

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Contraception in Women With Hereditary Thrombophilic Defects



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H&O How common is thrombophilia in women of childbearing age?

MC The term *thrombophilia* was once used to describe only patients who had prominent manifestations of venous thromboembolism (VTE). Patients were considered to have thrombophilia if they developed recurrent spontaneous VTE, VTE at a young age, VTE in the presence of a strong family history of VTE, or thrombosis in an unusual site, such as the splanchnic veins or the cerebral sinuses. According to this definition, all patients with thrombophilia had experienced at least 1 episode of VTE.

In the course of searching for biological explanations for this thrombotic tendency, numerous laboratory abnormalities and genetic variants that increase the risk of developing VTE have been identified. Most of these abnormalities affect the coagulation system, and have autosomal dominant inheritance. As a result of these discoveries, the term *thrombophilia* has expanded to encompass people with laboratory abnormalities associated with excessive thrombosis. Therefore, patients who have never experienced VTE can be diagnosed with thrombophilia.

The prevalence of thrombophilia is strongly dependent on the patient population that is tested. In the general population, the prevalence of thrombophilia is low: 5% to 10% in whites, and 1% to 5% in nonwhites. The prevalence is much higher, however, in patients who have had at least 1 episode of spontaneous VTE: 34%. The prevalence of thrombophilia also is elevated in first-degree family members of these patients, at 17%.

H&O Which hereditary defects put women at elevated risk for VTE?

MC Hereditary thrombophilias that consistently have been associated with an increased risk of VTE are deficiencies of any of the natural anticoagulants, including antithrombin, protein S, and protein C, as well as factor V G1691A (factor V Leiden) and prothrombin G20210A mutations. In patients who have never experienced VTE, the relative risk of VTE is 5 to 10 for deficiencies of antithrombin, protein C, or protein S, and 2 to 5 for factor V Leiden or prothrombin G20210A.

Persistently elevated levels of coagulation factor VIII (FVIII), meaning levels greater than 150% of normal, are associated with a 2- to 11-fold increased risk of VTE. Levels of FVIII are in part genetically determined. Patients with type A or B blood have FVIII levels that are 22% higher than those in patients with type O blood. Moreover, 40% of first-degree family members of patients with VTE in combination with FVIII levels greater than 150% of normal also have FVIII levels greater than 150% of normal, which is close to what one would expect from autosomal dominant inheritance.

A common genetic polymorphism often included in thrombophilia panels is c.C677T in the gene coding for the enzyme methylenetetrahydrofolate reductase (MTHFR). Homozygosity (677TT) is associated with a 20% to 25% increase in homocysteine levels compared with wild-type (677CC), and older studies associated it with a mild increase in VTE risk. More recent studies, however, including

Mendelian randomization studies, have failed to show any association between MTHFR 677TT and the risk of VTE. It is likely that the earlier positive association studies were confounded by selection or publication bias. MTHFR 677TT therefore should not be part of thrombophilia panels, if testing is considered. Similarly, other polymorphisms in the genes coding for fibrinogen, plasminogen, plasminogen activator inhibitor 1 (PAI-1), and thrombomodulin, and different haplotypes of the endothelial protein C receptor (EPCR) have been associated with increased VTE risk in some studies but not in others. In spite of these inconsistent associations, some of these polymorphisms are included in thrombophilia test panels.

H&O How often does thrombophilia go undiagnosed?

MC Assuming a 5% to 10% prevalence of thrombophilia in the general population, the vast majority of these patients go undiagnosed. This underdiagnosis probably is justified, given the lack of therapeutic benefits of diagnosing hereditary thrombophilia in patients who never have experienced VTE.

H&O Are oral contraceptives appropriate for women with thrombophilia?

MC In my opinion, oral contraceptives are appropriate for women with thrombophilia in most cases. For example, the risk of developing VTE for a 25-year-old woman who has never had VTE and has no first-degree relatives with VTE is 0.008% per year. If this woman has a factor V Leiden mutation, her risk increases to 0.057% per year. Is the absolute risk increase of 0.049% per year enough to advise against oral contraceptives? I do not think so. This small increase in risk needs to be balanced against the potential increased risk of unintended pregnancies in the absence of oral contraceptives. Moreover, such unintended pregnancies would lead to a VTE risk of about 0.2% to 1.0% per pregnancy.

The situation is different for women with thrombophilia combined with a first-degree family history of VTE. Interestingly, first-degree family members of patients who have had VTE have a 2-fold increased risk of developing VTE themselves, irrespective of the presence or absence of inherited thrombophilia. Women who have more than 1 first-degree relative who has had VTE have a 4-fold increased risk. This indicates the presence of other, unknown hereditary thrombophilias. Family studies of asymptomatic first-degree family members of VTE patients with antithrombin, protein C, or protein S deficiency have shown that deficient family members have a risk of VTE of 4.3% per year, compared with 0.7% per year in nondeficient family members. In this particular setting, 28 women

with a deficiency of antithrombin, protein C, or protein S and a positive family history would need to refrain from oral contraceptives to prevent 1 episode of VTE. However, if we consider a lower-risk thrombophilia, such as factor V Leiden, 333 first-degree relatives would need to refrain from oral contraceptives to prevent 1 VTE episode.

Overall, in patients who do not have a positive family history of VTE, the absolute risk increase is too small to advise against oral contraception in women with thrombophilia. Women with a first-degree relative who has had VTE should consider alternative contraception based on their family history, even if they do not have thrombophilia. The advice to consider alternatives is stronger in women with a high-risk thrombophilia, such as antithrombin, protein C, or protein S deficiency.

H&O Are there any guidelines for physicians to follow?

MC There is a current lack of authoritative evidence-based guidelines on this issue. The American College of Chest Physicians published guidelines in *Chest* in 2012 on thromboprophylaxis during and after pregnancy for women with inherited thrombophilia, but these guidelines do not deal with the risks of oral contraceptives. National guidelines from the United Kingdom by Baglin and colleagues provide useful recommendations on whom to test for hereditary thrombophilia that take into account both the family history and the specific thrombophilia. These recommendations are in line with my earlier conclusion. Finally, the American Society of Hematology is developing new clinical practice guidelines on VTE that are scheduled to be published in 2017. Thrombophilia is one of 10 selected topics for which specific recommendations will be made. Undoubtedly, thrombophilia and oral contraceptives will be part of these guidelines.

H&O Are there any recent studies that have shed light on this issue?

MC Most hereditary thrombophilias were identified between 1965 (antithrombin deficiency) and 1996 (prothrombin G20210A mutation). As a next step, the relative risks were confirmed in numerous case-control studies in patients with VTE, and also in patients with arterial cardiovascular disease or pregnancy complications such as (recurrent) miscarriage or preeclampsia. For clinicians and patients, absolute risk estimates were needed to guide decisions on prevention or treatment. Most of those studies were published before 2010. Since then, no significant new insights have been gained with respect to risks of patients with thrombophilia. Nevertheless, the usefulness of testing for thrombophilias continues to be

debated among specialists in the field, all interpreting the same evidence slightly differently.

H&O Should physicians screen women for thrombophilia before prescribing oral contraceptives?

MC Women without a family history of VTE should not be screened for thrombophilia. As mentioned, 439 women with factor V Leiden (without a family history of VTE) would need to refrain from oral contraceptives to prevent a single case of VTE. To identify these women among the general population (considering a prevalence of 4% to 7% among white women), between 6000 and 11,000 women would need to be tested to prevent 1 VTE episode. Similarly, approximately 20,000 women from the general population would need to be screened to identify 195 women with a deficiency of antithrombin, protein C, or protein S, all of whom would need to refrain from oral contraceptives to prevent a single case of VTE.

Screening women with a first-degree family member with VTE can be considered, especially in families with high-risk thrombophilias such as antithrombin, protein C, or protein S deficiency. However, a positive family history of VTE is a risk factor for VTE, even in the absence of known thrombophilias. Negative thrombophilia tests in women with a first-degree relative with VTE could therefore lead to false reassurance, and these women should consider alternative contraception irrespective of thrombophilia.

H&O What factors besides family history of VTE should hematologists take into account when evaluating women with thrombophilia for oral contraceptive use?

MC The next most important factor after family history of VTE is patient preference. In most instances, women should be able to choose between accepting an increased risk of VTE from oral contraceptives and the use of alternative modes of contraception that may lead to a higher risk of unintended pregnancies.

H&O What is your approach to counseling women with thrombophilia so they can make an informed choice about contraception?

MC I would discuss the woman's options for reliable contraception and the associated risks of VTE. Neither copper nor levonorgestrel-releasing intrauterine devices (IUDs) increase the risk of VTE, and both types of IUD are highly effective at preventing pregnancy. If an oral contraceptive is preferred, I recommend that women consider an oral contraceptive with 20 to 30 µg of ethinyl estradiol combined with levonorgestrel or norgestrel, a second-generation progestin. These second-generation oral contraceptives increase the risk of VTE by 1.5- to 4-fold, compared with 4- to 8-fold for oral contraceptives with higher ethinyl estradiol concentrations or other progestins such as desogestrel, gestodene, drospirenone, and cyproterone acetate.

In women with thrombophilia who do not have a family history of VTE (the diagnosis would have been based on tests ordered by someone else, because I do not test women in this category), I do not object to prescribing oral contraceptives if a woman decides that she prefers this method of contraception over alternatives. In women with a family history of VTE, I would recommend an IUD as the first choice. In the case of women who strongly desire an oral contraceptive, I would consider prescribing a low-risk oral contraceptive for women with a positive family history and factor V Leiden or prothrombin G20210A mutations. I would be more reluctant to prescribe an oral contraceptive for women with deficiencies of antithrombin, protein C, or protein S.

Suggested Readings

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