Thrombophilia: Factor V Leiden and Prothrombin Gene Mutation

Thrombosis Canada
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Objective:

- To review the frequency and clinical relevance of and diagnostic testing for factor V Leiden and prothrombin gene mutation G20210A.
- To review recommendations for management of affected individuals.

Background:

Hereditary thrombophilias are a group of conditions associated with an increased risk of developing venous thromboembolism (VTE). A point mutation (G1691A) in the gene that codes for clotting factor V produces an abnormal factor V protein known as **factor V Leiden (FVL)**. FVL is the most common inherited thrombophilia with an approximate incidence of 5% to 8% in the heterozygous form in Caucasians. Its incidence is lower in Asian Americans (0.45%), native Americans (1.2%), African Americans (1.2%) and Hispanic Americans (2.2%). The functional consequence of this mutation is impaired inactivation of factor V (also known as "activated protein C resistance"), resulting in increased thrombin generation and a decrease in the anticoagulant effect of activated protein C.

The second most frequent hereditary thrombophilia is a single nucleotide substitution (G20210A) in the promoter region of the gene for the clotting factor II (prothrombin). This **prothrombin gene mutation (PGM)** results in an increase in the concentration of prothrombin. The approximate incidence of heterozygous PGM is 1-4% in Caucasians and is infrequent in people of Asian or African ancestry.

Homozygous FVL, homozygous PGM, and compound heterozygotes (heterozygous for both FVL and PGM) are rare and affect less than 1% of the population.

These mutations are inherited in an autosomal dominant fashion. First degree relatives of heterozygous carriers of FVL or PGM have a 50% chance of also being carriers of the mutation.

Risk of Thrombosis with FVL and PGM:

Heterozygous FVL is present in approximately 20% of unselected, symptomatic VTE patients and in up to 40% of patients with a strong family history of VTE. In their heterozygous forms, FVL or PGM are associated with a modest increase in first time VTE risk (the hazard ratio [HR] for venous thrombosis varies between 2 and 5 in different reviews) and are not considered to be strong risk factors for recurrent VTE (HR varies from non-significant to less than 1.5). However, patients with homozygous FVL or PGM and patients with compound heterozygous FVL and PGM have a much greater risk of VTE and are at a higher risk of recurrence.

Although some 10-20% of individuals who are heterozygous for FVL or PGM will develop VTE over their lifetime, the overall VTE risk is compounded by family history of VTE, increasing age, oral contraceptive (OCP)

use, menopausal hormone therapy, pregnancy, and other VTE risk factors. Despite the thrombotic risk associated with these mutations, affected individuals have a normal life expectancy.

To understand and counsel patients on the risk of VTE associated with hormonal therapies or genetic risk factors, we advise discussing risk in the form of absolute risk of VTE per year. The incidence of VTE in women of child-bearing age who are not taking oral contraceptives is approximately 1 in 10,000 per year. The risk of VTE for those on combined oral contraceptive pill increases to 4 in 10,000 per year. In those with a first degree relative with a history of VTE, the risk doubles to 8 in 10,000 per year even in the absence of identifiable thrombophilia. The presence of both heterozygous factor V Leiden and use of combined oral contraceptive pills increases the risk of thrombosis to 35–40/10,000 per year, generously approximated at <1 in 200 per year, or a 0.5% risk of VTE per year.

Although there is a debated risk of atherothrombotic events in patients with FVL and PGM, the overall risk is likely to be small to insignificant.

Risk of Pregnancy Complications with FVL and PGM:

The majority of data suggests that women who are heterozygous for FVL or PGM are not at significantly increased risk of placental complications in pregnancy, including pregnancy loss, small-for-gestational-age, pre-eclampsia, or placental abruption.

Diagnosis and Screening:

The presence of FVL or PGM can be detected by DNA testing using a routine blood sample. Additionally, the presence of FVL can be screened for using the Activated Protein C Resistance ratio, a functional screening test. No functional test exists to detect the presence of PGM. **The practice of widespread thrombophilia testing is not effective at reducing adverse outcomes and rarely influences clinical** decision-making; thus, thrombophilia testing is not recommended as a screening procedure in healthy individuals.

The advantages and disadvantages of testing should be discussed with the patient and testing should be reserved for those in whom results will influence clinical decision-making. For example, FVL or PGM testing may be indicated in asymptomatic women with a first-degree relative with known FVL or PGM and a history of VTE who are pregnant/contemplating pregnancy or considering hormonal contraceptive use, **only if the result would change the decision** to use VTE prophylaxis or a contraceptive associated with an increased thrombotic risk.

There may also be little utility, for example, in requesting testing in a patient for whom indefinite anticoagulation will be indicated regardless of FVL or PGM status. This is in keeping with thrombophilia testing guidelines from the American Society of Hematology, which recommend **thrombophilia testing only in specific situations where the presence of thrombophilia will directly influence treatment decisions** regarding the choice and duration of anticoagulation. Otherwise, thrombophilia testing should not be requested. There is not only a cost-benefit argument, but a positive test result may also produce unnecessary anxiety for the patient and their family, may affect their eligibility for insurance, could lead to inappropriate denial of effective contraception, and may result in unnecessary anticoagulant use during periods of perceived risk.

Screening for FVL and PGM in women with a history of pregnancy complications and in patients with a history of arterial vascular disease are not recommended.

Treatment Of VTE:

The therapeutic options and duration of VTE treatment are generally not affected if FVL or PGM are present. Published data on the use of DOACs in patients with homozygous FVL or PGM are limited although there is no suggestion that DOACs are less effective in this setting. There is little, if any, difference in the risk of VTE recurrence, when anticoagulation is stopped, between those with FVL or PGM in the heterozygous form and the general population.

Prevention of VTE:

Individuals with FVL or PGM should receive appropriate thromboprophylaxis during periods of increased VTE risk. Women who are heterozygous for FVL or PGM do not warrant routine thromboprophylaxis during pregnancy unless they have previously experienced VTE. Postpartum prophylaxis is not recommended in asymptomatic women with heterozygous FVL or PGM and no other tisk factors for VTE. Antepartum and postpartum thromboprophylaxis is usually suggested in pregnant women who are homozygous for FVL or PGM or compound heterozygous for FVL and PGM.

OCP and menopausal hormone therapy use in carriers of FVL or PGM is associated with a further increase in VTE risk; therefore, the risk-benefit of OCP or menopausal hormone therapy use should be carefully discussed. In asymptomatic female carriers of FVL or PGM with no other VTE risk factors (such as a personal history of thrombosis) who cannot tolerate reliable, alternative forms of contraception, combined oral contraceptives containing estrogen can be considered on a case-by-case basis. It would require a careful discussion of risks and benefits and a consideration of the values and preferences of the patient.

Pediatrics:

Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism and those with confirmed or suspected thrombophilias. When this is not possible, a combination of a neonatologist/pediatrician and a pediatric hematologist or an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

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