INTRODUCTION

Inherited thrombophilia is thought to increase the risk of pregnancy-related venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE).

Pregnancy is a hypercoagulable state due to the increased concentration of coagulation factors, decreased natural anticoagulants and fibrinolytic activity. The pregnant woman is therefore at increased risk for VTE and this predisposition is much accentuated in patients with thrombophilia. Thus it is important to identify this group of patients before or early in pregnancy in order to tailor appropriate preventive means.

THE APPROACH TO VENOUS THROMBOEMBOLISM

The clinical approach to acute VTE is the same in patients with or without inherited thrombophilia. However, most patients with a confirmed episode of VTE will eventually undergo thrombophilia screening if acquired causes are excluded. Obviously, the clinical utility of testing is the a priori assumption that the test results are likely to improve health outcome. In this context, one should remember that screening is performed in the absence of disease, whereas testing is performed in the presence of symptoms or signs. It follows that in the case of thrombophilia the actual workup is for testing rather than for screening.

In contrast to the simple, reliable and inexpensive laboratory tests used to investigate bleeding disorders such as prothrombin time (PT) and partial thromboplastin time (PTT), no such diagnostic means exist for testing/screening of hypercoagulable states. Moreover, the literature holds that thrombophilia testing/screening is expensive. For example, Wu and colleagues calculated the incremental cost-effectiveness ratio (ICER; the lower the ICER the more cost-effective the strategy to avoid a major adverse clinical outcome) for universal screening prior to prescribing combined contraception, for example, is as high as £202,402 (UK), whereas for hormone replacement it is far less (£6824) (UK). Stated another way, it is not cost-effective to perform routine thrombophilia screening before prescribing hormonal therapy. Several authorities have maintained that screening the general population is not justified mainly because of the above-mentioned financial considerations. Therefore, in order to avoid indiscriminate thrombophilia screening and waste of health resources, one must consider the indication, advantages and pitfalls of such an investigation. Injudicious thrombophilia screening should therefore be discouraged.

Every testing/screening should be based on the prevalence of each inherited thrombophilic condition and the association of each with the risk of VTE. Several inherited thrombophilic conditions predispose to venous thrombosis. The most important are factor V Leiden mutation, prothrombin gene mutation, protein C,
protein S and antithrombin deficiency, elevated factor VIIIc and hyperhomocysteinemia. The frequency of the natural anticoagulant protein S, protein C and antithrombin deficiencies is low in the general population (<1% in total) as well as in patients with VTE (5% in total), but the frequency of gain of functional mutations – factor V Leiden and prothrombin gene mutation – is common in the general population (3–7% and 3%, respectively) as well as in patients with VTE (25% and 10%, respectively). The prevalence of factor V Leiden and prothrombin gene mutation is 10–15% in the Caucasian population but increases to about 50% in patients with recurrent thromboembolic phenomena.

Because selection for thrombophilia testing/screening is required, a rather long list of candidates has been created over the years. To simplify this list, these candidates have been grouped under three subheadings.

Venous thromboembolism

Age is the single most important factor for VTE, and hence, young patients (defined as <50 years) who experienced previous VTE after an event that is no longer present, such as minor surgery or bone fracture, should undergo evaluation. However, even if there is no identifiable risk factor for VTE, patients with unprovoked VTE at any age, should be screened for thrombophilia. Similarly, the association of VTE in the absence of any other risk factor except the use of exogenous estrogens (oral contraception and hormone replacement) or pregnancy, should lead to screening, as is the case for patients with recurrent VTE at any age or early age of onset. In addition to the common sites of DVT, it has been suggested that patients with superficial thrombophlebitis without malignancy and those with DVT at unusual sites (cerebral, mesenteric, portal or hepatic) under the age of 50 years also should be evaluated. This category includes the rare event of a neonate with purpura fulminans without sepsis. Because this circumstance is suspected to manifest a homozygous state of protein C and S deficiencies, first degree relatives should also be screened.

Warfarin decreases the level of the natural anticoagulant protein C and S, as well as vitamin K-dependent coagulation factors. In some patients receiving warfarin, the decrease in anticoagulants is faster than the decrease in coagulation factors, and they develop skin necrosis. Accordingly, patients who sustained warfarin skin necrosis are suspected to be heterozygous for protein C and S deficiency and should therefore be investigated.

Family history

Patients with first degree relatives who have had a VTE at a young age or as a pregnancy complication are candidates for screening.

Previous adverse pregnancy outcomes

The association of some adverse pregnancy outcomes with inherited thrombophilia is controversial. Since placenta-mediated pregnancy complications are thought to result from placental micro/macrothrombosis in blood vessels, one might assume that thrombophilia should increase thrombotic risk. However, conflicting data exist for the link between pregnancy complications and thrombophilic risk factors. A recent meta-analysis of 25 studies on 11,183 women found a significant association between pregnancy complications and thrombophilia, especially for early and late recurrent pregnancy loss associated with antiphospholipid antibodies (APLA), factor V Leiden and the prothrombin gene mutation.

Data evaluation demonstrated a strong association between factor V Leiden and recurrent pregnancy loss, as well as severity of pregnancy complications in the second and third trimesters compared to first trimester. The
Inherited thrombophilic disorders

evaluation, however, indicates that the relationship between thrombophilia and pregnancy complications is confounded by ethnicity, severity of illness and method of testing\textsuperscript{14}. In contrast, other recent studies failed to demonstrate an association between thrombophilia and adverse pregnancy outcome\textsuperscript{15-25}. While thrombophilias are associated with placental-mediated pregnancy complications, their causal contribution is weak. The association makes biological sense (consistent with the pathophysiological theory of the development of pregnancy complications) but the association is inconsistent, non-specific, without biological gradient and with no convincing evidence from clinical studies for causal association\textsuperscript{18,21}. Publication bias also plays a role in the interpretation of findings in relevant studies.

It is therefore not surprising that the latest American College of Chest Physicians (ACCP) guidelines on VTE, thrombophilia and antithrombotic therapy recommend that only women who have had recurrent early loss (three or more miscarriages), unexplained late pregnancy loss, and severe or recurrent pre-eclampsia or intrauterine growth restriction (IUGR) be screened for APLA\textsuperscript{26}.

WHEN TO TEST FOR THROMBOPHILIA?

Coagulation factors and natural anticoagulation levels change during acute VTE, under specific medication and during pregnancy\textsuperscript{7,27,28}. Biochemical evaluation can be postponed until the treatment duration (3–6 months) for an acute VTE is over, whereas polymerase chain reaction (PCR) tests for factor V Leiden and factor II mutation can be performed at any time. Similarly, lupus anticoagulant (LAC) and APLA levels do not change with acute VTE, but should be re-confirmed after a 12-week interval.

Clot based assays like protein S and factor VIII should not be performed during the acute phase of VTE, during pregnancy, or during oral contraception and warfarin treatment. Tests should be performed at least 2–3 months after pregnancy and withdrawal of oral contraception, and 1 month after warfarin treatment is completed.

Antithrombin levels may be determined during acute VTE before unfractionated heparin (UFH) or low molecular weight heparin (LMWH) treatments are initiated, as both interact with antithrombin. This is because antithrombin concentrate replacement may be necessary for acute VTE, together with heparin or LMWH treatment for severe antithrombin deficiency.

Screening seems to be unnecessary in patients on prolonged anticoagulant treatment (malignancy or recurrent VTE) because the decision for treatment has already been made. Likewise, in patients with a personal or familial VTE history, there is no need for routine preoperative screening, as the results will not change the recommended thromboprophylaxis policy in most of them\textsuperscript{7}.

WHY PERFORM THROMBOPHILIC TESTS?

The rationale to perform thrombophilia testing is mainly to establish the genetic basis of the VTE\textsuperscript{5,29}. Once known, the etiologic factor or presence of combined defects may be communicated to the patients and may influence the duration of treatment and establish the potential risk for recurrence. This knowledge also may help in providing thromboprophylaxis to high-risk patients and their first-degree relatives.

One potential advantage of thrombophilia testing is for consulting women with a personal or significant family history of VTE who may wish to use oral contraception, HRT, or to become pregnant. Advantages of testing are
more pronounced among women considering HRT than oral contraception, because of the much higher risk of VTE in middle-aged women. Ancillary advantages of family screening are to provide additional health benefits such as controlling blood pressure, lipid disorders, obesity and smoking.

From a scientific point of view, recognizing the prevalence of thrombophilia in minorities or in certain disease conditions unrelated to VTE or pregnancy complications may improve the true impact of such conditions in terms of public health.

WHY NOT PERFORM THROMBOPHILIA SCREENING?

Numerous arguments exist against screening for thrombophilia. The arguments related to the inaccuracy in establishing the correct laboratory diagnosis are beyond the scope of this chapter. Nor is the problem related to websites promoting genetic testing for thrombophilia without physician supervision. However, other relevant opinions should be heard.

First and foremost is the fact that in most cases the decision about duration and intensity of anticoagulant therapy can be made by clinical criteria without actually knowing the underlying cause. In simple terms, VTE patients with or without thrombophilia will be managed in a similar way in most cases.

Second, controversy exists regarding the ability of a given defect to predict which patient is likely to have a recurrent VTE. Stated differently, the presence of a positive test of several thrombophilias does not necessarily mean an increased risk of recurrence. Conversely, concern has been voiced that unnecessary testing may overestimate the risk with consequently needless and potentially hazardous treatment. In this respect, it is important to note that in the absence of randomized controlled trials that support treatment during pregnancy, one may question the wisdom of screening patients with adverse pregnancy outcomes.

Third, the arguments related to the cost-effectiveness of routine universal screening are cogent. For example, one would need to screen 2 million women for factor V Leiden before starting oral contraception in order to prevent one death from pulmonary embolism.

Fourth, there is a definite psychological effect of screening stress which may affect quality of life in patients with a potential rather than with a real risk. For example, a positive thrombophilia test does not necessarily mean VTE in the future, as 40% of women tested positive will never develop VTE. Conversely, false reassurance is unjustified in a patient with negative testing merely because our understanding of the coagulation cascade is incomplete, and the availability of commercial laboratory kits is limited. For example, protein Z deficiency or antibodies are known thrombophilic factors, but their assessment is vastly limited because the laboratory methodology is not widely available.

Finally, as noted above, a patient with a positive test may never have any health problem. Yet, some insurance companies may be reluctant to insure this patient or may increase the cost involved.

Preconception consulting for women with a history of pregnancy complications and documented thrombophilia should include the controversy of the association between the genetic defects and pregnancy outcome. It must be emphasized, however, that at present the association between thrombophilia and adverse pregnancy outcome is unclear, as thrombophilias are only weakly associated with adverse pregnancy outcomes. It appears that thrombophilias are but one of many factors involved in poor obstetric outcome.
WHAT IS THE MOST ECONOMICAL WAY TO SCREEN FOR INHERITED THROMBOPHILIA?

One way to reduce the costs of screening/testing is to look for specific thrombophilia factors rather than to test for every known factor for which a test is available. Table 1 shows the list of tests according to priority, which is set by the likelihood of inherited thrombophilia in a given case. The highest diagnostic yield is expected with the high priority tests mainly because they are also the most frequent.

Other inexpensive and useful means for screening patients with hypercoagulable states and pregnancy complications have been reported recently. The ProC Global assay is one that globally evaluates the functionality of the protein C pathway. The assay is based on the ability of endogenous activated protein C (APC), generated by a snake venom extract, to prolong an activated partial thromboplastin time (APTT). This assay can distinguish patients with or without protein C pathway abnormalities. It has been reported that the ProC Global assay can be used as the initial step in screening for factor V Leiden-related APC resistance and protein C deficiency in patients who are not on oral anticoagulants. This assay, however, has low sensitivity to protein S deficiency. The ProC Global test is claimed to screen for women with idiopathic pregnancy loss and to identify patients at increased risk for VTE.

ANTITHROMBOTIC THERAPY DURING PREGNANCY

Anticoagulation is indicated during pregnancy for the prevention of VTE, treatment of acute VTE, prevention of emboli in patients with mechanical heart valves, and in prevention of recurrent pregnancy loss in women with APLA.

Available antithrombotic drugs include UFH and LMWH, and the antiagregant agent commonly used is aspirin. LMWH is recommended over UFH for the prevention and treatment of VTE during pregnancy. UFH treatment has significant side-effects such as osteoporosis and heparin-induced thrombocytopenia (HIT), and requires laboratory monitoring. These side-effects are significantly less common with LMWH, and there is no need for routine laboratory testing during treatment (except for the infrequent need for dose-adjustments by measuring anti-Xa). LMWH has better bioavailability, longer plasma half-life and an improved safety profile over UFH according to the 8th edition of ACCP guidelines.

UFH and LMWH do not cross the placent and are not secreted in breast milk. A recent review showed a good safety profile of

Table 1  Testing according to high, intermediate and low priority of thrombophilia factors. Adapted from reference 28

<table>
<thead>
<tr>
<th>High priority</th>
<th>Intermediate priority</th>
<th>Low priority</th>
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<tr>
<td>APCR</td>
<td>Protein C activity</td>
<td>Dysfibrinogenemia</td>
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<tr>
<td>Factor V Leiden</td>
<td>Free protein S</td>
<td>Elevated fibrinogen level</td>
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<tr>
<td>Factor II mutation</td>
<td>Decreased antithrombin activity</td>
<td>Increased activity of factors IX and XI</td>
</tr>
<tr>
<td>Elevated homocysteine level</td>
<td>Increased anticardiolipin antibodies</td>
<td>MTHFR</td>
</tr>
<tr>
<td>Elevated factor VIII level</td>
<td>Lupus anticoagulant</td>
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APCR, activated protein C resistance; MTHFR, methylenetetrahydrofolate reductase
enoxaparin during pregnancy\textsuperscript{41}. In particular, the rates of bleeding complications and osteoporosis were low, and there were no cases of heparin-induced thrombocytopenia (HIT).

Women with a history of VTE or thrombophilia have an increased risk for pregnancy associated recurrent VTE\textsuperscript{42}, but no large clinical trials have assessed the role of prophylaxis in pregnant women with previous VTE. Retrospective and prospective studies demonstrated a good pregnancy outcome for women with previous VTE whether or not treated by heparin prophylaxis\textsuperscript{43,44}. This, however, was not true for women with APLA who are at high risk of VTE, pregnancy loss and pre-eclampsia\textsuperscript{45}. Data demonstrate that women with APLA and recurrent fetal loss have an improved pregnancy outcome when treated with combined therapy consisting of low-dose aspirin and heparin prophylaxis\textsuperscript{46}. In contrast, a randomized trial failed to confirm an improved pregnancy outcome by adding heparin to aspirin in this specific population of women\textsuperscript{47}.

Several meta-analyses have been performed to investigate the association between thrombophilia and pre-eclampsia\textsuperscript{48–50}. Factor V Leiden, MTHFR 677C>T polymorphism and other inherited thrombophilias were found to moderately increase the risk of pre-eclampsia, but the link is weak and routine screening for thrombophilia is not recommended. The effect of aspirin on the recurrence of pre-eclampsia has been studied in large trials, but no such trials have been performed with LMWH.

Small and uncontrolled studies on treatment with LMWH of women with inherited thrombophilia and pregnancy loss have suggested that prophylaxis with enoxaparin is effective (and safe) in improving pregnancy outcome and has a potential for reducing late pregnancy complications\textsuperscript{51,52}. Two recent randomized controlled trials\textsuperscript{53,54} demonstrated no reduction in pregnancy loss rate with antithrombotic intervention in pregnant women with two or more unexplained recurrent pregnancy losses. At present, women with a history of placenta-mediated pregnancy complications, with or without genetic thrombophilia, should not be treated routinely by anticoagulants, unless in the context of randomized controlled trials.

To date, no clear criteria or guidelines exist for the diagnosis and treatment of women with thrombophilia in pregnancy. Physicians may treat these women based on clinical judgment and on their own experience.

The most recent guidelines on VTE, thrombophilia, antithrombotic therapy and pregnancy were published by the ACCP\textsuperscript{26} and the Royal College of Obstetricians and Gynaecologists in 2009\textsuperscript{55}. The recommended thromboprophylaxis in pregnancy can be divided into two subgroups.

1. Prevention of recurrent VTE in pregnancy:
   
   a. A previous VTE event associated with a transient risk factor and no thrombophilia: clinical surveillance antepartum and anticoagulant prophylaxis postpartum;
   
   b. A previous VTE event associated with pregnancy or estrogen containing drug: antepartum clinical surveillance or prophylactic/intermediate-dose anticoagulant prophylaxis (LMWH/UFH) plus postpartum prophylaxis;
   
   c. Single idiopathic VTE event without thrombophilia: prophylactic/intermediate-dose anticoagulant (LMWH/UFH) or clinical surveillance antepartum plus postpartum anticoagulant;
   
   d. Single episode of VTE and laboratory confirmed thrombophilia without long-term anticoagulants: prophylactic/intermediate-dose anticoagulant (LMWH/UFH) or clinical surveillance antepartum plus postpartum anticoagulant;
   
   e. Single episode of VTE and high-risk thrombophilias (antithrombin deficiency, APLA, compound heterozygote for factor V Leiden and prothrombin...
Inherited thrombophilic disorders

1. Long-term anticoagulants for prior VTE: frequent pregnancy tests and substitution of adjusted/intermediate-dose UFH/LMWH when pregnancy is achieved. Postpartum, long-term anticoagulants should be resumed;

h. All women with previous VTE are advised to use graduated compression stockings;

i. Women with thrombophilia and no prior VTE: individual risk assessment;

j. Antithrombin deficiency and no history of VTE: antepartum and postpartum prophylaxis. Other thrombophilias without prior VTE: clinical surveillance or prophylactic anticoagulants (LMWH/UFH) antepartum plus postpartum anticoagulants.

2. Prevention of recurrent pregnancy complications in women with thrombophilia:

a. APLA and three or more events of pregnancy loss, no VTE or arterial thrombosis: antepartum prophylactic/intermediate UFH/LMWH, combined with aspirin;

b. High risk for pre-eclampsia: low-dose aspirin throughout pregnancy;

c. History of pre-eclampsia: UFH/LMWH is not recommended for subsequent pregnancies.

A woman with previous VTE or pregnancy complications, who wishes to get pregnant again, needs the consultation and co-management of an obstetrician, hematologist and coagulation expert. This team should counsel the woman about the recommended diagnostic tests, suggest available treatment protocols and supervise the subsequent pregnancy.

SUMMARY

Until we find useful and inexpensive screening tools, it is not recommended to test every patient or her/his relatives for thrombophilia. Screening should be limited to patients at high-risk of VTE. Each index case should be carefully evaluated by an expert physician who should tailor the laboratory testing as well as treatment modalities.

Thrombophilias are considered to be only weakly associated with adverse pregnancy outcome and are but one of many factors involved in such circumstances. At present, women with a history of placenta-mediated pregnancy complications, with or without genetic thrombophilia, should not be treated routinely with anticoagulants, unless in the context of randomized controlled trials.

In order to optimize the diagnosis and treatment of pregnant women with thrombophilia and previous VTE or pregnancy complications, a team made up of an obstetrician, hematologist and coagulation expert seems essential.

REFERENCES


dence of venous thromboembolism in asym-
ptomatic family members who are carriers of
*Blood* 2002;99:1938–42
5. Martinelli I. Pros and cons of thrombophilia
6. Haemostasis and Thrombosis Task Force, Brit-
ish Committee for Standards in Haematology.
Investigation and management of heritable
7. Nicolaides AN. Thrombophilia and venous
thromboembolism. International Consensus
Statement. Guidelines According to Scientific
Evidence. *Int Angiol* 2005;24:1–26
8. Jordaan DJ, Schoon MG, Badenhorst PN.
Thrombophilia screening in pregnancy.
*Obstet Gynecol Surv* 2005;60:394–404
9. Lockwood CJ. Inherited thrombophilias in
pregnant patients: detection and treatment
10. Caprini JA, Goldshteyn S, Glase CJ, Hatha-
way K. Thrombophilia testing in patients with
venous thrombosis. *Eur J Vasc Endovasc Surg*
2005;30:550–5
11. Mannucci PM. Laboratory detection of inher-
itated thrombophilia: a historical perspective.
*Semin Thromb Hemost* 2005;31:5–10
Factor V. Leiden Working Group. American
College of Medical Genetics consensus state-
ment on factor V Leiden mutation testing.
Thrombosis: Risk and Economic Assessment
of Thrombophilia Screening (TREATS) Study.
Thrombophilia in pregnancy: a systematic
philias and adverse pregnancy outcome - a
confounded problem! *Thromb Haemost* 2008;
99:77–85
15. Rey E, Kahn SR, David M, Shrier I. Thrombo-
philic disorders and fetal loss: a meta analysis.
*Lancet* 2003;361:901–8
coaugulation factors in women with unexplained
thrombophilias and unexplained pregnancy
loss: an incidental case-control study. *J Thromb
Haemost* 2009;7:306–11
18. Rodger MA, Padas M. Do thrombophilias cause
placental – mediated pregnancy complications?
*Semin Thromb Hemost* 2007;33:597–603
Absence of association of thrombophilia poly-
orphism with intrauterine growth restric-
20. Pabinger I. Thrombophilia and its impact on
21. Flacco F, You W, Grobman W. Genetic throm-
bophilias and intrauterine growth restriction:
a meta-analysis. *Obstet Gynecol* 2009;113:1206–16
22. Rodger MA. Thrombophilia and placenta-
mediated pregnancy complications: from the
bench to bedside to policy. *Thromb Res* 2009;
123S:100–4
gene G20210A mutation and obstetric compli-
thrombophilia polymorphism and pregnancy
outcome in nulliparous women. *Obstet Gynecol*
2010;115:5–13
25. The American College of Obstetricians and
Gynecologists. Inherited thrombophilias in
pregnancy. Practice bulletin no 113. *Obstet
Gynecol* 2010;116:212–22
Venous thromboembolism, thrombophilia, anti-
thrombotic therapy, and pregnancy: American
College of Chest Physicians Evidence Based
Clinical Practice Guidelines, 8th edn. *Chest*
2008;133:844–86
27. Carraro P; European Communities Confed-
eration of Clinical Chemistry and Laboratory
Medicine, Working Group on Guidelines for
Investigation of Disease. Guidelines for the
laboratory investigation of inherited throm-
bophilias. Recommendations for the first
level clinical laboratories. *Clin Chem Lab Med*
2003;41:382–91
28. Seligsohn U, Lubetsky A. Genetic suscep-
tibility to venous thrombosis. *N Engl J Med*
2001;344:1222–31
29. Cushman M. Inherited risk factors for venous
thrombosis. *Hematology (Am Soc Hematol Educ
Program)* 2005:452–7
30. Mack R, Chowdary D, Streck D, Dermody J.
Inherited thrombophilia genes in minorities.
Inherited thrombophilic disorders

55. Royal College of Obstetricians and Gynaecologists, RCOG Green-top guideline no 37.