coronary artery disease. The factor V Leiden mutation was found in 17% of venous thromboembolism cases and 6% of controls yielding an odds ratio of 3.3. Hormone replacement therapy carried an odds ratio of 4.5, but users with factor V Leiden had an odds ratio of 14.1 compared with noncarriers receiving placebo. Based on the incidence data from the trials, the authors estimate the risk of venous thrombosis in heterozygous carriers and noncarriers of factor V Leiden to be 15.2 and 5.8 per 1000 patient-years, respectively, compared with noncarriers receiving placebo. Based on the interactions between oral contraceptives and factor V Leiden, it was anticipated that carriers of the mutation receiving hormone replacement therapy would have a significantly increased risk of venous thromboembolism. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Herrington et al.8 report on a nested case-control study of women enrolled in the Heart and Estrogen Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis Trial. Both were randomized trials of hormone replacement therapy versus placebo in women with clinical evidence of coronary artery disease. The factor V Leiden mutation was found in 17% of venous thromboembolism cases and 6% of controls yielding an odds ratio of 3.3. Hormone replacement therapy carried an odds ratio of 4.5, but users with factor V Leiden had an odds ratio of 14.1 compared with noncarriers receiving placebo. Based on the incidence data from the trials, the authors estimate the risk of venous thrombosis in heterozygous carriers and noncarriers of factor V Leiden to be 15.2 and 5.8 per 1000 patient-years, respectively, compared with 2.0 per 1000 patient-years in noncarriers taking placebo. They estimate that the number of women with coronary disease needed to screen to prevent one episode of venous thromboembolism is 374.
The results of Herrington et al. are very similar to those of a recently published study from the United Kingdom. This case-control study of women aged 45 to 64 years with a first episode of venous thromboembolism found a 15-fold increased risk of venous thromboembolism in women on hormone replacement with the factor V Leiden mutation. Analogous to the data in women with the factor V Leiden mutation on oral contraceptives, this odds ratio was greater than the expected odds ratio for the combination of the two risk factors, and the risk was highest in the first year of use.

Estrogen in hormone replacement therapy has effects on the hemostatic system that are similar to those of oral contraceptives. Hormone replacement therapy leads to a dose-dependent increase in markers of prothrombin activation and fibrin generation, while enhancing fibrinolysis and decreasing the plasma levels of plasminogen activator inhibitor-1. It is clear that hormone replacement therapy should seldom be prescribed to women if they had a previous venous thrombotic event. For women known to have coronary heart disease and the factor V Leiden mutation without a personal history of venous thrombosis, Herrington and colleagues point out that the risk of venous thromboembolism will far exceed any potential benefits of hormone replacement. This is especially true given that hormone replacement therapy has not been shown to slow the progression of atherosclerotic lesions and may be associated with an increase in coronary events in several secondary-prevention trials including HERS. The administration of oral contraceptives or hormone replacement therapy to women with prothrombotic mutations and an established cardiac risk factor may be associated with an increased risk of myocardial infarction.

Millions of women are prescribed hormone replacement therapy which can be associated with serious side effects. Venous thromboembolism is by no means restricted to those with identifiable prothrombotic defects. As prospective trials have not yet shown that hormone replacement therapy reduces the risk of arterial thrombotic complications, it can be strongly argued that physicians should refrain from prescribing the drug for this purpose rather than screening women for mutations such as factor V Leiden to eliminate women at high risk for venous thrombotic complications.

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References

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