Prenatal Screening for Thrombophilias

Indications and Controversies, an Update

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KEYWORDS

• Thrombophilia • Adverse pregnancy outcomes • Venous thromboembolism • Inherited thrombophilias • Acquired thrombophilias • Pregnancy

KEY POINTS

- Thrombophilias are disorders of hemostasis that predispose a person to a thrombotic event.
- Acquired and inherited thrombophilias lead to an increased risk of venous thromboembolism (VTE) during pregnancy and in the postpartum period.
- Acquired thrombophilias are associated with adverse pregnancy outcomes.
- Universal screening of pregnant women is not cost-effective or indicated because of the low incidence of VTE during pregnancy.

INTRODUCTION

There are numerous procoagulant physiologic changes in pregnancy. There is an increase in levels of fibrinogen; von Willebrand factor; and clotting factors II, VII, VIII, IX, X[1,2]; there is a decrease in levels of physiologic anticoagulants such as protein S (PS), and an increase in protein C (PC) resistance. Pregnancy is associated with increased clotting potential, decreased anticoagulant activity, and decreased fibrinolysis.[3,4]

A thrombophilia is defined as a disorder of hemostasis that predisposes a person to a thrombotic event.[5] Data suggest that at least 50% of cases of venous thromboembolism[6] (VTE) in pregnant women are associated with thrombophilias.[7,8] Inherited

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and/or acquired thrombophilias have been associated with an increased risk of maternal thromboembolism and adverse pregnancy outcomes such as recurrent pregnancy loss, intrauterine fetal demise, preterm preeclampsia, and fetal growth restriction (FGR), although there is controversy regarding these associations. It is important to be able to identify which patients have indications for thrombophilia testing, and, in those who do, what laboratory testing should be performed.

INHERITED THROMBOPHILIAS

There are several types of inherited thrombophilias, including factor V Leiden (FVL) mutation, prothrombin (PT) gene (G20210A) mutation, PC deficiency, PS deficiency, and antithrombin III (ARIII) deficiency.[9–11]

Factor V Leiden

FVL mutation is present in approximately 5% to 9% of the white European population and is the most common heritable thrombophilia among this ethnic group. It is rare in populations of African and Asian ancestry.[9] In most cases, it is a result of a point mutation in the factor V gene located at nucleotide position 1691. This mutation leads to substitution of glutamine (Q) for arginine (R) at amino acid position 506 (FVR506Q or FV:Q506). This substitution impairs the proteolysis of factor V by activated PC (aPC), producing a hypercoagulable state.[10] This point mutation, first described in 1994, is the leading cause of aPC resistance and has an autosomal dominant inheritance pattern.[12,13]

Forty-four percent of patients presenting with VTE during pregnancy or postpartum are found to carry the FVL mutation, and most are heterozygotes.[14] In pregnant women who are heterozygotes for FVL and have never had a VTE or a first-degree relative with a VTE, there is a thrombotic risk of 0.5% to 1.2%. In women who are homozygous for FVL without a history or first-degree family history of VTE, the risk of VTE is 4%.[14,15] The thrombotic risk per pregnancy increases in women with a personal history of VTE, with a 10% probability in FVL heterozygotes and 17% in FVL homozygotes (**Table 1**).[11,14,16–20]

Screening can be performed by assessing aPC resistance using a second-generation coagulation assay followed by genotyping for the FVL mutation or simply gene analysis for the factor V exon to detect FVL.[10] DNA analysis for FVL is accurate during pregnancy, acute thrombotic events, and while on anticoagulation (**Table 2**).

Prothrombin Gene (G20210A)

The PT gene (G20210A) point mutation, discovered in 1996, leads to a substitution of guanine to adenine at nucleotide position 20210 in the factor II gene, causing hyperprothrombinemia.[21]

PT gene mutation is present in 3% of the white European population and is associated with 17% of the VTE in pregnancy (see **Table 1**).[14] The probability of VTE in patients without a history of a thrombotic event is 0.37% for PT heterozygotes, and 2% to 4% for homozygotes.[11,16] Individuals who are compound heterozygotes for FVL and PT mutations are characterized by further hypercoagulability. The incidence of compound heterozygosity is 1 in 10,000 people. The risk of VTE per pregnancy in this population is 4.7% without a personal or family history of VTE and is more than 20% with a positive history.[16]

Gene analysis using polymerase chain reaction is used to detect the PT gene mutation.[21] Increased plasma levels of PT should not be used for screening. Similar to