Chapter **2**

Inherited Thrombophilias

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SUMMARY

The last decades, many inherited thrombophilias have been detected and the pathophysiological insight has increased tremendously. However, despite the overwhelming observational evidence on the association between inherited thrombophilia and several women's health issues including VTE, thus far the implications for clinical practice are uncertain. Although there is firm epidemiological evidence that is helpful in counseling women with inherited thrombophilia in order to prevent a first or recurrent VTE, the uncertainty is particularly present for women who have other pregnancy complications such as recurrent pregnancy loss and pre-ecclampsia. For this group, well-designed placebo-controlled trials to assess the harm-benefit ratio are urgently needed.

INTRODUCTION

Thrombophilia is defined as a disorder associated with an increased tendency to venous thromboembolism, such as recurrent thrombosis, thrombosis at a young age or familial thrombosis. The first inherited thrombophilia was discovered by Egeberg in 1965 when he reported a Norwegian family with a remarkable tendency to venous thrombosis due to a deficiency in the natural anticoagulant antithrombin [1]. At present, this term is generally used to describe a laboratory abnormality (most often in the coagulation system) that increases the tendency to venous thromboembolism (VTE; venous thrombosis in any site or pulmonary embolism).

Thrombophilic abnormalities can be either acquired or inherited. An example of acquired thrombophilia is the antiphospholipid antibody syndrome which is characterised by a tendency toward venous or arterial thrombosis, recurrent pregnancy loss, 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 immobilisation, pregnancy and the postpartum period, and use of estrogen-containing medication, such as oral contraceptives and hormone replacement therapy. Following Egeberg's discovery of antithrombin deficiency, several inherited defects have been identified and studied to different extents in a large number of clinical studies. No less than 10,000 publications can be identified through a rough search in the Medline database with thrombophilia, introduced as a MeSH term in 1998, as a major topic heading.

Although the term thrombophilia traditionally used to apply to patients with unusual manifestations of VTE, such as recurrent spontaneous episodes, thrombosis at 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 thrombophia 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 10 years lower than in the general population, the vast majority of patients will have the first episode later in life [2]. 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 upon (clinical) risk factors, including increasing age [3].

As was already known for the aqcuired antiphospholipid antibody syndrome, most inherited thrombophilic disorders are also associated with pregnancy-related disorders such as (recurrent) fetal loss, stillbirth, intrauterine growth retardation,

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pre-eclampsia and the hemolysis-elevated liver enzymes-low platelets (HELLP) syndrome of pregnancy [4,5].

This review describes the currently accepted forms of inherited thrombophilia, the underlying pathophysiology and epidemiology, and its potential implications for women's health issues.

CLASSIFICATION, PATHOPHYSIOLOGY AND PREVALENCE OF INHERITED THROMBOPHILIA

An overview of the currently known abnormalities that cause inherited thrombophilia is shown in Table 1, and the mechanisms of action are depicted in Figure 1.

Antithrombin, protein C, and protein S function as physiological inhibitors of the coagulation cascade and are therefore referred to as natural anticoagulants. Deficiencies of one of these proteins lead to an imbalance in basal coagulation activity toward a pro-

Figure 1. Regulation of blood coagulation
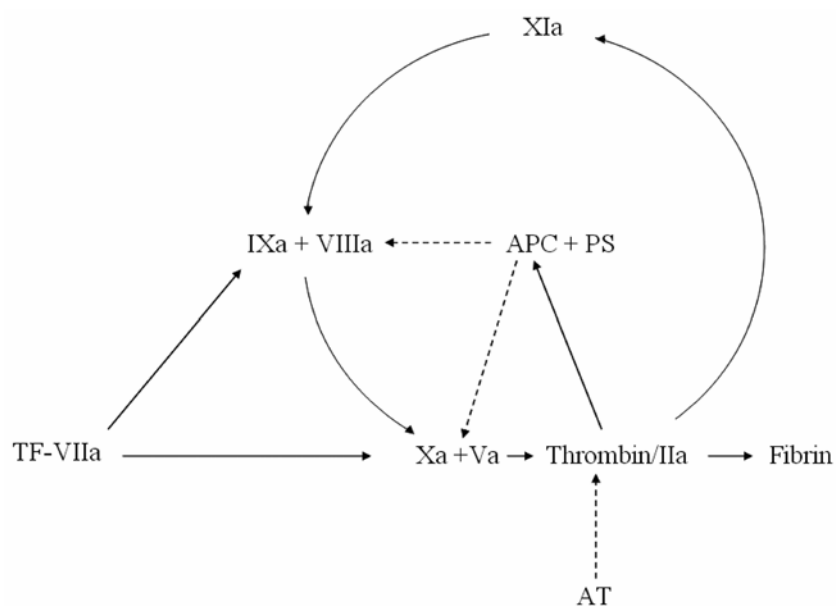
Coagulation is initiated by a tissue factor (TF)–factor VIIa complex that can activate factor IX or factor X. At high tissue factor concentrations, factor X is activated primarily by the TF-VIIa complex, whereas at low tissue factor concentrations the contribution of the factor IXa–factor VIIIa complex to the activation of factor X becomes more pronounced. Coagulation is maintained through the activation by thrombin of factor XI. The coagulation system is regulated by the protein C pathway. Thrombin activates protein C. Together with protein S, activated protein C (APC) is capable of inactivating factors Va and VIIIa, which results in a down-regulation of thrombin generation and consequently in an up-regulation of the fibrinolytic system. The activity of thrombin is controlled by the inhibitor antithrombin. The solid arrows indicate activation and the broken arrows inhibition.

Table 1. Causes of inherited thrombophilia

Definitely inherited	Multifactorial (and at least partly inherited)
Antithrombin deficiency	Elevated factor VIII:c levels*
Protein C deficiency	Mild hyperhomocysteinemia†
Protein S deficiency	
Factor V Leiden (V:Q^{506})	
Prothrombin 20210A mutation	

* Above the 75th percentile † Above the 95th percentile

thrombotic state, which has been confirmed in studies showing increased markers of thrombin generation in subjects with one of these deficiencies [6,7]. For antithrombin and protein C, two types of deficiencies are distinguished. In type I deficiency, levels of both antigen and activity are reduced and in type II, antigen levels are normal, but one or more functional defects in the molecule lead to a decreased activity. Protein S circulates in two forms: the active free protein S (approximately 40-50%) and protein S bound to complement component C4b-binding protein. In type I deficiency, total and free antigen levels and activity are reduced, in type II deficiency, both total and free antigen are normal, but activity is reduced and in type III deficiency, total antigen is normal, but free antigen and activity are reduced. Whether this classification into various types is of clinical significance, is largely unknown. These different types of deficiencies are caused by a large number of mutations, that are recorded in occasionally updated databases [8-10].

The factor V Leiden mutation is the most common inherited thrombophilic defect, and is found in approximately 20% of patients with VTE, and in 5% of Caucasian populations (Table 2). It is a point mutation in the gene coding for clotting factor V (G1691A), causing a replacement of arginine by glutamine in the cleavage site for activated protein C (APC, Q^{506}), thereby making activated factor V more resistant to inactivation by this physiological anticoagulant (APC resistance)(Figure 2b) [11,12].

The prothrombin 20210A mutation is a point mutation that leads to a normal protein but higher average levels of inactive factor II (prothrombin) compared to the wildtype genotype, which is the presumed mechanism of the prothrombotic phenotype [13].

Increased levels of clotting factor VIII:c at various cut-off levels of at least the 75th percentile of normal pooled plasma have been shown to be a risk factor for VTE [14]. The mechanism by which individuals tend to have elevated levels of factor VIII:c remains largely unknown. However, it has been shown that elevated levels are persistent over time and tend to cluster within families, indicating at least a partial genetic etiology [15-18].

Mild hyperhomocysteinemia has been associated with an increased risk of VTE [19]. A homozygous mutation in the gene coding for methylenetetrahydrofolate reductase

Figure 2. Pathophysiology of the factor V Leiden mutation
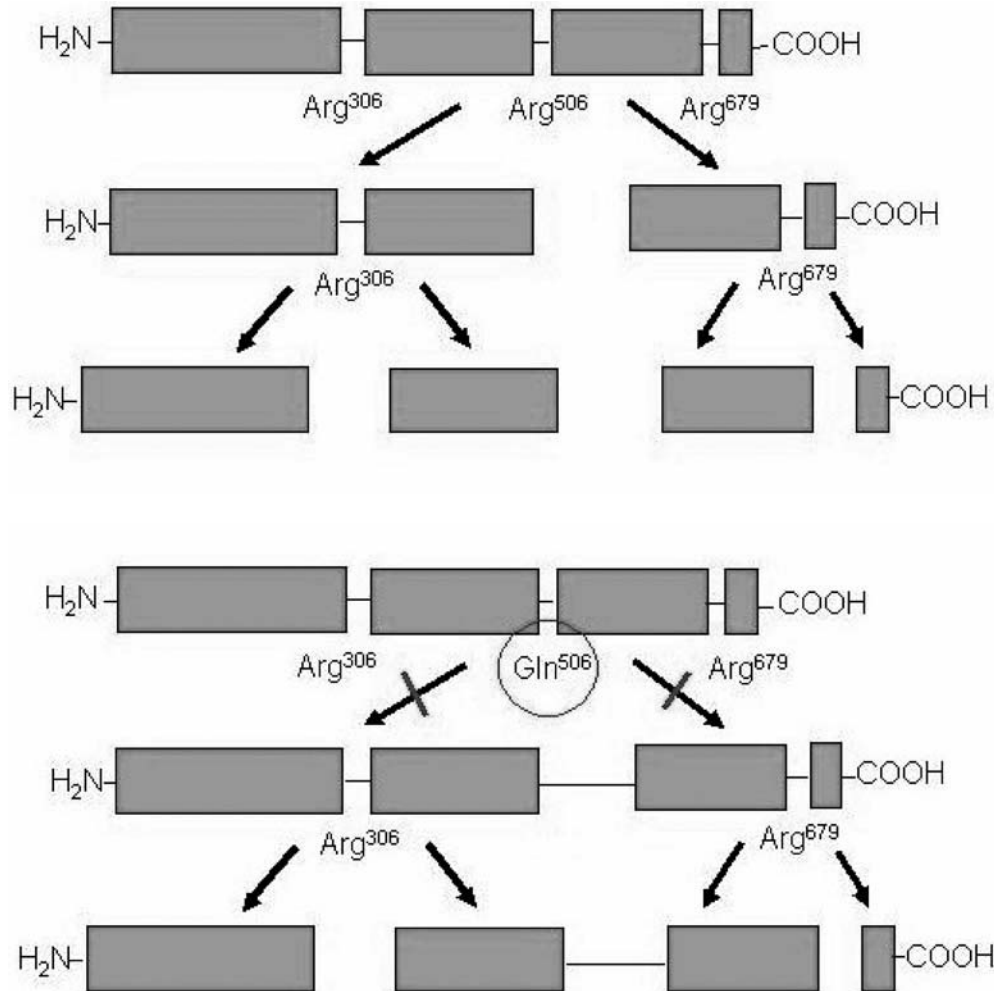
Activated protein C inactivates factor Va by cleaving the protein at the Arginine506 cleavage site (Figure 2a). In carriers of the factor V Leiden mutation, a point mutation in the gene coding for factor V, causes replacement of the amino acid Arginine by Glutamine at position 506 of the protein, making factor Va resistant to inactivation by activated protein C (i.e. APC-resistance; Figure 2b).

(MTHFR) causes an approximate 25% increase in average fasting homocysteine levels and is therefore often considered as a hereditary risk factor for thrombosis[20]. However, although hyperhomocysteinemia is clearly associated with thrombosis, this association is less clear for the MTHFR-mutation per se [21]. Therefore, we will not further discuss the MTHFR mutation in this chapter, but rather focus on mild hyperhomocysteinemia regardless of the presence of an underlying genetic polymorphism.

Deficiencies of one of the natural anticoagulants are found in less than 10% of consecutive patients with VTE [22], which is the main reason why thrombophilia tests were reserved to clinically severe cases of VTE in the past. Since the nineties of the last century however, after the discovery of the factor V Leiden and the prothrombin mutation, the diagnostic yield increased tremendously which has resulted in widespread testing for thrombophilia. The prevalences of the currently known inherited defects in both the general population and in patients with VTE are summarised in Table 2.

Table 2. Prevalence of inherited thrombophilia

	General population	Patients with VTE
Antithrombin, protein S, or Protein C deficiency	1% [26,27,82]	7% [22]
Factor V Leiden	Caucasians 4-7% [83,84]	21% [11]
	non-Caucasians 0-1%	
Prothrombin 20210A	Caucasians 2-3% [85,86]	6% [87]
	non-Caucasians 0-1%	
Elevated F.VIII:c levels	11% [14]	25% 14
Mild hyperhomocysteinemia	5% [88]	10% [88]

INHERITED THROMBOPHILIA AND THE RISK OF VTE

While well-performed case-control studies quantify associations between thrombophilic defects and VTE, the absolute risk in patients with thrombophilia cannot be directly concluded from this type of studies. There remains uncertainty in a risk estimate derived by multiplying the observed odds ratio's with baseline risks in specific populations since a baseline risk may not be valid for an individual patient. Knowledge of absolute risks for VTE as well as the bleeding risk of anticoagulants is necessary to make rational management decisions, and several available cohort studies give clinically relevant information [15,23-25]. It is important to note that these studies have been mainly performed in relatives of (consecutive) patients with a particular thrombophilic defect. Therefore, the overall absolute annual incidences of various forms of inherited thrombophilia depicted in Table 3 reflect risks for individuals with some degree of a family history of VTE, and may be much lower in healthy individuals in whom a defect is detected because of mass-screening or for scientific research purposes [26-28]. Table 3 also lists the absolute risks during and shortly after transient high risk situations. The risk for a spontaneous episode of VTE is approximately half of the overall risk.

From a pathophysiological and epidemiological point of view it is interesting to note that often there is interaction between inherited thrombophilia and acquired prothrombotic states, most notably oral contraceptive use and hormone replacement

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Table 3. Incidences of first VTE in individuals with inherited thrombophilia

	Antithrombin, protein S or protein C deficiency	Factor V Leiden	Prothrombin 20210A
Overall (%/year)	1.5 (0.7-2.8) [89]	0.5 (0.1-1.3) [24,90]	0.4 (0.1-1.1) [91]
Surgery/trauma/immobilization (%/episode)	8.1 (4.5-13.2) [24]	1.8 (0.7-4.0) [23,24]	1.6 (0.5-3.8) [25]
Pregnancy (%/pregnancy)	4.1 (1.7-8.3) [24]	2.1 (0.7-4.9) [23,24]	2.3 (0.8-5.3) [25]
● during pregnancy	1.2 (0.3-4.2)	0.4 (0.1-2.4)	0.5 (0.1-2.6)
● puerperium	3.0 (1.3-6.7)	1.7 (0.7-4.3)	1.9 (0.7-4.7)
Oral contraceptive use (%/year of use)	4.3 (1.4-9.7) [24]	0.5 (0.1-1.4) [23,24]	0.2 (0.0-0.9) [25]

therapy. For example, in carriers of the factor V Leiden mutation who use oral contraceptives, the relative risk of developing VTE is the product instead of the sum of the individual relative risks [29]. Whether a thrombophilic defect interacts in a multiplicative or additive manner with a specific transient risk factor has not been investigated systematically, but when considering preventive measures in thrombophilic individuals, the focus should again be on the absolute incidence in patients exposed to these transient risk factors rather than on relative risks.

Patients with VTE are at a high risk of recurrent events. This risk is estimated to be 4.5%/year in the first two years after the initial event [30]. Whether presence of a thrombophilic defect superimposes an additional risk upon the already high recurrence rate is a matter of continuing debate. Various studies examined the relationship between hereditary thrombophilia and recurrent venous thrombosis, and although results have been conflicting, potentially due to differences in selection of the studied population, the pooled hazard ratio is around 1.4 for all thrombophilic defects [31]. The absence of transient risk factors eliciting the first thromboembolic event appears to be a much stronger predictor of recurrence than the presence of hereditary thrombophilia [32].

INHERITED THROMBOPHILIA AND PREGNANCY ASSOCIATED COMPLICATIONS

Pregnancy-associated complications including recurrent pregnancy loss, as well as venous or arterial thrombosis are potential clinical manifestations of the acquired antiphospholipid antibody syndrome (APLS). This has led to investigations into the association of inherited thrombophilia with pregnancy loss as well as other, presumably vascular, pregnancy complications. It was first demonstrated that women with most forms of inherited thrombophilia have a slightly higher risk for pregnancy

Elevated FVIII:c levels	Mild hyperhomo-cysteinemia
1.3 (0.5-2.7) [92]	0.2 (0.1-0.3) [93]
1.2 (0.4-2.8) [15]	0.9 (0.1-3.4) [93]
1.3 (0.4-3.4) [15]	0.5 (0.0-2.6) [93]
0.3 (0.1-1.8)	0.0 (0.0-1.8)
1.0 (0.3-2.9)	0.5 (0.0-2.6)
0.6 (0.2-1.5) [15]	0.1 (0.0-0.7) [93]

complications than their relatives without thrombophilia [25,33-35]. Furthermore, case-control studies showed that thrombophilia is present more often in women with obstetric complications than in women who have had uncomplicated pregnancies. However, to date the pathophysiological mechanisms underlying these associations are not at all clear.

Approximately 3% of all women trying to conceive will experience recurrent pregnancy loss [36]. Various descriptions have been used for recurrent pregnancy loss, with the most common definitions being either at least two or three pregnancy losses which may or may not be consecutive [37]. Early pregnancy loss is usually defined as a miscarriage in the first 12 weeks of pregnancy, whereas late pregnancy loss concerns pregnancies that unintentionally ended after a gestational age of 12 weeks and implies loss of fetal heart activity on ultrasound [38]. Some studies include stillbirth or intra-uterine fetal death, usually defined as fetal death occurring after 20 weeks of gestation, in the category of late pregnancy loss. Established causes of recurrent pregnancy loss are structural chromosomal abnormalities in either the woman or the male partner, fetal chromosomal abnormalities, and the antiphospholipid antibody syndrome. However, in more than half of the couples with recurrent pregnancy loss no cause can be identified. Several meta-analyses have summarised the available case-control studies on the association between (recurrent) pregnancy loss and inherited thrombophilia [5,39-41]. The pooled odds ratios are summarised in Table 4. It has become increasingly clear that there seems to be a distinction between early and late pregnancy loss when considering the relation with inherited thrombophilia. However it should be noted that studies vary considerably in defining early and late pregnancy loss. There appears to be no statistically significant association between factor V Leiden and early non-recurrent pregnancy loss, whereas there is a 2-fold risk increase for early recurrent miscarriages in carriers of the factor V Leiden or prothrombin mutation. The data on protein C, protein S, and antithrombin deficiency are limited by numbers. As can be observed from Table 4, the overall impression is that the association between pregnancy loss and inherited thrombophilia becomes stronger with increasing numbers of pregnancy losses a woman has experienced as well as the occurrence at a later gestational age. One study reported a 4-fold increased risk of early recurrent pregnancy loss in 51 women with elevated factor VIII:c levels (above the 90th percentile) as compared to 51 women with normal FVIII:c levels [42]. This finding could not be confirmed in a family study in which 117 women with FVIII:c

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levels above the 75th percentile were compared to their 143 relatives with lower FVIII:c levels [43]. Finally, although hyperhomocysteinemia was found to increase the risk for recurrent early pregnancy loss 2- to 4-fold, depending on the definition, in a meta analysis of a limited number of case-control studies [44], in the same family study mild hyperhomocysteinemia could not be confirmed as risk factor [43].

Pre-ecclampsia, proteinuric hypertension in the second half of pregnancy, intra-uterine growth restriction (defined as estimated growth less than 10th percentile for gestational age), placental abruption and the HELLP syndrome are other pregnancy related complications that have been claimed to be associated with inherited thrombophilia. In the last decade case-control studies on pregnancy related complications have shown inconsistent results regarding the association with various inherited thrombophilias. Similar to the problems encountered in studies about pregnancy loss, the definitions of the pregnancy complications used differ substantially between studies. In a systematic review of 25 studies on both inherited and acquired thrombophilia, there was wide heterogeneity in the prevalence of thrombophilia among the studies, making firm conclusions difficult. Considering only inherited thrombophilia, women with pre-eclampsia were more likely to have the factor V Leiden or prothrombin mutation, or

Table 4. Association between inherited thrombohilias and pregnancy loss

Inherited Thrombophilias	Meta-analysis / systematic reviews	Early non-recurrent pregnancy loss OR (CI)	Early recurrent pregnancy loss OR (CI)
Factor V Leiden	Rey [5]	1.40 (0.66-2.97)	2.01 (1.13-3.58)
	Dudding [40]		
	Kovalesky [41]		2.0 (1.5-2.7)
	Alfirevic [39]		
Prothrombin 20210A	Rey [5]		2.32 (1.12-4.79)
	Kovalesky [41]		2.0 (1.0-4.0)
	Alfirevic [39]		
APC-resistance	Rey [5]	2.07 (0.40-10.67)	3.48 (1.58-7.69)
	Alfirevic [39]		
Protein C deficiency	Rey [5]	(recurrent fetal loss)	1.57 (0.23-10.54)
	Alfirevic [39]		
Protein S deficiency	Rey [5]		
	Alfirevic [39]		
Antitrombin deficiency	Rey [5]	(recurrent fetal loss)	0.88 (0.17-4.48)
	Alfirevic [39]		

Rey [5]: early pregnancy loss defined as <13 weeks gestation; for protein C and antithrombin deficiency no distinction
Kovalevsky [41]: recurrent pregnancy loss defined as ³ 2 losses in the first or second trimester
Alfirevic [39]: late pregnancy loss defined as > 20 weeks gestation
Dudding [40]: late pregnancy loss defined as third trimester

protein C or protein S deficiency. Women with unexplained stillbirth or intrauterine growth restriction, more often had the factor V Leiden mutation or protein S deficiency. The factor V Leiden and prothrombin mutation as well as mild hyperhomocysteinaemia were more often found in women with placental abruption, as compared with controls [39]. In another systematic review that considered only gene mutations (factor V Leiden and the prothrombin mutation) combined with a population-based study of 404 women with preeclampsia, no association with factor V Leiden mutation or the prothrombin mutation could be demonstrated, and the authors concluded that the sole association found was for the factor V Leiden mutation with severe preeclampsia [45]. Finally, there seems to be no relationship between elevated FVIII:c levels and preeclampsia, HELLP syndrome, and IUGR [46].

CLINICAL IMPLICATIONS OF HEREDITARY THROMBOPHILIA

Prophylaxis of VTE - general considerations

Management studies in asymptomatic individuals with thrombophilia or in patients with thrombosis and thrombophilia are rare, and therefore, recommended strategies in these patients are usually based on the interpretation of studies assessing risk and the efficacy/safety ratio of various interventions. As stated before, absolute rather than relative risks are important and need to be balanced against the absolute risks of the considered prophylactic measures in a patient known to have inherited thrombophilia.

Preventive strategies can consist of avoidance of additional transient risk factors, like withholding oral contraceptives, or it can involve prophylaxis with anticoagulants such as vitamin K antagonists or heparin (unfractionated or low-molecular-weight). Anticoagulant prophylaxis can be either recommended continuously or be restricted to periods

	Late non-recurrent pregnancy loss OR (CI)	Late recurrent pregnancy loss OR (CI)
	3.26 (1.82-5.83)	7.83 (2.83-21.67)
	2.8 (1.3-6.2)	10.7 (4.0-28.5)
	6.1 (2.8-13.2)	
	2.30 (1.09-4.87)	
	5.0 (2.0-12.4) (non recurrent fetal loss)	1.41 (0.96-2.07)
	7.39 (1.28-42.83)	
	16.2 (5.0-52.3)	
	(non recurrent fetal loss)	1.54 (0.97-2.45)

of a perceived high risk of thrombosis. In the latter case it should be realised that approximately half of the episodes in thrombophilic patients will occur spontaneously and will not be prevented by such an approach [23,47,48]. Lifelong anticoagulant prophylaxis with vitamin K antagonists reduces the risk for VTE by more than 90% [49] which is also the case in patients with thrombophilia [50]. However, this type of intervention is associated with an annual incidence of major bleeding of about 2-3%, and the rates of life-threatening or fatal bleeding are 1.0% and 0.25%, respectively [51,52].

Since a previous episode of VTE is a major risk factor for recurrence, regardless of the presence of thrombophilia, recommendations are distinctly different for prevention of VTE between asymptomatic thrombophilic patients and those with a history of VTE [47].

Prophylaxis of VTE for asymptomatic individuals with thrombophilia

The incidence of spontaneous VTE is approximately half the overall incidence. For all forms of inherited thrombophilia, the risk of a spontaneous VTE in asymptomatic individuals (Table 3) does not outweigh the bleeding risk induced by primary prevention with vitamin K antagonists, and such a preventive measure will therefore do more harm than good.

The risk of VTE after surgery remains elevated for a period of about two to four weeks [53,54]. Therefore, extending the period of post-operative prophylaxis after hospital discharge may be justified in individuals with a deficiency of antithrombin, protein S or C who seem to be at highest risk of the inherited thrombophilias (Table 3). For carriers of the factor V Leiden or prothrombin mutation and individuals with elevated levels of factor VIII:c or mild hyperhomocysteinemia, who seem to have a lower risk of post-operative thrombosis, a more vigorous approach than routine peri-operative prophylaxis may be superfluous.

The optimal management for asymptomatic pregnant women with inherited thrombophilia is uncertain and depends strongly on how the absolute risk of VTE is perceived by an individual woman and her treating physician. From retrospective family studies estimates of the risk of VTE during pregnancy are available and in absolute terms this risk is fairly low for all inherited thrombophilias (0.3-1.2%, Table 3). Therefore, it seems generally justified to withhold anticoagulant prophylaxis [55]. In the puerperium the risk of thrombosis is higher (1.0-3.0%, Table 3), so treatment with anticoagulants (either vitamin K antagonists or low molecular weight heparin) for 4-6 weeks should be considered, in particular for women with one of the deficiencies of the natural anticoagulants or combined thrombophilic defects [55].

The incidence of VTE during use of oral contraceptives in asymptomatic women with a deficiency of antithrombin, protein S or C who have a positive family history for VTE is about 4.0% per year [24], which is much higher than the risk of about 4 per

10,000 pill-years in young users in the general population [56]. Given this high risk the use of oral contraceptives and hormone replacement therapy is generally considered contraindicated. The risk for women with the factor V Leiden or the prothrombin mutation is considerably lower (0.2-0.5% per year, Table 3), and this probably allows for a more patient-tailored advice in which the woman's preference and the risk of an unwanted pregnancy should be taken into consideration. For women with elevated levels of factor VIII:c or mild hyperhomocysteinemia less data are available but the risks seem to be in the same range as of the mutations (Table 3). If an oral contraceptive is prescribed, levonorgestrel containing pills (second generation) are preferred because of a 50% lower risk of thrombosis than oral contraceptives containing desogestrel or gestodene (third generation) [56-58].

Prophylaxis of VTE for patients with thrombophilia and a history of VTE

The 7th ACCP guidelines for antithrombotic therapy for venous thromboembolic disease give evidence-based recommendations about prevention of VTE and detail which patients are eligible for prolonged anticoagulant treatment [59]. In these patients the risk of thrombosis outweighs the risk of bleeding in everyday life.

However, secondary prophylaxis for patients who are considered to have a lower risk for recurrent VTE and have thus discontinued anticoagulant treatment needs special consideration. Although there is no equivocal evidence that patients with thrombophilia have a clearly higher recurrence rate than patients without thrombophilia [32,50,60], the absolute incidence of recurrence is fairly high and this justifies a cautious approach during high risk situations.

Prolonged postoperative prophylaxis should be considered in any patient with thrombophilia and a history of thrombosis, because the risk of VTE remains increased for a period of 2-4 weeks [53,54].

There are no management studies for prophylaxis in pregnant women with thrombophilic defects and a history of deep-venous thrombosis. In two observational studies the risk of antepartum recurrent VTE in women with a history of VTE ranged between 2.4 and 6.2%.[61,62] In the first prospective study, an idiopathic first thromboembolic event as well as thrombophilia appeared to be risk factors for recurrence during the subsequent pregnancy [61], whereas this could not be confirmed in the second retrospective study [62]. In view of the high risk of recurrence, which was constant during all trimesters of pregnancy, anticoagulant prophylaxis throughout the entire pregnancy should be considered. Vitamin K antagonists are strictly contraindicated during the first and third trimester; for the first trimester, this is due to the teratogenicity, in the third trimester, the vitamin K antagonists (which cross the placenta) induce an increased risk of fetal intracranial haemorrhage during

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birth [55]. Furthermore, a recent study has shown that in utero exposure to vitamin K antagonists, also during the second trimester of pregnancy, has a negative effect on neurologic, behavioural and cognitive functions, measured at the age of 9-14 years [63-65]. Therefore, low molecular weight heparin (which does not cross the placenta and consequently does not affect the fetus) is the drug of choice. Studies with low molecular weight heparin prophylaxis in pregnant women have shown that recurrent venous thromboembolic events tend to occur most often in those treated with lower doses [66,67]. This finding suggests that intermediate dosages (75-150 anti-Xa units/kg/day) or even therapeutic dosages, aimed at anti-Xa-levels of at least 0.3 units/ml, might be preferred. Of note, since bioavailability and distribution volume of heparin may change in pregnancy, periodic measurement of anti-Xa plasma levels is advocated. Heparins should be discontinued at least 12 hours before delivery and restarted afterwards to avoid peripartum haemorrhage [55].

In women with mild hyperhomocysteinemia, the use of folic acid, pyridoxine and cyanocobalamin (vitamins B11, B6 and B12 respectively) beyond the 10th week of gestation can be considered. Although the strategy has shown to reduce homocysteine levels, a recent randomised controlled trial showed that 2.5 years of oral vitamin B suppletion did not reduce the risk of recurrence in patients with an idiopathic VTE [68].

Use of oral contraceptives or hormone replacement therapy after discontinuation of anticoagulant treatment for a first VTE is associated with a higher risk of recurrence [60,69,70], so that this is strongly discouraged in all women with a history of VTE regardless of the presence of inherited thrombophilia. Pre-menopausal women should be counselled about alternative methods of contraception.

Implications for women with inherited thrombophilia and recurrent pregnancy loss

With the hypercoagulable state present in inherited thrombophilia which possibly induces thrombosis of the placental vessels it is attractive to hypothesise that anticoagulants may have a beneficial effect on pregnancy outcome in women with thrombophilia and pregnancy loss. An impressively good result of a combination of aspirin and unfractionated subcutaneous heparin as compared to aspirin alone was found in one randomised controlled trial in women with such a history and the antiphospholipid antibody syndrome [71], although this result was not consistent across the scarse studies in this patient group [72]. A number of studies aimed to investigate the effect of antithrombotic therapy in women with inherited thrombophilia and pregnancy loss using various therapy schemes [73-75]. The results were inconsistent and it should be emphasised that none of these studies were randomised controlled trials and had several methodological limitations. For a Cochrane review on anticoagulant treatment

for women with recurrent or late pregnancy loss only two randomised controlled trials could be identified [76]. Only in one trial women with inherited thrombophilia were considered [77]. It should be noted that these women were only included if they had had one pregnancy loss after 10 weeks of gestation, and that there was no placebo-arm. The live-birth rate for the low-molecular-weight heparin group and aspirin groups were 86% and 26 % respectively. Thus far these results have not been confirmed by other studies. Recently, a randomised controlled trial between two doses of enoxaparin did not demonstrate a difference in live birth rate women with a history of recurrent pregnancy loss and inherited thrombophilia [78]. Unfortunately, also this study did not have a placebo-arm [79].

Implications for women with inherited thrombophilia and other pregnancy complications

The same therapeutic uncertainty exists for women with other pregnancy complications and inherited thrombophilia. Although aspirin has been suggested to be beneficial for the prevention of severe pre-ecclampsia, the largest study on primary prevention did not find an effect so that the beneficial findings from a Cochrane review may be the consequence of publication bias of small, positive studies [80,81]. Evidence on therapeutic and prophylactic management for women with inherited thrombophilia and pregnancy complications is limited which has led to recommendations made by the ACCP guidelines that all have a grade 2C level, meaning that the risk-benefit ratio is unclear and the recommendations are weak [55].

CONCLUSIONS

The last decades, many inherited thrombophilias have been detected and the pathophysiological insight has increased tremendously. However, despite the overwhelming observational evidence on the association between inherited thrombophilia and several women's health issues including VTE, thus far the implications for clinical practice are uncertain. Although there is firm epidemiological evidence that is helpful in counseling women with inherited thrombophilia in order to prevent a first or recurrent VTE, the uncertainty is particularly present for women who have other pregnancy complications such as recurrent pregnancy loss and pre-ecclampsia. For this group, well-designed placebo-controlled trials to assess the harm-benefit ratio are urgently needed.

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