Evolution of thrombophilia testing

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I Simposio Conjunto
EHA - SAH

HEMATOLOGÍA, Vol.17
Número Extraordinario
XXI CONGRESO
Octubre 2013

Abstract

Thrombophilia can be identified in many patients presenting with venous thromboembolism (VTE). Whether the results of such tests help in the clinical management of patients has not been settled. Thrombophilia testing in asymptomatic relatives may be useful in families with antithrombin, protein C or protein S deficiency, or homozygosity for factor V Leiden, but is limited to women who intend to become pregnant or who would like to use oral contraceptives. Careful counseling with knowledge of absolute risks helps patients make an informed decision in which their own preferences can be taken into account. Patients who have had VTE and have thrombophilia are, at most, at a slightly increased risk for recurrence. In the absence of trials that compared routine and prolonged anticoagulant treatment in patients testing positive for thrombophilia, testing for such defects to prolong anticoagulant therapy cannot be justified. Diagnosing antiphospholipid syndrome in patients with VTE and in women with recurrent miscarriage usually leads to a change in patient management, although the evidence to support this is limited. Over the past half century there has been an increase in our knowledge and greater possibilities for genetic testing have become available. Despite this, testing for thrombophilia serves only a limited purpose and should not be performed on a routine basis.

Learning goals

At the conclusion of this activity, participants should be able to:

- describe currently established thrombophilias;
- describe the risks of clinical manifestations associated with thrombophilias;
- discuss the pros and cons of thrombophilia testing in various clinical settings.

Introduction

To our knowledge, the term 'thrombophilia' was first used by Nygaard and Brown in 1937 when they described sudden occlusion of the large arteries, sometimes with co-existent venous thrombosis.[1] In 1956, Jordan and Nandorff extensively reviewed their own and published cases on the familial tendency in thrombo-embolic disease.[2] Nowadays, the term is generally used for a laboratory abnormality, most often in the coagulation system, which increases the risk of venous thromboembolism (VTE), i.e. venous thrombosis in any site or pulmonary embolism. In the past half century, thrombophilia has evolved from a very rare genetic disorder to a highly prevalent trait. This evolution is an immediate consequence of increasing insight into the blood coagulation system, as well as into genetic research possibilities, that made it possible to search for specific candidate abnormalities in the coagulation proteins and their encoding genes. Nowadays, some form of thrombophilia can be identified in approximately half of the patients presenting with VTE. Testing has increased tremendously for various indications,[3] but whether the results of such tests help in the clinical management of patients has not been settled.[4,5] In this educational session, we give a short overview of the history of thrombophilia research and review the currently most commonly tested thrombophilias, with a focus on an evidence-based approach to justify testing for thrombophilia in various patient groups.

A short history of thrombophilia research

Research into thrombophilia started by investigating candidate proteins or genes in highly thrombophilic families and linking abnormalities with the clinical phenotype within these families. As a next step, findings were confirmed in case control studies. These showed increased risk compared to controls, often taken from the general population. For clinicians and patients, an absolute risk estimate is more appropriate to guide decisions regarding prevention or treatment, and this was the subject of family studies of consecutive probands with a specific thrombophilic defect. The huge progress in genetic and bioinformatic techniques now allows all kinds of searches to be made, both in populationderived studies of cases with VTE and controls, and in thrombophilic families.6-8 In 1965, Egeberg identified a deficiency of the physiological anticoagulant antithrombin in a Norwegian family in which several members suffered from venous thrombosis.[9] In the early 1980s, deficiencies of the other anticoagulant proteins, i.e. protein C and protein S, were discovered as hereditary risk factors of VTE.[10,11]At this time, the genes could be cloned, and since then numerous mutations in the genes encoding antithrombin, protein C and protein S have been identified as underlying causes of low plasma levels of the anticoagulant proteins.[12-14] Another decade later, in 1993, Dahlbäck described the phenomenon of a poor anticoagulant response to activated protein C (APC), i.e. APC resistance, in a Swedish family with a high tendency of venous thrombosis.[15] In the original paper, Dahlbäck proposed that APC resistance was best explained by an inherited deficiency of a previously unrecognized cofactor to APC, after having ruled out several possible mechanisms, including deficiencies of protein S, protein C, or linkage with polymorphisms in the factor VIII or Von Willebrand factor genes. He then showed that this alleged 'co-factor' was identical to coagulation factor V.16 Soon thereafter, several laboratories independently reported the underlying genetic defect: a single G to A substitution in the gene of factor V at nucleotide position 1691, resulting in an amino acid change at position 506, the first cleavage site of factor Va for APC (FV Q506, also named FV Leiden).[17-20] In 1996, genetic analysis of candidate factor prothrombin revealed a G to A transition at position 20210 that was quite common in patients with VTE who had a family history of VTE. The mutation was linked to elevated levels of prothrombin.[21] Since then, various more common genetic variants that increase the risk of VTE to a greater or lesser extent have been identified and are included in diagnostic panels of thrombophilia testing.[22] For the more common thrombophilias that increase the risk at least 2-fold, a large number of clinical studies have led to reliable estimates of the relative and absolute risk for VTE; these will be summarized in this review.

Current thrombophilia test panel

The currently most commonly tested inherited thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations factor V Leiden and prothrombin G20210A, that impact either the anticoagulant or

procoagulant pathways.[4] Lupus anticoagulant, anticardiolipin antibodies, and anti-ß2-glycoprotein1 antibodies, which are laboratory features of the acquired thrombophilic antiphospholipid syndrome, are also generally included in a thrombophilia testing panel.[23] Elevated levels of several coagulation factors, including factors VIII, IX and XI, also increase the risk of VTE.[24-26] Although the levels of coagulation factors are in part determined genetically, factor VIII also increases with age and during various inflammatory diseases including VTE. It is worthy of note that some laboratories also include other, less well-established polymorphisms in their thrombophilia panel for which clinical implications are most uncertain. Examples are MTHFR 677TT and PAI-1 4G/5G that have at most only a weak association with VTE.[6]

Epidemiology of thrombophilia

General considerations Thrombophilic abnormalities can be either acquired or inherited. An example of acquired thrombophilia is the antiphospholipid antibody syndrome that is characterized by a tendency toward venous or arterial thrombosis, recurrent pregnancy loss or late pregnancy-related complications, in combination with persistent lupus anticoagulant or antiphospholipid antibodies. Furthermore, there are many acquired and/or transient conditions that lead to a prothrombotic state including cancer, surgery, strict immobilization, pregnancy and the postpartum period, and use of estrogen-containing medication, such as oral contraceptives and hormone replacement therapy. Although the term thrombophilia was traditionally used to apply to patients with unusual manifestations of VTE, such as recurrent spontaneous episodes, thrombosis at a young age, a strong family history, or thrombosis in an unusual site, we now know that thrombophilia tends to increase the risk for any episode of venous thrombosis or pulmonary embolism. Approximately half of the patients with inherited thrombophilia will develop their first VTE related to an acquired or transient prothrombotic risk situation. Furthermore, despite the fact that thrombosis at a young age was assumed to be a criterion for thrombophilia, and the mean age at time of a first thrombotic age is approximately ten years lower than in the general population, the vast majority of patients will have the first episode when they are over 45 years of age; a threshold that is often used to justify thrombophilia testing. The theoretical concept is that patients with thrombophilia have an intrinsic prothrombotic state which in itself is insufficient to cause thrombosis, but may lead to an event when superimposed on clinical risk factors, including increasing age.[27] It is also likely that selective testing in families with a strong history of VTE, and consequently co-segregation of known and unknown genes in the early days of thrombophilia research, has resulted in a perceived stronger risk increase than more contemporary studies have established.[28,29]

Prevalence of thrombophilia and association with various clinical conditions

Table 1 shows the prevalence of the various established thrombophilias in the general population, as well as their relationship with first and recurrent episodes of VTE, arterial thrombosis, and pregnancy complications. These defects are consistently associated with a first episode of VTE, with relative risk increases of 2 to 10.[4,30] However, inherited thrombophilias only modestly increase the risk of recurrent episodes.[4,31] Also, the association between thrombophilias and arterial thrombosis or pregnancy complications is not consistent.[32,33] Nevertheless, approximately half of all thrombophilia tests are being performed in the latter clinical settings.[3] The prevalence of persistent lupus anticoagulant or antibodies against phospholipid in the general population is not well known, since in most population-based studies these were only assessed once.[4]

Pros and cons of thrombophilia testing according to clinical factors

Testing for thrombophilia to modify the risk of a first VTE In clinical practice, requests for thrombophilia testing often come from asymptomatic individuals with a family history of VTE, in whom the index patients may or even may not have a known specific thrombophilic defect. Having a family history of VTE is a very poor predictor of the presence of thrombophilia.[34,35] However, VTE in one or more first degree relatives increases the risk of VTE by approximately 2-fold in the absence of an inherited thrombophilic defect, but even more so when both are present.[35] Still, a potential advantage of testing patients with VTE for thrombophilia may be the identification of asymptomatic family members in

order to take preventive measures if tested positive, and to withhold such measures if relatives have tested negative. An important requisite is that a test result does indeed differentiate between carriers and non-carriers in terms of their risk for a first episode of VTE. **Table 2** summarizes the absolute risks for a first episode of VTE as assessed in several retrospective and prospective family cohort studies with a similar design that have been summarized in a previous review.4 The overall annual incidence of a first VTE in individuals with antithrombin, protein C or protein S deficiency is approximately 1.5%, whereas this risk is approximately 0.5% for carriers of the factor V Leiden or prothrombin 20210A mutation. These estimates roughly correspond with multiplying the baseline risk in the general population with the relative risk estimates as listed in **Table 1**. Obviously, the 2% annual major bleeding risk associated with continuous anticoagulant treatment with vitamin K antagonists outweighs the risk of VTE.36 **Table 2** also shows that during high-risk situations such as surgery, immobilization, trauma, pregnancy, the postpartum period, and during the use of oral contraceptives the absolute risk is generally low, with the exception of women with some defects who use oral contraceptives or who are pregnant. For women who wish to use oral contraceptives and who have a positive first degree relative with VTE and a known thrombophilic defect, one can estimate the effect of avoidance of oral contraceptives on the number of prevented episodes of VTE by means of thrombophilia testing or, alternatively, by using a positive family history without thrombophilia testing. The results are listed in **Table 3**, in which the first column shows the observed incidence of VTE during one year of oral contraceptive use in carriers and noncarriers from thrombophilic families. From the risk difference between carriers and noncarriers (second column) the number of women who need to refrain from oral contraceptive use to prevent one episode of VTE can be calculated (third column). **Table 3** clearly indicates that women with antithrombin,

Table 1. Prevalence of thrombophilia and relative risk estimates for various clinical manifestations.

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden	Prothrombin 20210A mutation	Lupus anticoagulant*	Anti cardiolipin antibodies*	Anti 2 GPI antibodies
Prevalence in the general population	0.02%	0.2%	0.03-0.13%	3-7%	0.7-4%	1-8%	5%	3.4%
Relative risk for a first venous thrombosis	5-10	4-6.5	1-10	3-5	2-3	3-10	0.7	2.4
Relative risk for recurrent venous thrombosis	1.9-2.6	1.4-1.8	1.0-1.4	1.4	1.4	2-6	1-6	-
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9	10	1.5-10	-
Relative risk for pregnancy complications	1.3-3.6	1.3-3.6	1.3-3.6	1.0-2.6	0.9-1.3	No consistent data	No consistent data	-

Figures are derived from studies that are reviewed in detail elsewhere. *In most studies, presence of these thrombophilic risk factors was only assessed once.*

Table 2. Estimated incidence of a first episode of VTE in carriers of various thrombophilias (data apply to individuals with at least one symptomatic first-degree relative).

	Antithrombin, protein C, or protein S deficiency	Factor V Leiden,	Prothrombin 20210A mutation heterozygous	Factor V Leiden, homozygous
Overall (%/year, 95%CI)	1.5 (0.7-2.8)	0.5 (0.1-1.3)	0.4 (0.1-1.1)	1.8 (0.1-4.0)*
Surgery, trauma, or immobilization (%/episode, 95%CI)†	8.1 (4.5-13.2)	1.8 (0.7-4.0)	1.6 (0.5-3.8)	
Pregnancy (%/pregnancy, 95%CI)	4.1 (1.7-8.3)	2.1 (0.7-4.9)	2.3 (0.8-5.3)	16.3*
During pregnancy, %, 95%CI	1.2 (0.3-4.2)	0.4 (0.1-2.4)	0.5 (0.1-2.6)	7.0*
Postpartum period, %, 95%CI	3.0 (1.3-6.7)	1.7 (0.7-4.3)	1.9 (0.7-4.7)	9.3*
Oral contraceptive use (%/year of use, 95%CI)	4.3 (1.4 9.7)	0.5 (0.1 1.4)	0.2 (0.0 0.9)	

Figures are derived from numerous family studies which are reviewed in detail elsewhere. †These risk estimates reflect to a large extent the situation before thrombosis prophylaxis was routine patient care. *Based on pooled OR of 18 (8-40) and an incidence of 0.1% in non-carriers. *Data from family studies; risk estimates lower in other settings.*

Table 3. Estimated number of asymptomatic thrombophilic women or women with a positive family history for VTE who should avoid using oral contraceptives to prevent one VTE, and estimated number needed to test.

Thrombophilia	Risk on OC per year, %	Risk difference per 100 women	N. not taking OC to prevent 1 VTE	N. of female relatives to be tested
Antithrombin, protein C, or protein S deficiency				
Deficient relatives	4.3*	3.6	28	56
Non-deficient relatives	0.7*			
Factor V Leiden or prothrombin 20210A mutation				
Relatives with the mutation	0.5*	0.3	333	666
Relatives without the mutation	0.2*			
Family history of VTE				
General population, no family history	0.04#	0.03	3333	none
General population, positive family history	0.09#	0.06	1667	none

*Based on family studies as outlined in Table 2. #Based on a population baseline risk of VTE in young women of 0.01% per year,[37] a relative risk of VTE by use oral contraceptives of 4,[38] and a relative risk of 2 of VTE by having a positive family history.[39] OC: oral contraceptives.

Table 4. Estimated number of asymptomatic thrombophilic women who should use LMWH prophylaxis during pregnancy and/or the postpartum period to prevent pregnancy-related VTE, and estimated number needed to test.

Thrombophilia	Risk of VTE per pregnancy,§ %	Risk difference per 100 women	N. using prophylaxis to prevent 1 VTE^	N. of female relatives to be tested
Antithrombin, protein C, or protein S deficiency				
Deficient relatives	4.1*	3.6	28	56
Non-deficient relatives	0.5*			
Factor V Leiden or prothrombin 20210A mutation, heterozygous				
Relatives with the mutation	2.0*	1.5	66	132
Relatives without the mutation	0.5*			
Factor V Leiden or prothrombin 20210A mutation, homozygous				
Homozygous relatives	16.0	15.5	6	24
Relatives without the mutation	0.5			
Family history of VTE				
General population, no family history	0.5#	n/a	200	none
General population, positive family history	1.0#	0.5	200	none

§Antepartum and postpartum combined. *Based on family studies as outlined in Table 2. #Based on a population risk of pregnancy-related VTE of 0.5% per pregnancy,[38] and a relative risk of 2 of VTE by having a positive family history.[39] ^These estimates apply to women with a positive family history of VTE and assume an unrealistic 100% efficacy of prophylaxis with LMWH.

protein C or protein S deficiency have a high absolute risk of VTE provoked by use of oral contraceptives. However, in these families, women without a deficiency also have a markedly increased risk of oral contraceptive-related VTE compared to pill users from the general population (0.7% vs. 0.04% per year of use), reflecting a selection of families with a strong thrombotic tendency in which yet unknown thrombophilias have co-segregated. Thus, although selective avoidance of oral contraceptive use prevents VTE episodes in deficient women, for women from these families a negative thrombophilia test may lead to false reassurance. The risk estimates are very different for the more common and less severe thrombophilias, such as factor V Leiden and the prothrombin 20210A mutation, with a large number of women needing to avoid use of oral contraceptives to avoid 1 VTE, and 666 study subjects needed to power the results. Also, from these families, women without the mutation have a higher incidence of pill-related VTE than women in the general population (0.2% vs. 0.04% per year of use). **Table 4** indicates the number of study subjects needed to test to initiate prophylactic measurements around pregnancy, again applicable to women from thrombophilic families. For women with antithrombin, protein C or protein S deficiency, or those who are homozygous for factor V Leiden, the risks of 4% and 16%, respectively, during pregnancy and the postpartum period may outweigh the nuisance of daily subcutaneous low molecular weight heparin (LMWH) injections with frequently occurring skin reactions, and the very small risk of severe complications of anticoagulant therapy during pregnancy.[40-42] However, the optimal

dose of LMWH prophylaxis in pregnancy has not been established and the most often used regimen of lowdose LMWH is certainly not 100% effective.[42,43] Hence, the figures in Table 4 underestimate the true number of women that need to use prophylaxis (and be tested prior to this decision) in order to avoid pregnancy-related VTE. Whether the absolute risks of pregnancy-related episodes justifies prophylaxis for eight months during pregnancy, or the shorter postpartum period of six weeks is a matter of choice for the physician and patient. The risk of pregnancy-related VTE in women from these families who do not have the inherited thrombophilic defect is approximately 0.5%, compared to 0.2% in the general population.39 Hence, withholding prophylaxis from women from thrombophilic families who do not have the defect is supported by evidence from well-designed studies of individuals in the same clinical context.

Thrombophilia testing in patients with venous thromboembolism

Thrombophilia testing is most often considered in patients with VTE, particularly if they are young, have recurrent episodes, have thrombosis at unusual sites, or have a positive family history for the disease. However, although such a strategy may lead to an increased yield of testing, the main question is whether a positive test result should change patient management. VTE tends to recur, with a cumulative incidence of a second episode of approximately 25% in five years. Patients with a transient clinical risk factor such as surgery eliciting their first VTE have a very low risk of recurrence.[44,45] However, whether the presence of thrombophilia is able to predict recurrence is much less clear, with conflicting results in various studies that compared the prevalence of thrombophilia in patients with recurrent VTE with those in patients without recurrence.[4, 31] The relative risk of recurrent VTE for carriers of inherited thrombophilia found in most populationbased cohorts is estimated to be approximately 1.5 for most defects (**Table 1**). In a large pooled study of thrombophilic families, we observed a cumulative incidence of VTE recurrences after ten years of 55% in relatives with a deficiency of antithrombin, protein C or protein S deficiency, as compared to 25% in those with the factor V Leiden mutation, the prothrombin 20210A mutation or high levels of FVIII.[46] For homozygous or double heterozygous carriers of factor V Leiden and/or the prothrombin 20210A mutation, the estimated risks of recurrence vary widely between studies, with a pooled estimate of 2.7 (95%CI: 1.2-6.0).[47,48] Whether such a risk increase warrants prolongation of the duration of anticoagulation, particularly after provoked VTE, is a matter of debate.[49,50] Furthermore, given the rarity of homozygous or double heterozygous thrombophilias in unselected patients with VTE, the efficiency of testing is obviously very low.[5,51] A randomized controlled trial in which testing for thrombophilia in patients with a first episode of VTE is the intervention, and recurrent VTE is the outcome, would provide the ultimate evidence to decide whether this is justified. Testing should lead to a pre-defined strategy to prevent recurrence with, for instance, a longer or indefinite duration of anticoagulant therapy. To our knowledge, no such trials have been successfully performed.[52] In order to investigate whether testing for thrombophilia reduces the risk of recurrent VTE in patients after a first episode, for instance by prolonged use of anticoagulation, avoidance of high-risk situations, or intensified prophylaxis in highrisk situations, we selected 197 patients from the MEGA case control study who had had a recurrent event during follow up.[53] We compared the proportion of these patients who had been tested with the proportion of 324 control patients who did not have a recurrence during follow up, matched for age, sex, year of event and geographical region. Thrombophilia tests were performed in 35% of cases and in 30% of controls. The OR for recurrence was 1.2 (95%CI: 0.9-1.8) for tested versus non-tested patients, indicating that testing, with real-life clinical decisions based on the outcome of testing, does not reduce the risk of recurrent VTE in patients who have experienced a first episode. For patients with antiphospholipid syndrome the issue is more complicated. It is a heterogeneous syndrome, both clinically as well as due to problems in standardization of laboratory tests. There is no evidence to define the optimal treatment duration of consecutive patients with VTE and persistent laboratory criteria for antiphospholipid syndrome, although it is widely recommended to treat such patients for a prolonged period with anticoagulant medication.54 If the prevalence of persistently positive tests in patients with VTE is 10%, 10 patients would need to be tested in order to identify one patient with antiphos-

pholipid syndrome in whom prolonged anticoagulant treatment should be initiated. This seems to be a reasonable number, but most clinicians only test for antiphospholipid syndrome in patients with VTE in the absence of provoking risk factors, or when other clinical manifestations raise suspicion. Vitamin K antagonists at a higher than normal INR intensity do not decrease the risk of recurrence in patients with well-defined antiphospholipid syndrome, as compared to vitamin K antagonists at a target intensity of 2.0 to 3.0.55,56

Thrombophilia testing in patients with arterial cardiovascular disease

Numerous studies have investigated the association between thrombophilia and arterial cardiovascular diseases, and yielded conflicting results.[32] There is no evidence that the presence of inherited thrombophilia should lead to different secondary prevention, and testing in this clinical setting is not justified.

Thrombophilia testing in women with pregnancy complications

The association between inherited thrombophilia and pregnancy complications varies depending on the type of thrombophilia and the complication (**Table 1**).[33] Pregnancy complications are amongst the clinical manifestations of the antiphospholipid syndrome.[57] Aspirin and heparin treatment is suggested for women with antiphospholipid syndrome and recurrent miscarriage, although the evidence that this is efficacious is very limited.[42,58] Whether the association between pregnancy complications and inherited thrombophilia is causal is controversial, as many other factors play a role in this risk.[59,60] Therapeutic options to prevent pregnancy complications in women with inherited thrombophilia, like in antiphospholipid syndrome, include aspirin as well as LMWH. There is no current evidence supporting treatment since observational research is hampered by poor methodology or inconsistent results.[60,61] In women with unexplained recurrent miscarriage, two recent randomized controlled trials, i.e. the ALIFE and the SPIN studies, were unable to demonstrate a beneficial effect of anticoagulant therapy compared to no pharmacological treatment or placebo.[62,63] The HABENOX trial also did not demonstrate a difference in live birth between three active treatment arms, i.e. LMWH combined with aspirin, LMWH alone, and aspirin alone, in 207 women with recurrent pregnancy loss with or without inherited thrombophilia.62A subgroup analysis did not suggest a differential effect amongst the 25% women with thrombophilia. Although the ALIFE study was underpowered for subgroup analyses, an a priori planned analysis in women with inherited thrombophilia showed a relative risk for live birth of 1.31 (95%CI: 0.74 to 2.33) for the combined intervention compared to placebo, and 1.22 (95%CI: 0.69 to 2.16) for aspirin, with corresponding absolute difference in live birth rates of 16.3% (95%CI:−18.2 to 50.8) and 11.8% (95%CI: −21.1 to 44.6), respectively.[62] The possibility that one or both of these interventions might be beneficial in such women warrants further study in adequately powered, controlled trials. We have just started recruiting in the multicenter ALIFE2 trial (www.trialregister.nl; NTR3361) that compares LMWH with standard pregnancy care in women with thrombophilia and a history of recurrent miscarriage. Some trials have shown benefit of anticoagulant treatment for specific pregnancy complications in women with inherited thrombophilia. First, women with a single previous pregnancy loss after ten weeks' gestation and who had heterozygous factor V Leiden mutation, prothrombin G20210A mutation, or protein S deficiency, were allocated to enoxaparin 40 mg once daily (n=80) or to aspirin 100 mg (n=80).65 Women who were treated with enoxaparin had a higher chance of a live birth than those allocated to aspirin (86% and 29%, respectively, risk difference 57%, odds ratio 15.5, 95%CI: 7 to 34). However, methodological issues were raised regarding concealment of allocation, lack of generalizability due to very stringent inclusion criteria, and an unusually high prevalence of late miscarriage in the source cohort.66 Furthermore, women who experienced an early miscarriage after randomization were not taken into account.[67] The results of this single study have not been implemented in recent evidence-based guidelines.[42] Second, for women at moderate to high risk of preeclampsia, aspirin provides a modest benefit in reducing this risk, whereas anticoagulants are not considered useful.42,68,69 The recently published FRUIT trial evaluated the effect of adding LMWH to standard aspirin in 139 women who had had previous early-onset preeclampsia, HELLP syndrome, eclampsia and/or small for gestational age babies and had inherited throm-

bophilia without antiphospholipid antibodies.[70] LMWH with aspirin reduced the incidence of early onset recurrent hypertensive disorders (risk difference 8.7%, 95%CI: 1.9-15.5%). Whether this single, relatively small trial justifies testing and subsequent treatment in all women with a history of severe preeclampsia has not yet been settled. In conclusion, given the currently available evidence, using anticoagulant therapy to improve the prognosis of a pregnancy in women with recurrent pregnancy loss who do not have a diagnosis of antiphospholipid syndrome must be considered experimental.42,61 Furthermore, for women with other pregnancy complications including preeclampsia, testing for antiphospholipid syndrome or inherited thrombophilia at present can not be justified.[42]

General cons of thrombophilia testing

A disadvantage of testing patients with a VTE for thrombophilia is the high cost involved. Although two studies concluded that testing for thrombophilia in some scenarios could indeed be cost-effective, the underlying assumptions from inconsistent observational studies seriously hamper their interpretation.[71,72] The psychological impact and consequences of knowing that one is a carrier of a genetic thrombophilic defect are considered to be limited, although a qualitative study described several negative effects of both psychological and social origin.[73,74] Furthermore, difficulties in obtaining life or disability insurance are frequently encountered by individuals who are known carriers of thrombophilia, regardless of whether they are symptomatic or asymptomatic.[73]

Future of thrombophilia testing

Whereas a somewhat nihilistic approach may be the result of the currently available evidence in favor of thrombophilia testing in clinical practice, this obviously should not prevent investigators from acquiring more insight. To be able to better predict risk to the point where it will enable evidencebased decisions to be made would be of particular interest for patients with all clinical indications. It is possible that in the future, multiple SNP analyses of genes inside or outside the coagulation system will further improve and become feasible in clinical practice.[75,76]

Conclusion

Despite the increasing knowledge about the etiology of VTE, testing for thrombophilia serves only a limited purpose and should not be performed on a routine basis. Thrombophilia testing in asymptomatic relatives may be useful in families with antithrombin, protein C or protein S deficiency, or for siblings of patients who are homozygous for factor V Leiden, and is limited to women who intend to become pregnant or who would like to use oral contraceptives. Careful counseling with knowledge of the absolute risks helps patients make an informed decision in which their own preferences can be taken into account. Observational studies show that patients who have had VTE and have thrombophilia are, at most, at a slightly increased risk of recurrence. Furthermore, no beneficial effect on the risk of recurrent VTE was observed in patients who had been tested for inherited thrombophilia. In the absence of trials that compare routine and prolonged anticoagulant treatment in patients testing positive for thrombophilia, testing for such defects to prolong anticoagulant therapy cannot be justified. Diagnosing antiphospholipid syndrome would potentially lead to changes in treatment in selected patients with VTE and women with recurrent miscarriage, although the evidence to support this is limited.

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