THROMBOPHILIA: FACTOR V LEIDEN AND PROTHROMBIN GENE MUTATION

Thrombosis Canada
Thrombose Canada

OBJECTIVES:

- 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:

Thrombophilias are a group of inherited 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. The functional consequence of this mutation is impaired inactivation of factor V (also known as "activated protein C resistance"), resulting in increased thrombin generation.

The second most frequent 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.

Homozygosity for FVL or PGM and compound heterozygosity are much rarer, with prevalences of less than 1%.

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 VTE risk and are not considered to significantly increase the risk of recurrent VTE. However, patients with homozygous FVL or PGM and patients with compound heterozygous FVL and PGM have a greater risk of VTE and are at increased risk of recurrence.

Although most individuals who are heterozygous for FVL or PGM will not develop VTE over their lifetime, the overall VTE risk is compounded by 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.

Increased risk of arterial thrombosis in this population has not been clearly established. Limited and weak data suggest that FVL and PGM might be associated with a slightly increased risk of arterial stroke, particularly in young adults; however, the clinical significance of this finding is not clear.

Risk of Pregnancy Complications with FVL and PGM

Available data suggests that women who are heterozygous for FVL or PGM are not at significantly increased risk of these complications, 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, it is not recommended.**

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, <u>if the result would change the decision</u> to use VTE prophylaxis or a contraceptive associated with an increased thrombotic risk. A positive test result may 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 provision of unneeded anticoagulants during periods of perceived high risk. Screening in women with a history of pregnancy complications and in patients with a history of arterial vascular disease only is 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. 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. Antepartum and postpartum thromboprophylaxis is usually suggested in pregnant women who are homozygous for FVL or PGM or compound heterozygote 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.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Deep Vein Thrombosis (DVT): Treatment
- Pregnancy: Thromboprophylaxis
- Pulmonary Embolism (PE): Treatment

REFERENCES:

Baglin T, et al. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol. 2010;149(2):209-220.

Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 201827;2(22):3317-3359.

Chiasukul T, et al. Inherited thrombophilia and risk of arterial ischemic stroke: a systematic review and meta-analysis. J Am Heart Assoc. 2019;8:e012877.

Federici EH et al. High risk of thrombosis recurrence in patients with homozygous and compound heterozygous factor V R506Q (Factor V Leiden) and prothrombin G20210A. Thromb Res. 2019;182:75-78.

MacCallum P, et al. Diagnosis and management of heritable thrombophilia. BMJ 2014;349:g4387:1-9.

Meijer K, Schulman S. The absence of 'minor' risk factors for recurrent venous thromboembolism: a systematic review of negative predictive values and negative likelihood ratios. J Thromb Haemostasis 2009;7(10):1619-1628.

Middeldorp S, van Hylckama Vlieg A. Does thrombophilia testing help in the clinical management of patients? Br J Haematol. 2008;143(3):321-335.

Rodger MA, et al. Is thrombophilia associated with placenta-mediated pregnancy complications? A prospective cohort study. J Thromb Haemost. 2014;12(4):469-478.

Segal JB, et al. Predictive value of Factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. JAMA 2009;301(23):2472-2485.

Stevens SM, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis 2016;41(1):154-164.

van Vlijmen EF, et al. Combined oral contraceptives, thrombophilias and the risk of venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemostasis 2016;14(7):1393-1403.

Date of Version: 16Feb2020

Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.