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Issue:	Volume 13(5), September 2006, p 337-343						
Publication Type:	[Hemostasis and thrombosis]						
Publisher:	© 2006 Lippincott Williams & Wilkins, Inc.						
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Keywords: inherited thrombophilia, laboratory screening, pregnancy complications, recurrent venous thromboembolism



DOI: 10.1097/01.moh.0000239705.25050.ff ISSN: 1065-6251 Accession: 00062752-200609000-00007

Abstract

Purpose of review: The purpose of this review is to identify on the basis of available data and expert opinions who would benefit most from screening for thrombophilia.

Recent findings: Recent studies have clearly defined the risk of venous thromboembolism in members of families with inherited thrombophilia. Meta-analyses have shown the role of the most common thrombophilic conditions in increasing the risk of recurrent venous thromboembolism in carriers. Screening for thrombophilia in venous thromboembolism patients might help identify those at higher risk of recurrences even though it is unclear how this information can be of use in modifying their management. Thrombophilia seems to play a role in early fetal losses as also shown in women at their first intended pregnancy, which makes it interesting to screen women after only one bad pregnancy outcome.

Summary: Screening for thrombophilia can be performed particularly in young patients with venous thromboembolism. Carriers of inherited thrombophilia are at increased risk of venous thromboembolism recurrences. Screening families of venous thromboembolism patients with thrombophilia allows the identification of still asymptomatic carriers who may benefit from thromboprophylaxis. This may be true of women in fertile age belonging to thrombophilic families. In thrombophilic women with pregnancy complications prophylaxis may be offered to prevent recurrences.

Abbreviations FVL: factor V Leiden; HELLP: hemolysis, elevated liver enzymes, and low platelets count; HRT: hormonal replacement therapy; IUGR: intrauterine growth retardation; PTG20210A: prothrombin variant G20210A; VTE: venous thromboembolism.

Introduction

A lot of debate is currently in progress over whether screening for thrombophilia is to be performed in clinical practice in symptomatic patients with (recurrent) venous thromboembolism (VTE), in symptomatic or asymptomatic members of families of probands who are carriers of inherited thrombophilic conditions and in women who develop (recurrent) pregnancy complications or require oral contraceptive therapy or hormonal replacement therapy (HRT) [1-3,4••-6••,7].

Good reasons for screening may be the clarification of the cause of VTE or pregnancy complications, implications in the management of symptomatic carriers of thrombophilia and of asymptomatic carriers (often identified by means of family screenings) in high-risk situations for VTE and the potential benefits for the prevention of pregnancy complications in those women who are identified as carriers of thrombophilia. In addition, screening for thrombophilia might be considered in asymptomatic women belonging to thrombophilic families before administration of hormonal therapy, particularly in perimenopausal periods.

This review discusses some of these points in an attempt to clarify who should benefit most from screening for thrombophilia.

Screening of symptomatic patients with venous thromboembolism: an aetiological issue

Among the categories of individuals who may benefit from screening for thrombophilia, the first might be that of patients who develop an episode of VTE. In this group, in fact, the identification of inherited thrombophilic defects can clarify the cause of the first (recurrent) thrombotic event [7]. Doctors always wish to know why their patients have developed VTE and the identification of an underlying thrombophilic condition can be in many cases a satisfactory explanation. It should be considered, however, that inherited and acquired thrombophilic conditions may co-exist in the same patient [8,9]. Patients with still undiagnosed cancer who present with VTE may also be carriers of common thrombophilic polymorphisms such as factor V Leiden (FVL) mutation or prothrombin variant G20210A (PT G20210A). The laboratory diagnosis of thrombophilic defects in patients with VTE does not exclude the presence of other diseases associated with increased thrombotic risk. Thus, because of the multivariate cause of VTE [10], the results of screening for thrombophilia always need to be interpreted in the clinical context of each patient. The most important inherited thrombophilic conditions (Table 1) are clotting inhibitor deficiencies (including antithrombin, protein C and protein S defects) and resistance to activated protein C in most cases related to the presence of FVL mutation and PT G20210A [7]. Rarer inherited thrombophilic conditions include dysfibrinogenemias, whose clinical relevance has not yet been fully clarified. Other thrombophilic conditions potentially related to a genetic background are increased levels of factor VIII [11], factor IX [12] and factor XI [13]. Family studies which might support the hypothesis of the inheritance of high clotting factor levels are scarce and available only for increased FVIII levels [14]. Among the acquired thrombophilic conditions, antiphospolipid antibodies (lupus anticoagulant, anticardiolipin antibodies, anti-[beta]2-GPI antibodies) [15..., 16..., 17] and cancer [8,9] are the most relevant. Mild hyperhomocysteinemia and vitamin B levels are also implicated in the pathogenesis of venous and arterial thrombosis [18-20]. It was recently shown that combined vitamin B and folate treatment given to reduce homocysteine levels after myocardial infarction or in vascular peripheral disease did not prevent recurrences or progression of the diseases [21..., 22..., 23].

Cause	Association	Comments
Antithrombin defects	Confirmed	Deficiency and dysfunctional variants
Protein C defects	Confirmed	Deficiency and dysfunctional variants
Protein S defects	Confirmed	Deficiency and dysfunctional variants
Activated Protein C resistance	Confirmed	Associated with factor V Leiden mutation
Prothrombin variant G20210A	Confirmed	
Dysfibrinogenemias	Confirmed	Very rare
		Clinical relevance not yet clarified
Mild hyperhomocysteinemia	Confirmed	(프로그램 NY) 18년 18월 18일 - 2023년 18일
Elevated factor VIII levels	Confirmed	Genetics not yet established
Elevated levels of factor IX and factor XI	Under investigation	
Plasminogen deficiency	Under investigation	
Decreased fibrinolysis	Under investigation	
Elevated TAFI	Under investigation	
Thrombomodulin mutations	Under investigation	
Mutations in factor V gene other than factor V Leiden	Under investigation	HR2 haplotype, factor V Cambridge, etc.
Mutations in endothelial protein C receptor gene	Under investigation	···· · · · · · · · · · · · · · · · · ·

Table 1 Main causes of inherited thrombophilia

Which (thrombotic) patients are most likely to be carriers of inherited thrombophilia?

The presence of thrombophilia is suspected on clinical grounds and patients usually present with different clinical manifestations as follows: family history of VTE involving both males and females; unprovoked or provoked (risk period-related) VTE at a young age (<50 years); recurrent VTE; thrombosis in unusual sites (cerebral sinuses, mesenterial veins, portal vein);

recurrent fetal loss, preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets count) syndrome, intrauterine growth retardation (IUGR); vitamin K antagonist-induced skin necrosis; neonatal purpure fulminans (homozygous protein C or protein S deficiency) and resistance to treatment (antithrombin deficiency). It is important to note that there is no clear relationship between clinical manifestations and the type of underlying thrombophilic defect, which means that the diagnosis has to be done on the basis of laboratory testing. Carriers of thrombophilic defects usually present with thrombosis at a younger age than noncarriers. First thrombotic manifestations occurring later in life, however, may also be associated with thrombophilia, which in many cases remains the only aetiopathogenetic explanation for the event. Recently, some studies [24] showed the association between atherosclerosis and venous thromboembolism. It is likely that the presence of thrombophilic defects further potentiate the thrombotic risk in older patients with atherosclerosis.

Screening families for inherited thrombophilia

Patients with a family history of thrombosis are likely to be carriers of inherited thrombophilia [25-27]. It has been shown that among members of families of symptomatic patients with inherited thrombophilia there are many who have already experienced thrombosis at the time of the laboratory screening. Because of the autosomal dominant inheritance of most thrombophilic defects, both males and females may be affected by the disease. It may be expected that about one half of family members are carriers of the thrombophilic defect. Surprisingly enough, thrombosis is sometimes experienced by family members who are not carriers of the defect present in the family proband. In several cases, these events are explained by the presence of other known thrombophilic defects in the same family, which may also result in an increase in the risk of thrombosis in double heterozygous carriers [28]. In rarer cases, the combination of defects of opposite sign in the same families may result in increased thrombotic risk. This is true of pseudohomozygous activated protein C resistance where a heterozygous factor V deficiency is combined with a heterozygous FVL mutation. In these cases, the risk of VTE is similar to that of homozygous FVL carriers [29]. Thus, if family screening for thrombophilia is to be performed, extensive laboratory testing should be considered for both symptomatic and asymptomatic family members. Needless to say, other still unknown thrombophilic defects can be present in families with severe VTE manifestations. Overall, information obtained from family studies suggests that family members who are carriers of inherited thrombophilia present with approximately three to 15-fold increased risk of VTE as compared with noncarriers [7,25-28]; the risk seems to be somehow dependent on the type of defects, being higher in carriers of clotting inhibitors deficiencies [25, 28, 30], mild to moderate in carriers of FVL [25-27, 31] and lower in carriers of PT G20210A as compared with noncarriers [32]; thrombotic events occur in family members in high-risk situations (surgery, trauma, immobilization, pregnancy/puerperium, oral contraceptive therapy and HRT) in 50-75% of cases. Thus, asymptomatic family members who are carriers of thrombophilia may take advantage of this information for the prevention of VTE in high-risk situations. Even though prophylaxis with low-molecular-weight heparin or unfractionated heparin should be given to all individuals older than 40-45 years in risk situations for VTE, this is not often the case. Particularly, in individuals belonging to thrombophilic families who are less than 45 years old (and older than 15), primary VTE prophylaxis should be administered in many predisposing situations. Unfortunately, data concerning the best management of asymptomatic family members with inherited thrombophilia are not enough to enable us to draw any definite guidelines in different risk situations for VTE. It is maintained that screening for thrombophilia might be cost-effective if performed in fertile age female members of thrombophilic families, especially in those who are willing to become pregnant or use hormonal therapy.

Recurrent venous thromboembolism: is screening for thrombophilia required?

The most important causes of recurrences after a first episode of VTE are probably the presence of active cancer and the presence of antiphospholipid antibodies (particularly lupus anticoagulant) [33, 34••, 35-37]. Under these conditions, patients may also develop recurrences during treatment of the event or secondary prophylaxis [35, 37]. If cancer remains active or levels of antiphospholipid antibodies remain persistently high after interruption of anticoagulation, the rate of recurrences is elevated and at least twice as high as that of VTE patients without these conditions.

Recurrent venous thromboembolism is maintained to be a clinical presentation of carriers of inherited thrombophilia. Although the most severe thrombophilic defects (homozygous or double heterozygous defects, antithrombin defects, other combined defects) are likely to expose symptomatic VTE patients to recurrent events [1,38], the data regarding the role of single inherited defects in increasing the risk of recurrences remained controversial until recently [39]. Although most individual studies failed to show an association between the presence of heterozygous FVL or PT G20210A and recurrent VTE [1], three meta-analyses were in favour of a potential role at least of FVL (Table 2) [40-42]. Very recently, Ho *et al.* [43••] presented the most updated view on this topic in an exhaustive meta-analysis of all available studies. Pooled results from 10 studies involving 3104 patients with first VTE revealed that the presence of heterozygous FVL is associated with an increased odds of recurrent VTE of 1.41 (95% CI, 1.14-1.75). In addition, pooled results from nine studies involving 2903 patients with first VTE revealed that the presence of heterozygous PT

G20210A is associated with an increased odds of recurrent VTE of 1.72 (95%CI, 1.27-2.31). Thus, screening for thrombophilia allows the identification of a group of symptomatic patients at higher risk of VTE recurrences. The magnitude of the effect related to the presence of heterozygous FVL or PT G20210A is not too high, in the region of 40 and 70% increase in the relative risk, respectively. It has to be noted, however, that the risk of recurrences of VTE in noncarriers is about 20% after 8 years of follow-up and that the increase in the cumulative incidence of VTE recurrences due to these polymorphisms might not be negligible in the long-term follow-up. It is less clear whether this information can be useful in decision-making for duration or intensity of the secondary prophylaxis for VTE [44]. It is suggested that the patient should receive life-long anticoagulation after a first VTE in the presence of the most severe thrombophilic conditions, but the risk-to-benefit ratio of prolonging oral anticoagulation in carriers of other less severe thrombophilia (as well as the best dose regimen to be administered) is still unclear [44].

	Heterozygous factor V Leiden				Heterozygous PT G20210A				
	Odds ratio	95% confidence interval	Number of studies	Number of patients	Odds ratio	95% confidence interval	Number of studies	Number of patients	Comments
Marchetti et al., 2000 [40]	1.36	1.05-1.78	6	1721					
Vink et al., 2003 [41]	1.30	1.00-1.70	7	1984	1.40	0.9-2.0	5	1922	
Weitz et al., 2004 [42]	1.4	1.10-1.80	7		1.4	0.9-2.0	5		
Ho et al., 2006 [43**]	1.41	1.14-1.75	10	3104	1.72	1.27-2.31	9	2903	Only patients with first-ever VTE

Table 2 Meta-analysis on the association of heterozygous factor V Leiden or prothrombin variant G20210A with recurrent venous thrombolembolism

Thus, screening for thrombophilia in (recurrent) VTE patients can be useful for the assessment of the cause of the event, for the identification of patients at higher risk of recurrences for whom strategies for secondary prevention might not be different from those of nonthrombophilic subjects even though careful clinical observation might be required and for the identification of patients at very high risk of recurrences (the most severe thrombophilic conditions) for whom secondary prophylaxis for VTE is probably to be administered for life particularly if their first VTE is unprovoked.

Other issues still to be addressed deal with the role of high levels of factor VIII, factor IX and factor XI in increasing the risk of recurrent VTE [1], as well as the effect of sex [45]. In fact, there is a lot of debate on whether males have an increased risk of recurrences as compared with females.

Unusual site thrombosis and thrombophilia screening

Thrombosis in unusual sites, such as cerebral sinus venous thrombosis, mesenterial vein thrombosis, portal vein thrombosis, suprahepatic veins thrombosis (Budd-Chiari syndrome) is observed in young individuals with inherited thrombophilia [46-48]. The advantage of screening for thrombophilia lies in the clarification of the cause of the event, the possibility of screening family members if the patient is identified as a carrier of inherited thrombophilia. There is no clear evidence as to whether the management of thrombosis in these peculiar sites needs to be modified because of the presence of inherited thrombophilia.

Thrombosis in children and thrombophilia screening

Family studies have shown that healthy children belonging to thrombophilic families, even though they are carriers of thrombophilic defects, present with a very low (if any) incidence of VTE, similar to that of children who are noncarriers of defects [25,49]. As a consequence, there seems to be no benefit from screening for thrombophilia otherwise healthy family members under the age of 15 years. In contrast, in children who develop VTE, the prevalence of thrombophilic defects can vary depending on the selection criteria of the population [50,51]. Thus, thrombophilia appears to be an important aetiological factor in child thrombosis together with cancer, indwelling venous catheters, cardiac diseases and vascular diseases, including vasculitis. It is likely that inherited and acquired thrombophilia, in association with other predisposing conditions, may play a role in the development of thrombosis [53] in children. Thus, screening for thrombophilia in children with thrombosis may be helpful in the evaluation of the cause of the event. Management of children who are carriers of thrombophilia with previous thrombotic event possibly deserves particular clinical attention and prolongation of secondary prophylaxis. Data on these important issues are still lacking. An 'off-limits' and rare situation in which thrombophilia screening in paediatric age can be helpful is the neonatal purpura fulminans, often associated with severe deficiency (homozygous) of protein C or protein S. Replacement therapy with protein C

concentrates may be life-saving.

Women's health issues: hormones treatment and thrombophilia screening

Female members of families of symptomatic probands with VTE who are carriers of thrombophilia may take advantage of screening for inherited thrombophilia in high-risk situations for VTE. This is particularly true of women in the postpartum period and of those during pregnancy who are carriers of severe thrombophilic defects [25,26,30-32]. In fertile age women belonging to thrombophilic families, screening for thrombophilia may be useful for counselling on administration of oral contraceptives or hormonal replacement therapy. Asymptomatic women with severe thrombophilic defects should be discouraged from using hormonal therapy. In very rare situations in which hormones have to be given despite the high thrombotic risk, concomitant anticoagulant prophylaxis should be considered. In the majority of cases, however, asymptomatic women identified following family screening are carriers of the less severe thrombophilic defects (heterozygous FVL or PT G20210A). Appropriate counselling on the relative risk of VTE is needed when hormonal therapy is administered to these women. The decision on whether or not hormonal therapy is to be given should be based on an accurate evaluation of the risk-to-benefit ratio of the treatment. In addition, even in the presence of single less severe thrombophilic defects in women belonging to families with a strong history of thrombotic manifestations, the use of hormonal therapy should be discouraged because of the possible co-existence of other unknown thrombophilic defects in the same family.

Universal screening for thrombophilia before the administration of hormonal therapy is not maintained to be cost-effective [5••,6••]. This is mainly based on the analysis of the costs incurred in the identification of women at higher risk of VTE because they are carriers of thrombophilia and to prevent or to treat hormonal related VTE in these women. Selective screening of postmenopausal women with a family history of thrombosis before administration of hormonal replacement therapy is the most cost-effective approach among those which can be considered before administration of any hormonal therapy (oral contraceptives or hormonal replacement therapy). Under these circumstances, however, recommendation for (selective) screening is based on how much one is willing to spend to prevent one VTE event [5••].

Women's health issues: pregnancy complications and thrombophilia screening

Despite clear evidence of increased risk of VTE in women with congenital thrombophilia, routine universal screening of pregnant women for these defects is not recommended [54••]. Screening in pregnant women who have had VTE can be reasonable in order to offer antepartum and postpartum secondary prophylaxis if a thrombophilic condition is identified. There is still no evidence, however, that screening and subsequent prophylaxis can reduce the risk of recurrent VTE or death following pulmonary embolism. Even though there is no consensus, women without a personal history of VTE but with a family history of VTE might also take advantage of thrombophilia screening [25, 30-32].

Also, women with particular inherited thrombophilic defects may present with an increased risk of other pregnancy complications such as fetal loss, IUGR, preeclampsia or HELLP syndrome [54••]. Although various studies show inconsistencies, the presence of inherited thrombophilic defects is associated with increased risk of (recurrent) fetal losses in the second and third trimester of pregnancy in carriers as compared with noncarriers [55,56]. Recent data concerning first intended pregnancy have shown that pregnancy losses (from the 10th week) were associated with the presence of heterozygous FVL or PT G20210A [57•]. In addition, thrombophilia also seems to play a role in vascular disorders of the placenta that may result in preeclampsia, abruption or IUGR since an eightfold increased risk has been shown in carriers of thrombophilia as compared with non-carriers.

Available data are still insufficient to suggest that screening for thrombophilia in women with (recurrent) first trimester foetal loss is advisable. It is commonly accepted, however, that in patients with recurrent pregnancy loss, including a second-trimester miscarriage, intrauterine death and stillbirth, screening for thrombophilia might be useful. An antithrombotic prophylaxis/therapy may be offered to these women based on the results of small but convincing clinical trials [58•,59•]. Evidence on the best management of these situations is required and this can derive only from large clinical trials, which are urgently needed.

Conclusion

Even though there are many indications for thrombophilia screening based on the possible utility in identifying the cause of thrombosis for the management of carriers of inherited defects, there is still uncertainty over whether such an approach is really cost-effective. A limited number of clinical studies are available on the management of symptomatic or asymptomatic thrombophilic patients in different risk situations. Thus, indications on who should be tested for thrombophilia have obvious limitations and this is often left to the opinion of experts in the field. These opinions are summarized as follows: thrombophilia

screening can be recommended in patients with a personal history of recurrent VTE; a first VTE at an age younger than 50 years; a first unprovoked VTE at any age; a first VTE at an unusual site; a first VTE related to pregnancy and puerperium, oral contraceptives or hormonal replacement therapy. In addition, it can be recommended in women with two or more pregnancy losses and in children with VTE or arterial thrombosis (including ischemic stroke). Thrombophilia screening may be indicated in asymptomatic adult family members of probands with known clotting inhibitor defect or FVL mutation (particularly if there is a strong family history of thrombosis); asymptomatic female family members belonging to thrombophilic families who are pregnant or are considering oral contraceptive therapy or HRT use or pregnancy; selected cases of women with unexplained severe eclampsia, IUGR, HELLP syndrome, abruptio placentae; and patients older than 50 years with a first provoked VTE in the absence of cancer, chronic myeloproliferative disorders, antiphospholipid antibodies syndrome or autoimmune diseases, or other diseases commonly associated to thrombosis.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 389).

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Keywords: inherited thrombophilia; laboratory screening; pregnancy complications; recurrent venous thromboembolism

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