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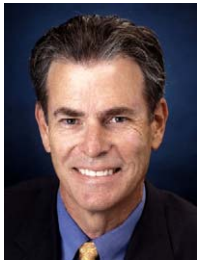
Foreword

Thrombophilia and Women's Health



William F. Rayburn, MD
Consulting Editor

Several important regulatory proteins act as inhibitors to the coagulation cascade. Genetic or acquired deficiencies of these inhibitory proteins are referred to collectively as thrombophilias, which can lead to hypercoagulability conditions and to recurrent venous thromboembolisms. Information concerning thrombophilias is accruing rapidly, causing certain confusions in diagnosis and management.

This issue of the *Obstetrics and Gynecology Clinics of North America*, guest edited by Dr. Isaac Blickstein, presents a state-of-the-art overview of the most important hypercoagulable states in women. The nature of this propensity toward intravascular (venous or arterial) clotting is defined, and screening is summarized. Adverse thrombogenic actions in most circumstances are mitigated by anticoagulant therapy. Although thrombophilias usually are discovered when evaluating an untoward event, their overall high incidence in healthy individuals leads the practitioner to question the need to prescribe anticoagulants for asymptomatic women.

Considerable attention has been directed toward thrombophilias and specific pregnancy complications. More than half of all thromboembolic events during pregnancy are attributable to thrombophilias. Furthermore, many thrombophilias are linked with recurrent abortion, fetal growth restriction, stillbirth, and preeclampsia and eclampsia, especially the HELLP syndrome. Some thrombophilias also are associated with placental findings of abruption and intervillous or spiral artery thrombosis.

The outstanding group of experts in this issue addresses many questions of current clinical interest. Guidelines in this interdisciplinary volume will be

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valuable to health care providers from various fields of medicine, including obstetrics and gynecology, family and community medicine, internal medicine, hematology, and neonatology.

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Preface

Isaac Blickstein, MD
Guest Editor

The term *thrombophilia* describes a range of conditions in which there is an increased tendency, frequently recurrent, for thrombus formation in the venous as well as in the arterial vascular systems. Thrombophilia is caused by inherited or acquired conditions and may cause symptoms related to the place in which the thrombosis occurred, the extent of thrombosis, and whether embolization occurred in other organs.

This issue of the *Obstetrics and Gynecology Clinics of North America* presents an interdisciplinary discussion of recent advances in this gyneco-hematological (or hemato-gynecological) field. First, the nature (genetic and acquired) of this propensity for intravascular (venous or arterial) clotting is defined. Second, this issue acknowledges that certain situations in women's lives, such as pregnancy, puerperium, and exposure to exogenous hormones qualify as hypercoagulable states. Third, this issue considers the possibility that adverse pregnancy outcomes may also qualify as thrombophilia-related events. Finally, screening and management guidelines are discussed.

This state-of-the-art issue is dedicated to the most important hypercoagulable states in women's health and will be of value to caregivers from various disciplines, including obstetrics and gynecology, hematology, and neonatology, as well as to general practitioners.

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Thrombophilia and Women's Health: An Overview

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Circulation (the flow of blood through the vascular system) is based on three imperative prerequisites: keeping the vascular system intact, maintaining blood in the liquid state, and driving blood in the appropriate direction. If the integrity of the vascular system is breached, blood in the liquid form leaks and is lost from the circulation. To avoid this loss, a complex coagulation system exists that is triggered to form a blood clot that seals the leak from the vascular system. Despite the fact that blood is in a liquid state, it has an inherent potential to form clots. This crucial coagulation mechanism should not be activated within an intact vascular system; hence, another parallel mechanism should exist to restrict the coagulation system. In the absence or failure of this restriction, a hypercoagulable state with a higher tendency for blood clotting is created, and these thrombotic tendencies are collectively known as thrombophilia.

Blood clotting, which is the transformation of a liquid into a (semi)solid state, attracted the attention of medical scholars from times of yore [1]. Great minds in the history of medicine proposed so many theories that by the mid-twentieth century, there were more theories related to the coagulation process than investigators and observers [2]. Theories of blood coagulation have firm roots in ancient postulations by Hippocrates and Aristotle [2]. The latter, in his treatise *On the Generation of Animals*, compared the coagulation of blood with that of semen and envisaged the process as the action of fig juice in the clotting of milk or as the setting of mud [3]. The term "thrombus" is attributed to Galen, who was among the first to ask why blood clotting does not normally occur within the body [2]. The pathophysiology of thrombosis and embolism was not elucidated until Rudolph Virchow in the mid-nineteenth century realized that a venous thrombus

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could detach, crumble away, and lead to secondary occlusion in remote vessels [4]. The notorious triad of predisposing factors related to venous thrombosis and pulmonary embolism, namely, stasis of blood, vessel injury, and what is currently termed a hypercoagulable state, is also attributed to Virchow [2,4].

The essence of Virchow's triad suggests that although the tendency of blood to clot is inherent, thrombus formation does not usually happen unless it is facilitated or triggered. Thrombophilia (ie, the presence of a tendency for intravascular clotting) occurs frequently. Hence, a set of circumstances should coexist in order that a thrombophilia would display the thrombotic tendency. Such situations, also represented in Virchow's triad, are collectively known as hypercoagulable states and may be acquired or inherited. Certain situations in women's life, such as pregnancy, puerperium, exposure to hormonal contraception and hormonal replacement therapy, have seemed to qualify as hypercoagulable states. It became apparent that thrombotic events, such as deep vein thrombosis and pulmonary embolism (collectively known as venous thromboembolism [VTE]), are not the only complications associated with the combination of thrombophilia and a permissive hypercoagulable state. Conditions such as repeated embryonic loss (so-called recurrent abortions), fetal loss (stillbirth), placental abruption, intrauterine growth restriction, and severe pre-eclampsia were also considered as quasithrombotic events and therefore as manifestations of thrombophilia.

In the past, only two anticoagulants were available for therapy: warfarin (coumadin) and heparin. The advent of low-molecular-weight heparins (LMWHs) significantly simplified treatment, especially during pregnancy, and avoided many of the drawbacks associated with warfarin and heparin in terms of safety [5] and patient compliance. The range of indications for LMWH therapy has become increasingly wider and includes subtle or even unsupported indications. Although thrombophilia in women's health is one of the hot topics in perinatal medicine and is not unknown to clinicians, some may find such hemato-obstetric or hemato-gynecologic subjects intimidating in the sense that too much basic hematology may be involved in clinical obstetrics and gynecology, or, conversely, that too many obstetric and gynecologic considerations are involved in a primary hematologic issue. This article is a prelude to the state-of-the-art discussions found in this volume of *The Clinics*, which is dedicated to the most important hypercoagulable states in women's health.

Acquired versus inherited thrombophilias

An increased tendency for thromboembolic events might arise from inborn and acquired thrombophilias. The former include genetic conditions, and the latter are associated with a wide range of disease conditions.

Some environmental factors are known to enhance thrombus formation, such as smoking, obesity, fractures, surgery, and immobility. In the female patient, several additional thrombosis-enhancing factors are well recognized, such as oral contraception, hormone replacement therapy, pregnancy, and puerperium.

A considerable interaction exists between inborn thrombophilia and environmental enhancing conditions. For example, Figure 1 shows the exponentially (extrapolated) increased risk of VTE attributed to the multiplicative combination between the state of factor V Leiden with or without oral contraception [6].

Another important aspect is that not all thrombophilias carry the same risk for VTE. For example, Figure 2 shows the various lifetime risk of venous thrombosis attributed to various inherited thrombophilias [7]. It seems that the lowest excess risk is attributed to the heterozygous state of factor V Leiden and protein C deficiency, whereas the highest is attributed to antithrombin III deficiency. A combination of thrombophilic factors is shown to carry an increased risk of lifetime risk of venous thrombosis. For example, the homozygous state of factor V Leiden increases the excess risk from 7% to 80%.

Venous versus arterial thrombosis

Thrombophilias may be classified by location (ie, whether the thrombus occurred in a vein, artery, or both). Arterial thrombosis is different from venous thrombosis in several characteristics. First, arterial thrombosis is primarily a result of atherosclerotic endothelial injury and platelet activation, whereas inborn thrombophilias are rarely involved. In contrast, inborn thrombophilias are frequently associated with VTE, and platelets play only a relatively minor role. Second, the consequence of arterial thromboembolism is arterial occlusion leading to ischemia and infarction in the

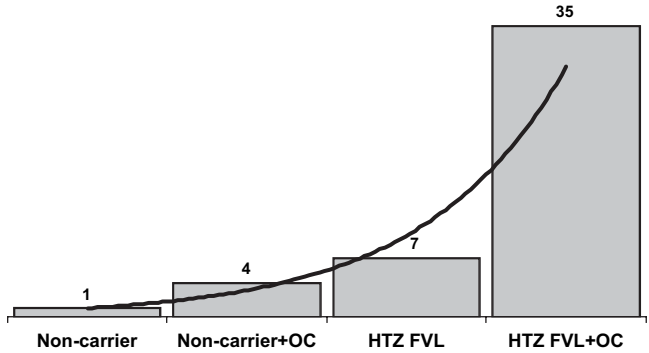

Fig. 1. Risk of VTE as related to the combination between heterozygotic carrier state to Factor V Leiden (HTZ FVL) and oral contraception (OC).

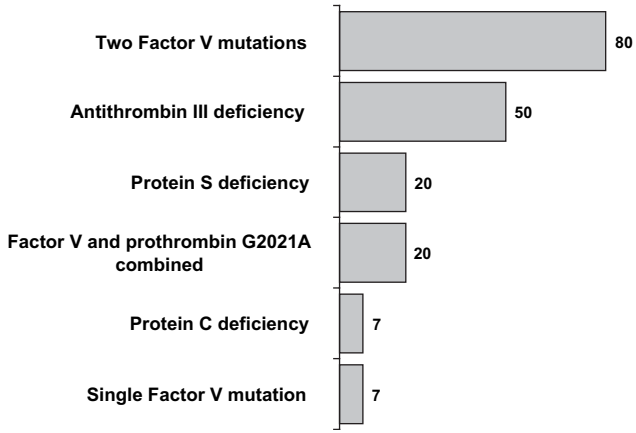

Fig. 2. Lifetime risk increase above general population risk of various inherited thrombophilias. The highest excess risk (%) is depicted. (*Data from* Reich LM, Bower M, Key NS. Role of the geneticist in testing and counseling for inherited thrombophilia. Genet Med 2003; 5:133–43.)

affected organs, such as the heart or brain. Finally, of the long list of thrombophilic factors, it seems that only hyperhomocystinemia and the antiphospholipid syndrome are associated with arterial and venous thrombosis.

Frequency of thrombophilic factors in different populations

Because of natural selection, a genetic trait leading to serious disease states is expected to be rare. However, data from several studies have documented two important observations: (1) several inborn thromboembolic factors are common in the population at large and (2) the frequency is further increased among patients who exhibit the phenomena of VTE.

The best example comes from the most prevalent inborn thrombophilia: factor V Leiden. The heterozygous state occurs in 1 in 12 to 1 in 33 (3–8%) of the general American and European populations, whereas the rate of the homozygous state is about 1:5000. The prevalence of the heterozygous state is rare in Asians, Africans, and native Australians and is highest in Europeans [8]. The range within Europeans varies, with a prevalence of 10% to 15% reported from southern Sweden and Greece and 2% to 3% reported from Italy and Spain [8]. The varied prevalence is represented in the diverse United States population, whereby the lowest prevalence of heterozygous state for factor V Leiden (0.45%) is reported in Americans of Asian origin, 1.2% is reported among African Americans, 1.25% is reported among indigenous Americans, 2.2% is reported among Hispanic Americans, and the highest prevalence (5.2%) is reported in Caucasian Americans [9].

The prevalence of a thrombophilic factor is increased within a subpopulation manifesting some form of VTE. For example, factor V Leiden is found

in as many as 50% of patients who have recurrent VTE compared with about 15% to 20% of patients having the first thrombotic event or in those who have so-called "estrogen-related thrombosis."

Because of the varied prevalence of inborn thrombophilia in different populations, it is more likely that a rare adverse outcome in association with a thrombophilia would occur in a population that has a high prevalence of a given mutation. Conversely, many women who have thrombophilia never have complications despite exposure to environmental factors. The precise risk of serious complications in women with genetic or acquired thrombophilia is unknown [10]; therefore, case-control studies should be interpreted with caution, particularly among patients who have a high prevalence of thrombophilia (ie, Caucasians) [10].

Are all thrombophilias known?

Over the years, students of the subject of thrombophilia have witnessed a steady increase in the number of mutations that may increase the risk of thrombosis. For example, a selected list from the Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov) depicts a list of mutations in factor V, named after the city where the mutation was established (ie, Leiden, Hong Kong, Cambridge, Liverpool, etc.). It could be shown that the number of mutations of factor V and other thrombophilias and new factors like factor Z and TAFI parallels the advent of modern and sophisticated laboratory analyses. It is thus expected that more mutations and new thrombophilic factors will be identified. Therefore, a patient who does not have thrombophilia should more appropriately be defined as a patient who does not have a known thrombophilia.

The view held by many authorities that some thrombophilias are probably unknown has considerable clinical consequences. For example, how should one consider a patient who has a strong history of thrombophilia but has no proven deficit? Or, what should be the extent of screening for thrombophilia given the cost involved in finding a rare mutation?

Causality

The identification of increasingly more thrombophilias, the findings of thrombophilia-associated pathology, and the advent of (relatively) convenient and almost side-effect free anticoagulation may increase the temptation to treat patients without a clearly established cause-and-effect relationship. Irrespective of the views expressed in this volume, one should bring up front the relevant issue of causality.

A causal relationship exists when certain criteria are met, none of which is conclusive by itself. These criteria include temporal relationship, consistency, degree of the association, biological gradient, specificity of the

association, biological plausibility, and coherence. A critical evaluation of the available data in terms of causality follows.

Temporal relationship

Temporal relationship (ie, that the condition [thrombophilia] was present before an adverse outcome) is perhaps the strongest argument to support a causal relationship. A temporal relationship has been documented for thrombophilia and VTE and with many adverse pregnancy outcomes.

Consistency

Consistency means that independent authors using different populations reported the same associations. Although consistency is a strong argument supporting a causal relationship between thrombophilia and VTE, some of the reported adverse pregnancy outcomes do not share adequate consistent evidence. Care should be exercised in the interpretation of these studies because some bias or uncontrolled confounders may have been duplicated across studies, leading to a false sense of consistency.

Extent and trend of the association

Extent and trend of the association suggests that a causal relationship is more plausible with large and precise risk estimates. In addition, causality is even more probable if a dose-response relationship exists. The trend line constructed for the association between risk estimates for VTE and the various exposures to hormonal contraception in combination with factor V Leiden mutations shown in Figure 1 represents a quasi (dose–response) relationship. Not all thrombophilias display such relationships.

Specificity

Specificity is the proportion of healthy patients for whom there is a correctly negative test. The notion that not all thrombophilias are known or detectable reduces the strength of causality. Moreover, there is no unique effect of the same thrombophilia—one individual may have VTE, whereas another may have recurrent pregnancy loss. Furthermore, an individual who has thrombophilia may not have any adverse outcome, or, conversely, an individual who has thrombophilia may have different thromboembolic events.

Coherence and biological plausibility

Coherence and biological plausibility suggest that some logic exists behind the alleged cause–effect relationship and that this logic does not conflict with other known biological phenomena. Under these circumstances, VTE in a patient who has thrombophilia is logical. There is some ambiguity

about the plausibility of the association between thrombophilia and non-thrombotic events, such as pre-eclampsia [11].

Effect of treatment

The addition of LMWH to the armamentarium of obstetricians was associated with some conceptual change in the practice of anticoagulation. First, LMWHs are at least as effective and safe as alternative drugs in the prevention and initial treatment of VTE. Second, the fixed-dose, once- or twice-daily dosing regimens, without laboratory monitoring to achieve adequate levels of anticoagulation, makes them physician friendly. Finally, LMWH treatment is patient friendly because of a low incidence of side effects [12], which leads to higher compliance.

Care should be exercised in the interpretation of various risks and the potential of anticoagulation as a remedy to reduce that risk. This is perhaps best illustrated in the case of recurrent abortions. The risk of abortion is generally estimated to be 15% in a population at large and increases with each consecutive repeated abortion. At the same time and despite the so-called recurrent abortion status, the chance of live birth is significantly higher than the risk of a subsequent abortion. Put differently, a patient with three consecutive abortions has a 60% to 70% chance of a live birth even without any treatment. It follows that any therapy that allegedly leads to a favorable outcome should have a higher success rate than that achieved by chance alone. Moreover, the fewer successive abortions a patient has, the greater the likelihood of a favorable outcome with or without therapy. Thus, if treatment is assumed to improve a pretreatment condition by, for example, 20%, the success rate after treatment for certain conditions should exceed an unachievable 100%.

Screening

Screening tests are offered to an otherwise healthy population and are supposed to identify a subgroup of patients who have a disease (''true positives'') along with as few as possible patients who do not have the disease (''false positives''). In this respect, most, if not all, tests to identify a thrombophilic state are not intended for screening. First, the majority of tests does not screen but rather diagnose a certain thrombophilia. Second, tests are not offered to the general population but are offered to index cases of suspected thrombophilia (ie, VTE) or with a strong familial history of thrombophilia-related conditions. Finally, we are unable to identify all thrombophilias: The current panel of tests is flawed with false-negative and true-negative results for thrombophilia carriers; hence, it is impossible to screen for all thrombophilias.

A related question is the cost-effectiveness of thrombophilia screening. Most of these tests may add up to a considerable cost, but the effectiveness

is low. It is not recommended to perform thrombophilia tests on patients who do not have a past history of thrombophilic events or on patients who do not have a strong familial history.

The question of cost may raise some secondary problems. Consider a young woman who wishes to use oral contraception. Despite the low risk of VTE in oral contraception users who have a heterozygotic state of factor V Leiden, the risk of VTE is almost twice that of women without this thrombophilia (Figure 1). The justification to perform the test or a panel of tests in all candidates for oral contraception depends on cost-effectiveness ratios rather than on medical rationalization.

The false-positive case

Some conditions are diagnosed by finding the exact mutation (eg, the prothrombin mutation), whereas other thrombophilias are diagnosed by an abnormal level or function (activity) of a given thrombophilic factor (eg, levels of protein C or protein S). Although normal ranges are known for most factors, there might be differences in the diagnostic method, and there is some overlap between normal and abnormal results, especially during pregnancy. For example, protein S deficiency is diagnosed using tests for the free protein S antigen or by functional protein S activity. These tests are associated with lower values during pregnancy and during acute blood clotting. It follows that an abnormal low level of protein S (ie, protein S deficiency) found after a thrombotic event during pregnancy may be within the normal range when tested in the nonpregnant state and remote from the thrombotic event. Consequently, it is possible to reach a false-positive diagnosis when testing thrombophilic factors during pregnancy or immediately after an acute thrombosis.

The consequences of false-positive results are not restricted to incorrect labeling of thrombophilia carrier status; false-positives may translate to unnecessary treatment. Sometimes an erroneous diagnosis may translate to repeated interventions during subsequent pregnancies or to withholding the use of oral contraception and hormone replacement therapy during the reproductive and postreproductive years, respectively [13]. Careless history taking may also lead to a false-positive ''familial background'' or ''adverse pregnancy outcome,'' where an apparently nonthrombotic etiology exists. For example, myocardial infarction is an arterial disease, and its association with a thrombophilia specific to the venous system is improbable, thrombotic stroke should be differentiated from a hemorrhagic one, and intrauterine fetal demise associated with a lethal malformation is unlikely related to thrombophilia. With these caveats in mind and given the low incidence of side effects with LMWHs, it is not surprising that within a clinical setup many clinicians believe that thrombophilia is possibly overtreated.

Evidence-based versus experience-based management

> Experience is the ability to repeat the same mistake but, each time, with increasing confidence. (unknown author)

Although experience is what makes medicine an art rather than a technique, the cited quote should be kept in mind whenever management is experience based and not evidence based. Despite the fact that not every treatment option could or even should be tested in a randomized control trial (RCT), caution should be exercised before accepting or rejecting a proposed management protocol.

Evidence-based medicine or practice is usually interpreted by assigning grades to the recommendation, which are primarily based on the level of the evaluated study(ies) [13]. Generally, grades range from A (best) to D (worst). A hierarchy exists starting from the bottom (grade D) with expert opinion statements, followed, in successive order, by case series, case control comparisons, and cohort studies. At the other side of the spectrum are single high-quality RCTs, surpassed by heterogeneous (in terms of variations in the directions and degrees of results between individual studies) systematic reviews, to the ultimate—grade A recommendations—that are based on consistent results from large number of high-quality RCTs (eg, double-blind, intention-to-treat, or complete follow-up). With respect to thrombophilia, none of the guidelines issued by the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy [14] is an evidence-based grade of A, and most are level C.

Summary

Thrombophilia, whether inherited or acquired, is one of the hot topics in women's health. Several factors, some of which are specific to the female patient, enhance thrombus formation in the presence of thrombophilia and include oral contraception, hormone replacement therapy, pregnancy, and puerperium. Thrombotic events are not only restricted to venous thromboembolism but also are believed to cause repeated embryonic loss, fetal loss, placental abruption, intrauterine growth restriction, and severe pre-eclampsia. It seems that some thrombophilias, and a combination of thrombophilic factors, carry a greater risk than others for a given adverse outcome. The addition of LMWH to the armamentarium was associated with conceptual change in the practice of anticoagulation. Care should be exercised in the interpretation of various risks and the potential of anticoagulation as a remedy to reduce that risk.

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Inherited Thrombophilias

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The term thrombophilia was first introduced by Egeberg in 1965 when he reported a Norwegian family who had a remarkable tendency to venous thrombosis because of 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 acquired (discussed elsewhere in this issue) or inherited. An example of acquired thrombophilia is the antiphospholipid antibody syndrome, which is characterized by a tendency toward venous or arterial thrombosis or recurrent pregnancy loss in combination with persistent lupus anticoagulant or antiphospholipid antibodies. Furthermore, there are many acquired or transient conditions that lead to a prothrombotic state, including cancer, surgery, strict immobilization, pregnancy and the postpartum period, and use of estrogen-containing medications, 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 several 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 who have 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 who have inherited thrombophilia develop their

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first VTE related to an acquired or transient prothrombotic risk situation. Furthermore, despite that thrombosis at a young age was assumed to be a criterion for thrombophilia and the mean age at time of a first thrombotic event is approximately 10 years lower than in the general population, the vast majority of patients have the first episode later in life [2]. The theoretical concept is that patients who have thrombophilia have an intrinsic prothrombotic state that in itself is insufficient to cause thrombosis, but may lead to an event when superimposed on (clinical) risk factors, including increasing age [3].

As was already known for the acquired antiphospholipid antibody syndrome, most inherited thrombophilic disorders are also associated with pregnancy-related disorders, such as (recurrent) fetal loss, stillbirth, intrauterine growth retardation, pre-eclampsia, and the hemolysis-elevated liver enzymes-low platelets (HELLP) syndrome of pregnancy [4,5].

This article describes the currently accepted forms of inherited thrombophilia, their underlying pathophysiology and epidemiology, and their 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 Fig. 1.

Antithrombin, protein C, and protein S function as physiologic 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 prothrombotic state, which has been confirmed in studies showing increased markers of thrombin generation in patients with one of these deficiencies [6,7]. For antithrombin and protein C, three types of deficiencies are distinguished. In type I deficiency, levels of 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% to 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, total and free antigen are normal, but activity is reduced; and in type III deficiency, total antigen is normal, but free antigen

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	

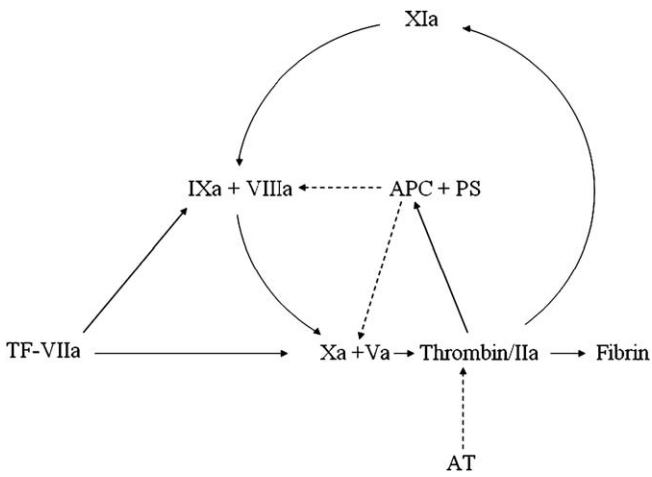

Fig. 1. Regulation of blood coagulation. Coagulation is initiated by a tissue factor (TF)–factor VIIa complex that can activate factor IX or factor X. At high tissue factor concentrations, factor X is activated primarily by the TF–VIIa complex, whereas at low tissue factor concentrations the contribution 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 downregulation of thrombin generation and consequently in an upregulation of the fibrinolytic system. The activity of thrombin is controlled by the inhibitor antithrombin. The solid arrows indicate activation and the broken arrows inhibition.

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 who have 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 physiologic anticoagulant (APC resistance) (Fig. 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 with the wild-type 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 seventy-fifth 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. It has been

Table 2
Prevalence of inherited thrombophilia

	General population	Patients with VTE
Antithrombin, protein S, or protein C deficiency	1% [27,81,82]	7% [22]
Factor V Leiden	Caucasians 4%–7% [83,84] Non-Caucasions 0%–1%	21% [11]
Prothrombin 20210A	Caucasians 2%–3% [85,86] Non-Caucasians 0%–1%	6% [87]
Elevated FVIII:c levels	11% [14]	25% [14]
Mild hyperhomocysteinemia	5% [88]	10% [88]

shown, however, 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 for VTE [19]. A homozygous mutation in the gene coding for methylenetetrahydrofolate reductase (MTHFR) causes an increase of approximately 25% in average fasting homocysteine levels and is therefore often considered a hereditary risk factor for thrombosis [20]. Although hyperhomocysteinemia is clearly associated with thrombosis, however, this association is less clear for

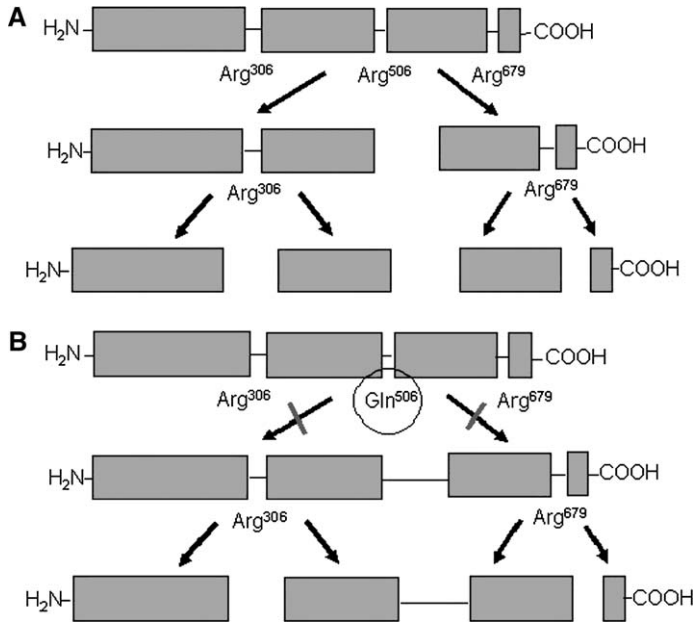

Fig. 2. Pathophysiology of the factor V Leiden mutation. Activated protein C inactivates factor Va by cleaving the protein at the Arginine^{506} cleavage site (*A*). In carriers of the factor V Leiden mutation, a point mutation in the gene coding for factor V causes replacement of the amino acid arginine by glutamine at position 506 of the protein, making factor Va resistant to inactivation by activated protein C (ie, APC-resistance) (*B*).

the MTHFR-mutation per se [21]. The authors therefore will not discuss the MTHFR mutation in this article, but rather will 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 who have VTE [22], which is the main reason thrombophilia tests were reserved for clinically severe cases of VTE in the past. Since the 1990s, however, after the discovery of the factor V Leiden and the prothrombin mutation, the diagnostic yield increased tremendously and resulted in widespread testing for thrombophilia. The prevalence of the currently known inherited defects in the general population and in patients who have VTE is summarized in Table 2.

Inherited thrombophilia and the risk for venous thromboembolism

Although well-performed case-control studies quantify associations between thrombophilic defects and VTE, the absolute risk in patients who have thrombophilia cannot be directly concluded from this type of study. There remains uncertainty in a risk estimate derived by multiplying the observed odds ratios with baseline risks in specific populations, because a baseline risk may not be valid for an individual patient. Knowledge of absolute risks for VTE and the bleeding risk for anticoagulants is necessary to make rational management decisions, and several available cohort studies give clinically relevant information [15,23–25]. These studies have been mainly performed in relatives of (consecutive) patients who have a particular thrombophilic defect. The overall absolute annual incidences of various forms of inherited thrombophilia depicted in Table 3 therefore 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 pathophysiologic and epidemiologic point of view, it is interesting to note that an interaction often exists between inherited thrombophilia and acquired prothrombotic states, most notably oral contraceptive use and hormone replacement therapy. For example, in carriers of the factor V Leiden mutation who use oral contraceptives, the relative risk for 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 who have VTE are at a high risk for recurrent events. This risk is estimated to be 4.5% per year in the first 2 years after the first event [30]. Whether presence of a thrombophilic defect superimposes an additional risk

Table 3
Incidences of first VTE in individuals who have inherited thrombophilia

	Antithrombin, protein S, or protein C deficiency	Factor V Leiden	Prothrombin 20210A	Elevated FVIII:c levels	Mild hyperhomocysteinemia
Overall (%/year)	1.5 (0.7–2.8) [89]	0.5 (0.1–1.3) [24,90]	0.4 (0.1–1.1) [91]	1.3 (0.5–2.7) [92]	0.2 (0.1–0.3) [93]
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]	1.2 (0.4–2.8) [15]	0.9 (0.1–3.4) [93]
Pregnancy (%/pregnancy)	4.1 (1.7–8.3) [24]	2.1 (0.7–4.9) [23,24]	2.3 (0.8–5.3) [25]	1.3 (0.4–3.4) [15]	0.5 (0.0–2.6) [93]
During pregnancy	1.2 (0.3–4.2)	0.4 (0.1–2.4)	0.5 (0.1–2.6)	0.3 (0.1–1.8)	0.0 (0.0–1.8)
Puerperium	3.0 (1.3–6.7)	1.7 (0.7–4.3)	1.9 (0.7–4.7)	1.0 (0.3–2.9)	0.5 (0.0–2.6)
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]	0.6 (0.2–1.5) [15]	0.1 (0.0–0.7) [93]

on 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 because of differences in selection of the studied population, the pooled hazard ratio is approximately 1.4 for all thrombophilic defects [31]. The absence of transient risk factors eliciting the first thromboembolic event seems to be a much stronger predictor of recurrence than does the presence of a hereditary thrombophilia per se [32].

Inherited thrombophilia and pregnancy-associated complications

Pregnancy-associated complications, including recurrent pregnancy loss and 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 and other, presumably vascular, pregnancy complications. It was first demonstrated that women who have most forms of inherited thrombophilia have a slightly higher risk for pregnancy complications than their relatives without thrombophilia [25,33–35]. Furthermore, case-control studies showed that thrombophilia is present more often in women who have obstetric complications than in women who have had uncomplicated pregnancies. To date, however, the pathophysiologic mechanisms underlying these associations are not at all clear.

Approximately 3% of all women trying to conceive experience recurrent pregnancy loss [36]. Various descriptions have been used for recurrent pregnancy loss, with the most common definitions being at least two or three losses that 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 intrauterine 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 the woman or the male partner, fetal chromosomal abnormalities, and APLS. In more than half of the couples who had recurrent pregnancy loss, however, no cause can be identified. Several meta-analyses have summarized the available case-control studies on the association between (recurrent) pregnancy loss and inherited thrombophilia [5,39–41]. The pooled odds ratios are summarized 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. Studies vary considerably, however, in defining early and late pregnancy loss. There seems to be no statistically significant association between factor V Leiden and early nonrecurrent pregnancy loss, whereas there is a twofold

Table 4
Association between inherited thrombophilias and pregnancy loss

Inherited thrombophilias	Meta-analysis/ systematic reviews	Early nonrecurrent pregnancy loss OR (CI)	Early recurrent pregnancy loss OR (CI)	Late nonrecurrent pregnancy loss OR (CI)	Late recurrent pregnancy loss OR (CI)
Factor V Leiden	Rey [5]	1.40 (0.66–2.97)	2.01 (1.13–3.58)	3.26 (1.82–5.83)	7.83 (2.83–21.67)
	Dudding [40]			2.8 (1.3–6.2)	10.7 (4.0–28.5)
	Kovalesky [41]		2.0 (1.5–2.7)		
	Alfirevic [39]			6.1 (2.8–13.2)	
Factor II mutant	Rey [5]		2.32 (1.12–4.79)	2.30 (1.09–4.87)	
	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]			5.0 (2.0–12.4)	
Protein C deficiency	Rey [5]	(Recurrent fetal loss)	1.57 (0.23–10.54)	(Nonrecurrent fetal loss)	1.41 (0.96–2.07)
	Alfirevic [39]				
Protein S deficiency	Rey [5]			7.39 (1.28–42.83)	
	Alfirevic [39]			16.2 (5.0–52.3)	
Antithrombin deficiency	Rey [5]	(Recurrent fetal loss)	0.88 (0.17–4.48)	(Non recurrent fetal loss)	1.54 (0.97–2.45)
	Alfirevic [39]				

Rey [5]: Early pregnancy loss defined as <13 weeks' gestation; for protein C and antithrombin deficiency no distinction was made between early and late pregnancy loss.

Kovalevsky [41]: Recurrent pregnancy loss defined as ≥ 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.

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 small sample size. As can be seen in Table 4, the overall impression is that the association between pregnancy loss and inherited thrombophilia becomes stronger with increasing numbers of pregnancy losses that a given woman has experienced and the occurrence at a later gestational age. One study reported a fourfold increased risk for early recurrent pregnancy loss in 51 women who had elevated factor VIII:c levels (above the ninetieth percentile) as compared with 51 women who had normal factor VIII:c levels [42]. This finding could not be confirmed in a family study in which 117 women who had factor VIII:c levels above the seventy-fifth percentile were compared with their 143 relatives who had lower factor VIII:c levels [43]. Finally, although hyperhomocysteinemia was found to increase the risk for recurrent early pregnancy loss two- to fourfold, depending on the definition, in a meta-analysis of a limited number of case-control studies [44], in the family study mentioned earlier, mild hyperhomocysteinemia could not be confirmed as a risk factor [43].

Pre-eclampsia, proteinuric hypertension in the second half of pregnancy, intrauterine growth restriction (defined as estimated growth less than the tenth 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 inherited and acquired thrombophilia, a wide heterogeneity existed in the inter-study prevalence of thrombophilia, making firm conclusions difficult. Considering only inherited thrombophilia, women who had pre-eclampsia were more likely to have the factor V Leiden or prothrombin mutation or protein C or protein S deficiency. Women who have 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 and mild hyperhomocysteinemia were more often found in women who had placental abruption as compared with control subjects [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 who had pre-eclampsia, no association with factor V Leiden mutation or the prothrombin mutation could be demonstrated, and the investigators concluded that the sole association found was for the factor V Leiden mutation with severe pre-eclampsia [45]. Finally, there seems to be no relationship between elevated factor VIII:c levels and pre-eclampsia, HELLP syndrome, and IUGR [46].

Clinical implications of hereditary thrombophilia

Prophylaxis of venous thromboembolism

General considerations

Management studies in asymptomatic individuals who have thrombophilia or in patients who have thrombosis and thrombophilia are rare; 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, 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 recommended continuously or can be restricted to periods of a perceived high risk for thrombosis. In the latter case it should be realized that approximately half of the episodes in thrombophilic patients occur spontaneously and are not prevented by such an approach [3,47,48]. Lifelong anticoagulant prophylaxis with vitamin K antagonists reduces the risk for VTE by more than 90% [49], which is also the case in patients who have thrombophilia [50]. This type of intervention, however, is associated with an annual incidence of major bleeding of approximately 2% to 3%, and the rates of life-threatening or fatal bleeding are 1.0% and 0.25%, respectively [51,52].

Because 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 who have a history of VTE [48].

Asymptomatic individuals who have thrombophilia

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

The risk for VTE after surgery remains elevated for a period of approximately 2 to 4 weeks [53,54]. Extending the period of postoperative prophylaxis after hospital discharge therefore may be justified in individuals who have a deficiency of antithrombin, protein S, or protein C who seem to be at highest risk for the inherited thrombophilias (see Table 3). For carriers of the factor V Leiden or prothrombin mutation and individuals who have elevated levels of factor VIII:c or mild hyperhomocysteinemia and who seem to have a lower risk for postoperative thrombosis,

a more vigorous approach than routine perioperative prophylaxis may be superfluous.

The optimal management for asymptomatic pregnant women who have inherited thrombophilia is uncertain and depends strongly on how the absolute risk for VTE is perceived by an individual woman and her caregiver. From retrospective family studies, estimates of the risk for VTE during pregnancy are available, and in absolute terms this risk is fairly low for all inherited thrombophilias (0.3%–1.2%, see Table 3). It therefore seems generally justified to withhold anticoagulant prophylaxis [55]. In the puerperium the risk for thrombosis is higher (1.0%–3.0%, see Table 3), so treatment with anticoagulants (vitamin K antagonists or low molecular-weight heparin) for 4 to 6 weeks should be considered, in particular for women who have 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 who have a deficiency of antithrombin, protein S, or protein C who have a positive family history for VTE is approximately 4.0% per year [24], which is much higher than the risk for approximately 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 contraindicated. The risk for women who have the factor V Leiden or the prothrombin mutation is considerably lower (0.2% to 0.5% per year, see Table 3), and this probably allows for more patient-tailored advice in which the woman's preference and the risk for an unwanted pregnancy should be taken into consideration. For women who have elevated levels of factor VIII:c or mild hyperhomocysteinemia, fewer data are available, but the risks seem to be in the same range as for the mutations (see Table 3). If an oral contraceptive is prescribed, levonorgestrel-containing pills (second generation) are preferred because of a 50% lower risk for thrombosis than oral contraceptives containing desogestrel or gestodene (third generation) [56–58].

Patients who have thrombophilia and a history of venous thromboembolism

The Seventh 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 for thrombosis outweighs the risk for bleeding in everyday life.

Secondary prophylaxis for patients who are considered to have a lower risk for recurrent VTE and have thus discontinued anticoagulant treatment, however, needs special consideration. Although there is no equivocal evidence that patients who have 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 who has thrombophilia and a history of thrombosis, because the risk for VTE remains increased for a period of 2 to 4 weeks [53,54].

There are no management studies for prophylaxis in pregnant women who have thrombophilic defects and a history of deep venous thrombosis. In two observational studies the risk for antepartum recurrent VTE in women who had a history of VTE ranged between 2.4% and 6.2% [61,62]. In the first prospective study, an idiopathic first thromboembolic event and thrombophilia seemed 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 for recurrence, which remained 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 because of the teratogenicity, in the third trimester, the vitamin K antagonists (which cross the placenta) induce an increased risk for fetal intracranial hemorrhage during 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, behavioral, and cognitive functions, measured at the ages of 9 to 14 years [63–65]. Low molecular-weight heparin (which does not cross the placenta and consequently does not affect the fetus) therefore 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/d) or even therapeutic dosages aimed at anti-Xa levels of at least 0.3 U/mL, might be preferred. Of note, because 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 afterward to avoid peripartum hemorrhage [55].

In women who have mild hyperhomocysteinemia, the use of folic acid, pyridoxine, and cyanocobalamin (vitamins B11, B6, and B12, respectively) beyond the tenth week of gestation can be considered. Although the strategy has shown to reduce homocysteine levels, a recent randomized controlled trial showed that 2.5 years of oral vitamin B supplementation did not reduce the risk for recurrence in patients who have 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 for recurrence, [56,60,69], thus the use of exogenous hormones is strongly discouraged in all women who have a history of VTE regardless of the presence of inherited thrombophilia. Premenopausal women should be counselled about alternative methods of contraception.

Implications for women who have 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 hypothesize that anticoagulants may have a beneficial effect on pregnancy outcome in women who have thrombophilia and pregnancy loss. An impressively good result of a combination of aspirin and unfractionated subcutaneous heparin as compared with aspirin alone was found in one randomized controlled trial in women who had such a history and APLS [70], although this result was not consistent across the scarce studies in this patient group [71]. Several studies aimed to investigate the effect of antithrombotic therapy in women who have inherited thrombophilia and pregnancy loss using various therapy schemes [72–74]. The results were inconsistent and it should be emphasized that none of these studies were randomized controlled trials and some had several methodologic limitations. For a Cochrane review on anticoagulant treatment for women who have recurrent or late pregnancy loss, only two randomized controlled trials could be identified [75]. Only in one trial were women who had inherited thrombophilia considered [76]. These women were only included if they had had one pregnancy loss after 10 weeks of gestation and there was no placebo-arm. The live birth rate for the low molecular-weight heparin group and aspirin groups were 86% and 26%, respectively. These results have thus far not been confirmed by other studies. Recently a randomized controlled trial between two doses of enoxaparin did not demonstrate a difference in live birth rate in women who had a history of recurrent pregnancy loss and inherited thrombophilia [77]. Unfortunately this study also did not have a placebo-arm [78].

Implications for women who have inherited thrombophilia and other pregnancy complications

The same therapeutic uncertainty exists for women who have other pregnancy complications and inherited thrombophilia. Although aspirin has been suggested to be beneficial for the prevention of severe pre-eclampsia, the largest study on primary prevention did not find an effect, so the beneficial findings from a Cochrane review may be the consequence of publication bias of small, positive studies [79,80]. Evidence on therapeutic and prophylactic management for women who have inherited thrombophilia and pregnancy complications is limited, leading to grade 2C level recommendations made by the ACCP guidelines and meaning that the risk–benefit ratio is unclear and the recommendations are weak [55].

Summary

Many inherited thrombophilias have been detected and the pathophysiologic insight has increased tremendously during the last decades. Despite,

however, 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 epidemiologic evidence that is helpful in counseling women who have inherited thrombophilia 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-eclampsia. For this group, well-designed placebo-controlled trials to assess the harm–benefit ratio are urgently needed.

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Acquired Thrombophilia during Pregnancy

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Of the three mechanisms of thrombosis defined by Virchow in the 19th century—vessel wall injury, stasis, and hypercoagulability—the last two predominate as a causal factor of venous thromboembolism (VTE). The term thrombophilia was introduced by Egeberg in 1965 to describe a tendency to venous thrombosis in a Norwegian family that was shown to have antithrombin deficiency [1]. Since then, and with a better understanding of the coagulation cascade in conjunction with the development of sensitive molecular investigations, the definition of thrombophilia has been broadened to include any disorder that is associated with VTE. Thrombophilia can be inherited or acquired; antithrombin deficiency and dysfibrinogenemia were the first inherited thrombophilias to be described [1,2]. Since 1993, and after the discovery of resistance to activated protein C [3], inherited thrombophilias are commonly classified as secondary to reduced coagulation inhibitor levels or increased levels or function of coagulation factors [4].

The principal acquired thrombophilic states include antiphospholipid antibody syndrome, hyperhomocystinemia (HHC) [5], pregnancy, cancer, the use of oral contraceptives or hormone replacement therapy, heparin-induced thrombocytopenia, Behçet's disease, and active inflammatory bowel disease [6] (Box 1). This article focuses on antiphospholipid antibody syndrome and HHC.

Antiphospholipid antibody syndrome

The presence of acquired circulating anticoagulants was first described by Conley and colleagues [7] in 1948 in a patient who had systemic lupus

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Box 1. Principle acquired thrombophilic states

- Antiphospholipid antibody syndrome
- Hyperhomocystinemia
- Pregnancy
- Cancer
- Oral contraceptives
- Hormone replacement therapy
- Heparin-induced thrombocytopenia
- Behçet's disease
- Active inflammatory bowel disease

erythematosus (SLE) presenting with hemorrhagic diathesis. Fifteen years later, Bowie [8] described thrombosis in SLE patients with circulating anticoagulants. Many laboratory assays for these coagulation inhibitors have been described [9,10]. Antiphospholipid antibodies (APLA) occur at a rate of 1% to 5% in normal healthy control subjects and are much more common in patients who have autoimmune disorders, such as SLE. In common clinical practice, antiphospholipid antibodies are usually reported as ''lupus anticoagulants'' or ''anticardiolipin antibodies''; many patients have both types of antibody [11]. The prevalence of antiphospholipid antibodies increases with age, particularly in individuals who have coexistent chronic conditions [11]. Patients who have APLA seem to have an increased risk of first episode of venous thrombosis [12]. In 1975, Nilsson [13] found a circulating lupus-like anticoagulant in the plasma of a young woman who had recurrent miscarriage; subsequent case reports established a link between APLA and recurrent miscarriage [14,15]. The mechanism through which APLA promote thrombosis is not understood; hypothetical mechanisms include endothelial cell perturbation, oxidant-mediated injury of the vascular endothelium, and interference or modulation of the function of phospholipids-binding proteins involved in the regulation of the coagulation.

A recent consensus statement provides simplified criteria for the diagnosis of the antiphospholipid antibody syndrome (APS) (Box 2) [16]. These guidelines also establish the ''minimal criteria'' required to link APLA with pregnancy loss or complications. Patients are required to have at least one of the two clinical criteria (pregnancy complications or thrombosis) and one laboratory criteria to be labeled as having APS.

Anticoagulant therapy is the mainstay of treatment for patients who have APS. These treatments are based on the observation that patients who have APLA are at increased risk of first, and recurrent, thrombosis and that anticoagulant therapy seems to reduce this risk [12,17–23].

Pregnancy complications associated with APLA include recurrent pregnancy loss, pre-eclampsia, intrauterine growth restriction, and thrombosis.

Box 2. Criteria for the diagnosis of antiphospholipid syndrome*

Clinical criteria

- Vascular thrombosis

One or more clinical episodes of arterial, venous, or small-vessel thrombosis, occurring within any tissue or organ

- Complications of pregnancy

One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation, one or more premature births of morphologically normal neonates at or before 34th week of gestation, or three or more unexplained consecutive spontaneous abortions before the 10th week of gestation

Laboratory criteria

- Anticardiolipin antibodies

Anticardiolipin IgG or IgM antibodies present at moderate or high levels in the blood on two or more occasions at least 6 weeks apart

- Lupus anticoagulant antibodies

Lupus anticoagulant antibodies detected in the blood on two or more occasions at least 6 weeks apart

*A diagnosis of definite antiphospholipid syndrome requires the presence of at least one of the clinical criteria and at least one of the laboratory criteria.

Adapted from Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309–11.

Women who have antiphospholipid antibodies may have an unusually high proportion of pregnancy losses within the fetal period (10 or more weeks of gestation) [24,25]. In contrast, in unselected women with sporadic or recurrent miscarriage, pregnancy loss occurs more commonly in the pre-embryonic period (>6 weeks of gestation) or the embryonic period (6–9 weeks of gestation).

The mechanisms of adverse pregnancy outcome in women who have APS are not clearly understood. Early pregnancy failure may result from impaired development of the trophoblast and failure to establish an effective feto–placental circulation. Other hypothesized mechanisms include thrombosis of the uteroplacental vasculature as a result of displacement of trophoblastic annexin V by the APLA [26]. Potential nonthrombotic mechanisms include autoantibody-mediated failure of implantation or failure of development of normal utero–placental vasculature as a result of autoantibody binding to the trophoblast or maternal spiral arteries [27]. Late loss (in the fetal period)

is usually due to massive thrombosis of the placenta; the mechanisms of other complications associated with APLA (such as pre-eclampsia) are unknown.

Evidence-based recommendations for the treatment of pregnancy complications in patients who have APS are difficult to provide, given the lack of large randomized clinical trials. Furthermore, treatments proposed for this condition are associated with significant risk to the mother and fetus. As a result, any treatments used should be based on the best possible evidence in concert with a full and frank discussion with the patient. Patients should be treated only if there is evidence that their risk of APLA-mediated complications exceeds the risks of the proposed treatments. Factors that seem to predict adverse outcomes during pregnancy include anticardiolipin antibody titre and previous obstetric history.

Corticosteroids were once widely used to prevent APLA-related complications in patients who have APS. This practice has largely been abandoned as a result of a study published by Laskin and associates [28]. This study found, in a subgroup analysis, that treatment of patients who have APLA complications during pregnancy was associated with increased maternal morbidity without evidence of improved fetal outcome. As a result of this evidence, corticosteroids should be reserved for women who have APS complicated by clinically important thrombocytopenia or coexistent SLE; patients on long-term corticosteroids should be monitored for the development of complications such as gestational diabetes or hypertension, which may be precipitated by the corticosteroid treatment.

Aspirin inhibits thromboxane formation, reducing the risk of platelet-mediated vascular thrombosis. Aspirin may be used throughout pregnancy and has minimal maternal or fetal complications. It can be continued until delivery, and the use of low-dose aspirin should not affect the use of regional anesthesia during labor because there is no evidence that it increases the risk of epidural hemorrhage [29]. As a single agent for the treatment of APLA-associated pregnancy complications, aspirin has been tested in two randomized clinical trials [30,31]. In the first trial, Cowchock and colleagues [30] randomized pregnant women who had APS but no previous thrombosis or miscarriages to aspirin (81 mg/d) or usual care. No advantage in pregnancy outcome was seen, although the study was small and therefore underpowered to detect even modest improvements in outcome rates. The second trial randomized women who had APS and three or more previous fetal losses to aspirin (75 mg/d) or placebo [31]. Women who had SLE requiring treatment or a history of prior thromboses were excluded. This small study also failed to demonstrate improved outcome in the aspirin-treated group compared with the patients receiving supportive care alone; the live-birth rate in both arms of the study was around 80%. Limitations of this study include its small size (40 patients) and the inclusion of many patients who had low-titre anticardiolipin antibodies.

Heparin may improve pregnancy outcomes in women who have APS (Table 1). At least two randomized trials have found the combination of

Table 1
Trials that used heparin in women with recurrent miscarriages

Study	Patients (n)	Inclusion criteria	Exclusion criteria	Intervention	Outcomes
Rai et al, 1997 [32]	90	≥3 consecutive pregnancy losses	Chromosomal or uterine abnormalities, previous thrombosis, SLE, thrombophilias	UFH 5000 U bid + aspirin 75 mg versus aspirin 75 mg	71% live births versus 42% live births
Kutteh et al, 1996 [33]	50	≥3 consecutive pregnancy losses	SLE	Heparin (aPTT 1.2–1.5 baseline) + aspirin 81 mg versus aspirin 81 mg	80% live births versus 44% live births
Farquharson et al, 2001 [34]	98	≥3 consecutive pregnancy losses or ≥2 consecutive losses with proven fetal death after 10 wk	Chromosomal or uterine abnormalities, previous thrombosis, SLE requiring treatment, thrombophilias	LMWH 5000 U daily + aspirin 75 mg versus aspirin 75 mg	78% live births versus 72% live births

Abbreviations: aPTT, activated partial thromboplastin time; LMWH, low-molecular-weight heparin; SLE, systemic lupus erythematosus; UFH, unfractionated heparin.

aspirin and unfractionated heparin (UFH) to be associated with improved outcomes when compared with aspirin alone in women who had recurrent miscarriages [32,33]. A third trial compared the efficacy of low-molecular-weight heparin (LMWH) as adjunctive therapy in patients treated with low-dose aspirin [34,35]. In this study, LMWH-treated patients had the same outcome rate as those treated with aspirin alone. This latter study differed from the previous two studies in its definition of pregnancy loss and the laboratory and clinical criteria required for entry; however, the high live-birth rate in the control (non-LMWH arm) suggests that improved antenatal care may account for some of the benefit of UFH seen in previous studies.

In other settings, LMWH has been compared with UFH; in all such settings, LMWH was as good as, or better than, UFH for the prevention or treatment of thromboembolism. Data from observational studies and systematic reviews support the use of LMWH as a safer alternative to UFH in pregnancy [36,37]. LMWH has been associated with a lower incidence of heparin-induced thrombocytopenia and osteoporosis [38,39]. Finally, when used in therapeutic doses, LMWHs do not require laboratory monitoring or dose adjustment unless the patient's weight changes significantly [40].

Management of patients who have APLA and prior objectively confirmed arterial or venous thrombosis during pregnancy usually consists of conversion from therapeutic dose oral vitamin K antagonists at the time of a positive pregnancy test to therapeutic dose LMWH carried on throughout the pregnancy. If the patient is also receiving aspirin, it may be continued. To reduce the risk of bleeding at the time of delivery, many experts recommend induced vaginal delivery at 37 weeks, followed by reinstitution of LMWH, converted to oral vitamin K antagonists, as soon as hemostasis is achieved. Variations on these recommendations include the use of therapeutic-dose UFH after 37 weeks, allowing spontaneous labor and the use of oral vitamin K antagonists during the second and early third trimester. If the patient has a history of thrombosis and is not treated with therapeutic-dose oral vitamin K antagonists at the time of the pregnancy test, many experts would recommend the use of prophylactic-dose LMWH throughout pregnancy because the intra- and immediately post-partum period are associated with an increased risk of recurrent thrombosis. These treatment recommendations are based on anecdote because there is little or no prospective evidence to guide treatment in such patients.

Warfarin should be avoided during pregnancy, especially during the first trimester, because it crosses the placenta and is potentially teratogenic. Warfarin use in pregnancy is associated with a high incidence of fetal loss, congenital malformations, and physical disability, although such outcomes might be due to underlying maternal morbidity, which necessitated the use of warfarin [41]. Warfarin might be considered in the second and early third trimester for women who have specific contraindications to UFH or LMWH; however, its use in this period may be associated with central nervous system abnormalities, such as optic atrophy, mental retardation, delayed development, seizures, and microcephaly [42,43]. It is not clear that warfarin or underlying maternal morbidity accounts for these adverse outcomes. Warfarin should be avoided after the early third trimester because it crosses the placenta and causes fetal anticoagulation; if present during labor and delivery, it may be associated with fetal bleeding, including intracerebral hemorrhage.

Intravenous immune globulin is not recommended for pregnant women who have APS. This recommendation is based on a lack of clear evidence of benefit and one small randomized trial that found no evidence of benefit of IVG in reducing adverse obstetrical outcomes in pregnant women who have APS in comparison with treatment with heparin and aspirin [44].

In conclusion, corticosteroids and intravenous immune globulin are not recommended in the treatment of pregnant women who have APS. Warfarin is generally contraindicated, and its use is limited to special conditions. Aspirin and prophylactic-dose UFH or, preferably, LMWH are recommended in many pregnant women who have APS because they are relatively safe. Enthusiasm for their use is tempered by recent studies that failed to find

that these agents improved live birth rate when compared with aspirin and aggressive antenatal care.

Hyperhomocystinemia

HHC can be caused by genetic or environmental factors. Genetic HHC may be due to a deficiency of cystathionine beta-synthase or 5,10-methylenetetrahydrofolate reductase (MTHFR). Environmental factors that affect homocysteine (HCY) levels include reduced folate, vitamin B12, and B6 intake; increased methionine intake; smoking, coffee drinking; renal impairment; thyroid deficiency; and the use of drugs such as methotrexate, anticonvulsants, cyclosporine, or steroids (Box 3). Furthermore, plasma HCY concentrations are higher in men than in women, increase with age, and are increased in patients who have renal insufficiency. On the other hand, pregnancy and estrogen administration are associated with a fall in plasma HCY concentrations [5]. Severe HHC characterized by fasting levels of HCY of >100 μmol/L is most often caused by homozygous cystathionine beta-synthase deficiency. Affected individuals develop homocystinuria, characterized by ectopic lens, skeletal abnormalities, premature vascular disease, thromboembolism, and mental retardation [45]. Mild-to-moderate forms of HHC (fasting levels of HCY between 15 and 100 μM) are caused by genetic defects, acquired conditions, or, more frequently, a combination of both [46]. HHC is considered a risk factor for VTE because in a combined

Box 3. Environmental factors that reduce homocysteine levels

- Reduced intake of folate
- Reduced intake of vitamin B12
- Reduced intake of vitamin B6
- Increased methionine intake
- Smoking
- Coffee drinking
- Renal impairment
- Thyroid deficiency
- Drugs
  - Methotrexate
  - Anticonvulsants
  - Cyclosporine
  - Steroids
- Gender
- Age
- Pregnancy
- Estrogen

analysis of 10 case-control studies, HHC as defined by a concentration above the 95th percentile or a mean plus two standard deviations for control groups was associated with an odds ratio of 2.5 (95% confidence interval, 1.8–3.5) for VTE [47–53], and a more recent meta-analysis published by the same authors found that in three prospective studies (n = 1517) an increase of total plasma HCY levels by 5 μmol/L is associated with a 27% higher odds of venous thromboembolism [54]. In a prospective, multicenter study of 264 patients who had had an objectively documented single episode of idiopathic venous thromboembolism, Eichinger and colleagues [55] showed that the risk of recurrent venous thromboembolism is higher (relative risk, 2.7; 95% confidence interval, 1.3–5.8) in patients who had HHC than in patients who had normal tHcy levels. This finding was not confirmed in a more recent prospective study [56]. Plasma homocysteine levels are lower in normal human pregnancy [5,57]. Increases in the glomerular filtration rate and in plasma volume with associated hemodilution and a postulated increased uptake of homocysteine by the fetus may cause this fall [58].

Elevated levels of plasma homocysteine are associated with an increased risk of neural tube defects [59,60]. Furthermore, increased plasma homocysteine levels have been associated with placental vascular thrombosis, in particular pre-eclampsia and placental abruption, and with recurrent early pregnancy loss. Several studies have reported significantly higher plasma homocysteine concentrations in women who have pre-eclampsia compared with normal pregnant control subjects [61–63].

HHC has also been associated with placental abruption in several studies [64,65]. Low concentrations of folic acid and vitamin B12 have also been implicated in the pathogenesis of placental vasculopathy, which may lead to pregnancy morbidity [66]. A systematic review of studies published between 1966 and 1999 confirmed an association between placental abruption/infarction and HHC and folate deficiency. The same analysis failed to demonstrate and association with vitamin B12 deficiency [67].

Finally, HHC has been associated with recurrent pregnancy loss [68,69]. A meta-analysis found a pooled risk of 2.7 (1.4–5.2) and 4.2 (2.0–8.8) for fasting and afterload plasma homocysteine concentrations, respectively [70]. MTHFR 677 TT mutation was associated with a pooled risk of 1.4 (1.0–2.0). Proposed mechanisms through which HHC might contribute to thrombosis include endothelial dysfunction or apoptosis mediated by impaired nitric oxide bioavailability and induction of tissue factor activity, impairment of antioxidant regulation, alteration in platelet reactivity, smooth muscle cell proliferation, disruption of the prostacyclin pathway, inhibition of tissue plasminogen activator binding to its endothelial cell receptor, inhibition of protein C activation via thrombomodulin mechanisms, or reduced antithrombin activity [71]. In women who have had recurrent placental abruption, it has been hypothesized that high levels of homocysteine might interfere with cellular proliferation as a result of reduced availability of methyl groups required for DNA synthesis.

Vitamin supplementation reduces homocysteine plasma levels in most patients, including some patients who have high levels as a result of genetic defects in critical enzymes in the homocysteine metabolic pathway. A recent meta-analysis showed that folic acid at a dose of 0.5 to 5 mg daily reduced HCY levels by 25%, whereas vitamin B12 at a dose of 0.5 mg/d reduced HCY levels by an additional 7%. In this analysis there was no evidence of effect due to vitamin B6 supplementation [72].

Although therapy can reduce the levels of homocysteine, there is little evidence that these reductions are associated with a reduction in the risk of complications attributed to elevated homocysteine levels. Thus, folate supplementation reduces the incidence of neural tube defects, although this likely occurs through mechanisms other than reductions in the levels of homocysteine [73,74]. Whether vitamin therapy reduces the risk of other pregnancy complications is unknown.

Vitamin therapy may seem to be a low-risk intervention and thus might be recommended even in the absence of evidence. Enthusiasm for the use of these therapies should be tempered by recent observations in other clinical areas where reducing homocysteine did not reduce the risk of complications or seemed to increase the risk of these complications. Thus, a large randomized controlled trial failed to show any effect of vitamin supplementation in reducing death and recurrence of cerebral infarction or coronary heart disease in patients who have had a previous cerebral infarction [75]. Another randomized, placebo-controlled trial including patients who had undergoing coronary stenting found an increased risk of re-stenosis in patients randomized to vitamin supplementation [76]. Nonrandomized data have shown that it is possible to correct with vitamin supplements the metabolic abnormality in a subsequent pregnancy in women who have HHC who suffered from a pre-eclampsia [77]. Furthermore, treatment with folic acid (5 mg/d) is effective in reducing severe recurrence of pre-eclampsia and in increasing mean gestational age and birth weight. These data are not randomized, and it is uncertain to what extent the improvement in outcome was due to the effect of multiparity and better antenatal care that would inevitably be associated with participation in a clinical trial.

In summary, HHC is a common and easily treated potential cause of venous and arterial thrombosis. However, evidence linking reduced levels of homocysteine with reduced risk of thrombosis is lacking, suggesting that therapies administered to reduce the levels of these coagulation factors should be undertaken with care. It is possible that such therapy may increase the risk of thrombosis.

Other acquired thrombophilic states

Elevated levels of coagulation factors VIII, IX, and perhaps XI are a proven risk factor for venous thrombosis outside pregnancy. Levels of these factors may rise further in pregnancy, presumably as a physiologic

response directed to reducing the risk of hemorrhage at the time of childbirth. This rise is associated with an increase in the activity of the coagulation cascade, and this observation may explain the increase in the risk of venous thrombosis seen during pregnancy [77]. There is no evidence that specific therapy can reduce the levels of these coagulation factor or that such reductions would reduce the risk of first or recurrent thrombosis. Furthermore, there is no evidence-based role for the use of prophylactic anticoagulation in patients who have elevated coagulation factor levels or evidence of activation of their coagulation cascade in the absence of a prior history of thrombosis. Patients who have had prior thrombosis might benefit from prophylactic-dose anticoagulation through pregnancy and in the immediate postpartum period; however, this therapy is not evidence based.

Cancer is a common cause of venous thrombosis. Pregnant patients with cancer-associated thrombosis should be treated with therapeutic-dose LMWH throughout pregnancy. Delivery should be managed as discussed previously. Other cancer-specific factors, such as the need for chemotherapy or cancer therapy, may further increase the risk of thrombosis; prophylactic-dose UFH or LMWH might be considered in pregnant patients who have these additional risk factors for venous thrombosis.

Summary

Acquired thrombophilic states are common causes of thrombosis and other forms of pregnancy-associated complications. A growing body of evidence is available to guide the use of anticoagulants in patients who have antiphospholipid antibodies; unfortunately, the results of these studies are conflicting, and solid, evidence-based treatment recommendations cannot be made. Other forms of acquired thrombophilia are uncommon or of unknown clinical significance. Treatments aimed at mitigating the impacts of these states lack clear evidence to support their use.

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Screening for Thrombophilia

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The clinical approach to acute venous thromboembolism (VTE) is not different in patients who have inherited thrombophilia or those without. Most patients who have had a confirmed episode of VTE undergo thrombophilia screening if acquired causes have been excluded. The clinical utility of testing is the a priori assumption that the test results are likely to improve health outcome. In this context, one should remember that screening is performed in the absence of disease, whereas testing is performed in the presence of symptoms or signs. It follows that in the case of thrombophilia, the workup is for testing rather than for screening.

In contrast to simple, reliable, and inexpensive laboratory tests used to investigate bleeding disorders, such as prothrombin time and activated partial thromboplastin time, no such characteristics exist for the testing and screening of hypercoagulable states. The literature holds that thrombophilia testing and screening is expensive. For example, Wu and colleagues [1] calculated the incremental cost-effectiveness ratio (the lower the ratio the more cost-effective the strategy to avoid a major adverse clinical outcome) for universal screening before prescribing combined contraception to be as high as 202,402 UK pounds, whereas the value for hormone replacement is 6824 UK pounds. Several authorities maintained that screening for the general population is not justified mainly because of these economical considerations [2–4]. Therefore, to avoid indiscriminate thrombophilia screening and the waste of health financial resources, one must consider the indication, advantages, and pitfalls of such investigation.

Every testing or screening should be based on the prevalence of each inherited thrombophilia and the association of each with the risk of VTE. There are several inherited thrombophilic conditions that are known to predispose to venous thrombosis, and the most important are Factor V Leiden mutation; prothrombin II gene mutation; protein C, protein S, and

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antithrombin deficiency; elevated factor VIIIc; and hyperhomocysteinemia [5]. The frequency of natural anticoagulants protein S and C and antithrombin deficiencies is low in the general population (<1%) and in patients who have VTE (5%), but the frequency of gain-of-function mutations (factor V Leiden and prothrombin mutation) is common in the general population (3–7% and 3%, respectively) and in patients who have VTE (25% and 10%, respectively). The prevalence of factor V Leiden and prothrombin mutation is 10% to 15% in the Caucasian population but increases to about 50% in patients who have recurrent thromboembolic phenomena.

Who should be tested for thrombophilia?

Because selection for thrombophilia testing/screening is required, a long list of candidates has been created over the years. To simplify this list, these candidates were grouped under three subheadings [6–12].

VTE

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

Warfarin decreases the level of the natural anticoagulants protein C and S and vitamin-K–dependent coagulation factors. In some patients receiving warfarin, the decrease in anticoagulants is faster than the decrease in coagulation factors, and these patients develop skin necrosis. Thus, patients who have sustained warfarin skin necrosis are suspected to be heterozygotes for protein C and S deficiency and should be investigated.

Family history

Patients who have first-degree relatives who have had VTE at young age are candidates for screening.

Adverse pregnancy outcomes

The association of some adverse pregnancy outcomes with thrombophilia is at best controversial. Nonetheless, patients who have had two consecutive abortions, three nonconsecutive abortions, severe unexplained intrauterine growth restriction, one intrauterine fetal death, placental abruption, or severe or early onset pre-eclampsia are candidates for screening. Recent data suggest that screening for inherited thrombophilia is not required for patients who have embryonic losses occurring at less than 10 weeks.

When to test for thrombophilia?

Coagulation factors and natural anticoagulation levels change during acute VTE, under specific medication, and during pregnancy [6,13,14]. Biochemical evaluation can be postponed until the treatment period (3–6 months) is over, whereas polymerase chain reaction (genetic) tests for factor V Leiden and factor II mutation can be performed at any time. Similarly, lupus anticoagulant and anticardiolipin antibodies levels do not change with acute VTE but should be reconfirmed after 12 weeks.

Clot-based assays, such as protein S and factor VIII, should not be performed in the acute-phase VTE, during pregnancy, or during oral contraception and warfarin treatment. Tests should be performed at least 2 to 3 months after pregnancy and oral contraception and 1 month after warfarin treatment.

Antithrombin levels may be determined during acute VTE because antithrombin concentrate replacement may be necessary together with heparin or LMWH treatment for severe antithrombin deficiency.

Screening seems to be unnecessary in patients on prolonged anticoagulant treatment (eg, malignancy or recurrent VTE) because the decision for treatment has been made. Likewise, in patients who have personal or familial VTE history, there is no need for routine preoperative screening because the results do not change the thromboprophylaxis policy in most of them [6].

Why perform thrombophilic tests?

The rationale to perform thrombophilia testing is mainly to establish the genetic basis of the VTE [4,15]. Once known, the etiologic factor or presence of combined defects is communicated to patients and may influence the duration of treatment and establish the potential risk for recurrence. This knowledge may help in providing thromboprophylaxis to high-risk patients and their first-degree relatives.

One potential advantage of thrombophilia testing is for consulting with women who have a personal or significant family history of VTE who may wish to use oral contraception or hormone replacement therapy or to become pregnant. The advantages of testing are more pronounced among

women considering hormone replacement therapy than oral contraception because of the much higher risk of VTE in middle-aged women.

The ancillary advantage of family screening is to provide additional health benefits, such as controlling blood pressure, lipid disorders, obesity, and smoking.

From a scientific point of view, the prevalence of thrombophilia in minorities [16] or in certain disease conditions unrelated to VTE or pregnancy complications may improve the true impact of such conditions in terms of public health.

Why not perform thrombophilia screening?

Numerous arguments exist against the screening of thrombophilia [17,18]. The arguments related to the inaccuracy in establishing the correct laboratory diagnosis are beyond the scope of this article [14,15], as is the problem related to web sites promoting genetic testing for thrombophilia without physician supervision. However, other relevant opinions should be voiced. First and foremost is the fact that in most cases the decision about duration and intensity of anticoagulant therapy can be made by clinical criteria without knowing the underlying cause. In simple terms, VTE patients with or without thrombophilia are managed in a similar way in most cases. Second, controversy exists regarding the ability of a given defect to predict which patient is likely to have a recurrent VTE [18]. Put differently, the presence of a positive test of several thrombophilias does not necessarily mean an increased risk of recurrence [19]. Conversely, concern has been voiced that unnecessary testing may overestimate the risk and may lead to the consequently needless and potentially hazardous treatment. In the absence of randomized controlled trials that support treatment during pregnancy, one may question the wisdom of screening patients who have adverse pregnancy outcomes. Third, there are arguments related to the cost-effectiveness of routine universal screening. For example, one needs to screen about half a million women for Factor V Leiden before starting oral contraception to prevent one death from pulmonary embolism [20]. Fourth, there is a psychologic effect of screening stress that may affect quality of life in patients who have a potential rather than a real risk. For example, a positive thrombophilia test does not necessary mean VTE because 40% of women tested positive never develop VTE [21]. Conversely, false reassurance is unjustified in a patient who has a negative testing merely because our understanding of the coagulation cascade is incomplete and the availability of commercial laboratory kits is limited. For example, protein Z deficiency or antibodies are known thrombophilic factors, but their assessment is limited because the laboratory methodology is not widely available. Finally, a patient who has a positive test may never have any health problem. Yet, some insurance companies may be reluctant to insure this patient or may increase the cost involved.

What is the most economical way for screening for inherited thrombophilia?

One way to reduce the costs of screening and testing is to look for specific thrombophilia factors rather than to test for every known factor for which a test is available. Box 1 shows the list of tests according to priority, which is set by the likelihood of inherited thrombophilia in a given case [14]. The highest diagnostic yield is expected with the high priority tests mainly because they are also the most frequent.

Other inexpensive and useful means for screening patients who have hypercoagulable states and pregnancy complications have been reported recently in the literature. Thromboelastography (TEG) is used to describe the trace produced from the measurement of the viscoelastic changes associated with fibrin polymerization [22,23]. The term ROTEG refers to rotational thromboelastometry performed by the ROTEM instrument. TEG/ROTEM has been successfully used in the assessment of hemostasis, particularly in cases of bleeding disorders, and with hepatic and cardiac surgery. In recent years, this technique has been used to provide a measure for hypercoagulability. For example, a significant association exists between TEG parameters and midtrimester pregnancy loss but not with other adverse pregnancy outcomes [22].

Box 1. Testing according to high, intermediate, and low priority of thrombophilia factors

High priority
- APCR
- Factor V Leiden
- Factor II mutation
- Elevated homocysteine level
- Elevated Factor VIII level
- Lupus anticoagulant

Intermediate priority
- Protein C activity
- Free protein S
- Decreased antithrombin activity
- Increased anticardiolipin antibodies

Low priority
- Dysfibrinogenemia
- Elevated fibrinogen level
- Increased activity of factors IX and XI
- 5,10-methylenetetrahydrofolate reductase

The ProC Global is an assay that globally evaluates the functionality of the protein C pathway [24–27]. The assay is based on the ability of endogenous activated protein C, generated by a snake venom extract, to prolong an activated thromboplastin time. This assay can distinguish patients with or without protein C pathway abnormalities. It has been reported that the ProC Global assay can be used as the initial step in screening for factor V Leiden–related activated protein C resistance and protein C deficiency in patients who are not on oral anticoagulants. This assay has low sensitivity to protein S deficiency. The ProC Global test is used to screen for women who have idiopathic pregnancy loss [26] and in identifying patients at increased risk for VTE [27].

Summary

Thrombophilia screening may be useful in patients at high risk of VTE because it may improve clinical outcome. Family screening allows primary prophylaxis for high-risk situations and counseling of women considering hormonal therapy and pregnancy. Until we find useful and inexpensive screening tools, it is not recommended to test every patient or her/his relatives. Each index case should be carefully evaluated by an expert physician who should tailor the laboratory testing and treatment modalities.

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Monitoring the Effects and Managing the Side Effects of Anticoagulation during Pregnancy

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Anticoagulant/antithrombotic treatments are used during pregnancy to prevent and treat vascular pathologies in the mother (venous thromboembolism and systemic embolism in patients who have mechanical heart valves). In women who have previous pregnancy-related complications (eg, pregnancy loss, pre-eclampsia, placental abruption, and intrauterine growth retardation) and in those who test positive for antiphospholipid antibodies or other thrombophilias, an emerging indication under evaluation is the secondary prevention of these adverse outcomes.

The therapeutic compounds whose use has been documented during human pregnancy include vitamin K antagonists, heparins (unfractionated heparin [UFH] and low-molecular-weight heparin [LMWH]), and one heparinoid (danaparoid)—low-dose aspirin—as the single available platelet inhibitor (Box 1). Other medications (short- and long-acting synthetic pentasaccharide, thienopyridines, univalent and bivalent direct thrombin inhibitors, and direct factor Xa inhibitors) cross the placenta and have not been evaluated during pregnancy. This article focuses on the anticoagulants

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Box 1. Complications of antithrombotic treatment

Oral anticoagulants (fetal)
- Embryopathy
- CNS abnormalities (Dandy-Walker malformation, optic atrophy)
- Fetal bleeding

Heparins (maternal)
- Bleeding manifestations
- Allergic skin reactions
- Heparin-induced thrombocytopenia
- Osteoporosis

(vitamin K antagonists, UFH, LMWH, danaparoid) that are used as preventive or curative regimens.

Vitamin K antagonists

Oral anticoagulant drugs cross the placenta and can produce a characteristic embryopathy, central nervous system abnormalities, or fetal bleeding [1]. Coumarin-induced embryopathy (the so-called "fetal warfarin syndrome") consists of nasal hypoplasia, stippled epiphyses, or both and has been reported only with exposure during the second half of the first trimester (ie, from the beginning of the 6th to the end of the 9th week of gestation). These agents may be safe during the first 6 weeks of gestation. Hall and colleagues [1] collected reports of 418 women during pregnancy who were treated with oral anticoagulants. Sixteen (3.8%) were considered as warfarin embryopathy, although the authors agree that correct data could be obtained only prospectively. In a small prospective study of 72 pregnancies in patients who had valvular heart disease [2], embryopathy was reported in 20 infants exposed to warfarin between the 6th and 12th weeks of gestation, and no embryopathy occurred in 19 patients in whom heparin was substituted for warfarin during this period. Because there have been relatively few reported cases, it is difficult to believe that the incidence could be as high as these authors suggest.

Dandy-Walker malformation and ventral midline dysplasia (characterized by optic atrophy) have been reported with exposure to coumarin during any trimester [1]. In a review of 970 pregnancies associated with oral anticoagulant therapy, there were 26 cases of central nervous system abnormalities; however, because most of the cases came from descriptive studies, this rate may not be reliable [3]. One cohort study reported that coumarins given during the last two trimesters were not associated with major

abnormalities in growth and development of the offspring [4]. The authors noted minor neurologic dysfunction and low intelligence quotient (<80) to be more frequent in children exposed to coumarin during the last two trimesters of pregnancy, with a dose-response relationship between the clinical risk and the dose of coumarin derivative prescribed per day.

Vitamin K antagonists induce an anticoagulant effect in the fetus. Cases of fetal intraventricular hemorrhage and cerebral micro-bleedings, which may result in microcephaly and mental retardation, have been reported. At the time of delivery, trauma can lead to bleeding (including intracranial) in the neonate.

Women receiving vitamin K antagonists should be systematically counseled about the risks related to pregnancy before pregnancy occurs. Vitamin K antagonists should not be used during pregnancy, especially during the second half of the first trimester. Some so-called ''anticoagulation clinics'' have developed pregnancy guidelines for anticoagulant therapy to prevent embryonic exposure to coumarin between the 6th and 9th weeks of gestation [5], a procedure that should be generalized. In the case of planned pregnancy, two approaches are commonly applied: (1) repeated early pregnancy tests and substitution of heparin for vitamin K antagonists as soon as the test is positive and (2) replacement of vitamin K antagonists with heparin before conception is attempted. Neither of these approaches is perfect: The first needs a compliant patient, and the second increases the costly duration of heparin treatment. The first approach has been favored due to its convenience and apparent safety [6].

A retrospective survey on the outcome in pregnant women who have a mechanical heart valve concluded that warfarin was safe (ie, no embryopathy occurred) and that heparin was associated with higher rates of thromboembolic and bleeding complications than warfarin [7]. However, the subsequent systematic review performed by Chan and colleagues [8] showed that the use of vitamin K antagonist in pregnant women who have a mechanical heart valve is associated with the lowest rate of valve thrombosis and systemic embolism (3.9%) but increases the risk of embryopathy (6.4% of live births), whereas using UFH between 6 and 12 weeks gestation was associated with an increased risk of valve thrombosis (9.2%) and a reduced rate of embryopathy. The overall pooled maternal mortality rate remains high (2.9%), and major bleeding (2.5%) occurs mostly during delivery. The relative failure of UFH might be explained by a target activated partial thromboplastin time (aPTT) ratio that was not uniformly set as at least twice the control value. Limited reports on the use of LMWH are available despite their current use by many physicians during pregnancy in women who have mechanical valves. Some failures have been reported. A warning from a manufacturer regarding their safety in such situation has led to controversy. The true incidence of valve thrombosis in pregnant women who have mechanical valves treated with LMWH remains unknown [6].

Due to insufficient findings to make definitive recommendations, the following grade 1C recommendations have been proposed by experts of the 7th American College of Chest Physicians [6]: (1) adjusted-dose, twice-daily LMWH throughout pregnancy in doses adjusted to keep a 4-hour postinjection anti-Xa heparin level at approximately 1.0 to 1.2 U/mL (preferable) or according to weight; (2) aggressively adjusted UFH throughout pregnancy (ie, administered subcutaneously every 12 hours in doses adjusted to keep the midinterval aPTT controlled at least twice or to attain an anti-Xa heparin level of 0.35–0.70 U/mL); and (3) LMWH or UFH until the 13th week, switching to warfarin until the middle of the third trimester, and then restarting LMWH or UFH. Long-term vitamin K antagonists are resumed postpartum with all regimens. A grade 2C recommendation (the addition of 75–162 mg/d aspirin) is added for women who have prosthetic heart valves who are at high risk.

For patients using vitamin K antagonists during the second and the third trimester of pregnancy (third recommendation), the laboratory test used for monitoring the effects of the vitamin K antagonists on the coagulation system is the international normalized ratio (INR), which is defined as the observed prothrombin-time ratio International Sensitivity Index. The International Sensitivity Index is related to the thromboplastin preparation used to perform the prothrombin time (PT). The therapeutic range during pregnancy does not differ from the nonpregnant state and refers to the clinical indication of vitamin K antagonists. Using the INR is possible if the pretherapeutic PT value is normal. The INR cannot be used in the case of an abnormal pretherapeutic PT value (eg, in a woman who has a partial factor VII, factor V, factor X, or factor II deficiency). One of the solutions may be to monitor the plasma procoagulant activity of a vitamin K–dependent coagulation factor, found to be normal before starting vitamin K antagonists, factor II (prothrombin). If the INR range that corresponds to the clinical indication of vitamin K antagonists in a given patient is known, the underlying corresponding range of observed PT ratios can easily be calculated, depending upon the chosen thromboplastin reagent. The same thromboplastin reagent can be used to assess the plasma factor II procoagulant activity. The results are given as the corresponding coagulation time, and the factor II patient time/factor II control time ratio should correspond to the calculated range of PT ratios [9].

Much confusion regarding the presence of vitamin K antagonists into breast milk may stem from the fact that different agents possess different chemical properties. A review of the chemical structure of different coumarin derivatives and clinical evidence suggest that warfarin sodium is not excreted into breast milk and can be safely given to women who require therapeutic anticoagulation postpartum. Women using this drug should be encouraged to breast feed. For the rare patient who cannot tolerate warfarin sodium, the use of dicoumarol or acenocoumarol is preferred rather than the use of anisindione, phenprocoumon, ethylbiscoumacetate, and fluindione, which are excreted into breast milk.

Heparins

For many years, unfractionated heparin was the reference anticoagulant used during pregnancy. In nonpregnant women who have a normal renal function, LMWHs have replaced UFH for the prevention and treatment of venous thromboembolism. Preliminary data showing that LMWHs do not cross the placenta [10–14], some individual medical initiatives in France and in Europe during the late 1980s [15–18], and the advantages of LMWH over UFH (eg, longer plasma half-life, more predictable dose response, and less frequent side effects) initiated a progressive shift in the medical attitudes despite the absence of a specific clinical trial. As experience and confidence with the use of LMWHs during pregnancy increased, this practical attitude was supported by retrospective case studies that provided reassuring safety-related and efficacy-related data [19–21]. A recent systematic review confirmed these issues [22]. LMWHs are, despite their price, the leading and most widely accepted anticoagulant for the treatment or prevention of pregnancy-related venous thromboembolic events. A potential new and controversial indication, thromboprophylaxis of adverse pregnancy outcome, is under evaluation.

Monitoring heparins during pregnancy

Unfractionated heparin

UFH remains the anticoagulant of choice in women who have renal insufficiency. Three dosing regimens can be used, according to the medical context: mini-dose UFH (UFH 5000 U subcutaneously every 12 hours for low-risk preventive treatments), moderate-dose UFH (UFH subcutaneously every 12 hours in doses adjusted to target an anti-Xa level of 0.1–0.3 U/mL for high-risk preventive treatments), and adjusted-dose UFH (UFH subcutaneously every 12 hours in doses adjusted to target a midinterval aPTT into the therapeutic range for treatment of venous thromboembolism) [6]. A platelet count must be performed before the initiation of treatment and on days 5 to 7 of treatment to exclude heparin-induced thrombocytopenia (HIT).

For the treatment of VTE, UFH is initiated by an intravenous bolus (80–100 IU/kg), followed by a continuous infusion (18–20 IU/kg/h) or by an adjusted-dose subcutaneous UFH to maintain the aPTT in the therapeutic range for at least 5 days, followed by an adjusted-dose subcutaneous UFH for the rest of the pregnancy. In the case of extensive disease (eg, iliofemoral deep vein thrombosis or massive pulmonary embolism), initial intravenous heparin should be given for 7 days or longer [23]. After the first week, the midinterval aPTT should be monitored every 1 to 2 weeks because UFH requirements vary during advanced pregnancy. The elevated levels of factor VIII, which are associated with pregnancy, often result in an attenuation of the aPTT response to UFH, leading to ''heparin resistance.'' For

example, in patients who need more than 35,000 U every 24 hours, antifactor Xa plasma levels are preferred, and the dose should be adjusted to obtain a 6-hour postdose anti-Xa level of 0.3 to 0.7 U/m [24] (aPTT and anti-Xa ranges being equivalent to a heparin level of 0.2 to 0.4 U/mL by protamine titration) [25]. Antifactor Xa plasma levels should be the only test used if the pretreatment aPTT value is abnormally high (eg, in a woman who has a lupus-like anticoagulant or factor XII heterozygous deficiency). Discontinuing the weight-adjusted UFH therapy 24 hours before elective induction of labor is recommended.

Low-molecular-weight heparins

LMWHs are recommended throughout pregnancy in women who have normal renal function [6,25]. Three dosing regimens can be used, according to the medical context: prophylactic-dose LMWH (enoxaparin 40 mg [ie, 4000 U], once daily, tinzaparin 4500 U once daily, dalteparin 5000 U once daily); intermediate-dose LMWH (enoxaparin 40 mg subcutaneously every 12 hours, dalteparin 5000 U subcutaneously every 12 hours); and weight-adjusted, full-treatment doses of LMWH administered once or twice daily (enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily, dalteparin 100 U/kg every 12 hours or 200 U/kg every 24 hours, tinzaparin 175 U/kg once daily) [6]. Platelet counts must be performed before treatment, every 4 days during the first 3 weeks, and then once a month.

Treatment of a thromboembolic event is initiated with a weight-adjusted dose according to the manufacturer's recommendations. Because the half-life of LMWH decreases during pregnancy, twice-daily regimens may be preferable to once-daily dosing [6] because pregnancy is associated with physiologic changes in cardiovascular, hemostatic, and renal function and with the production of placental heparinase, all of which lead to changes in the maternal dose response to LMWH. An initial antifactor Xa plasma activity level is generally evaluated 4 to 6 hours after the morning dose to adjust the dose of LMWH to an antifactor Xa level of approximately 0.5 to 1.2 U/mL for a twice-daily LMWH regimen [6]. The corresponding target anti-Xa range with a once-daily LMWH regimen is expected to be somewhat higher.

There are some limitations in laboratory monitoring of LMWH therapy, including the poor comparability between commercially available anti-Xa chromogenic assays, the different anti-Xa activities of the various LMWH preparations, and the importance of timing the blood sampling after LMWH administration [26]. The selection of an anti-Xa assay method could influence patient management because the dose required to achieve a therapeutic range would differ according to the assay used [27]. Moreover, each LMWH preparation has its own pharmacodynamic pattern that increases the variability because the mean peak concentration is different for each compound. Thus, a peak concentration of 1.0 U/mL may be appropriate

in an enoxaparin-treated patient but may be an overdose in a dalteparin-treated patient [28].

As pregnancy progresses, the potential volume of distribution and glomerular filtration rate increase. Three options are available. The first is to maintain the initial dose throughout the pregnancy. There is no clinical work showing another approach leading to a medical benefit. The second is to change the dose in proportion to the change in maternal weight. The third is to perform regular antifactor Xa levels (once every 3 months) and to adjust the dose of LMWH to obtain an adequate antifactor Xa level. Clinical experience suggests that few dose adjustments are required, and monitoring is rarely needed [6]. However, it is probable that under certain conditions, such as an enhanced bleeding risk, borderline renal function, or extreme weight (< 50 kg or > 90 kg), monitoring antifactor Xa activity levels may be warranted, and adjustments may be needed by modifying the dosages of 10 U/kg/d (enoxaparin, dalteparin). Discontinuing weight-adjusted LMWH therapy 24 hours before elective induction of labor is recommended.

Prophylactic or intermediate-dose LMWH treatments during pregnancy are generally not monitored. Some teams have evaluated the effectiveness of LMWH prophylaxis of venous thromboembolic disease by looking at activation markers like D-dimers [29] and have reported that LMWH has to be adjusted to the gestational age to keep levels within the normal range. It has not been demonstrated that levels of D-dimers reflect the thromboembolic risk during pregnancy.

A study performed by Brenner and colleagues [30] in women who have thrombophilia and a history of recurrent pregnancy loss showed that levels of anti-Xa at 10 to 15 weeks gestation were higher in women with a successful pregnancy outcome than in the abortion group. These are preliminary results, and it is unknown if adjusting LMWH prophylactic doses to obtain higher anti-Xa levels leads to favorable outcomes or if intermediate-dose LMWH is more clinically effective than the prophylactic-dose regimen [31]. We compared low-dose aspirin with prophylactic LMWH in women who had thrombophilia and a previous fetal loss and found that the latter treatment was not monitored except for regular platelet counts [32].

Managing the side effects of heparins during pregnancy

The main side effects that have been reported for the use of heparins during pregnancy are bleeding, allergic skin reactions, HIT, and osteoporosis. The recent systematic review performed by Greer and Nelson-Piercy [22] on the efficacy of LMWH during 2777 pregnancies also evaluated safety. The following mean global incidences, for all medical indications and all LMWHs, could be calculated: bleeding, 1.98% (higher limit: 2.57%); antenatal bleeding, 0.43% (0.75%); postpartum hemorrhage (PPH) exceeding 500 mL, 0.94% (1.37%); wound hematoma, 0.61% (0.98%); allergic skin

reactions, 1.80% (2.37%); osteoporosis, 0.04% (0.20%); HIT, 0.00% (0.11%); and thrombocytopenia $< 100 \times 10^9$/L, 0.11% (0.32%).

The observed rate of bleeding compares favorably with one of a recent population-based cohort study that showed, in 3464 nontreated nulliparous Dutch women, incidences of mild PPH (500–1000 mL) and severe PPH ($\geq$ 1000 mL) reaching 19% and 4.2%, respectively [33]. In most PPH cases, there was a primary obstetric cause for bleeding, although the concomitant use of LMWH may have increased blood loss. Specific LMWH-related bleeding complications seem to be uncommon. In a study of 100 pregnant women who received various doses of UFH, the rate of major bleeding was 2% and was similar to that in the normal, nontreated population [34]. The reviewed data suggest that allergic skin reactions were significantly more common with dalteparin and nadroparin than with enoxaparin.

No cases of HIT associated with thrombosis were reported from the 2777 pregnancies under review. Three cases of thrombocytopenia were documented, which is an underestimate because benign gestational thrombocytopenia occurs in up to 7% of normal pregnancies [35]. It seems that a handful of HIT cases have been described in women who undergo a LMWH treatment during pregnancy [22]. Women who have strong antiphospholipid antibodies are known to be more prone to thrombocytopenia during heparin treatment [36], and anti–beta2-glycoprotein I antibodies recognizing platelet factor 4-heparin complex have been described in patients who have the antiphospholipid syndrome [37].

UFH may lead to symptomatic vertebral fractures in up to 3 out of 100 people on long-term therapy. During pregnancy, prophylactic UFH led to lower bone mineral density (BMD) than prophylactic dalteparin, whereas women treated with LMWH did not differ from untreated control subjects [38]. No baseline measurements of bone densities were performed. Concerning LMWHs, the overall low risk of symptomatic osteoporosis calculated in the review of Greer and Nelson-Piercy are derived from a single observation—a woman who received high doses of dalteparin (15,000 IU daily for 36 weeks). Recently, other cases have been reported. The assessment of BMD by densitometry in patients receiving LMWH or acenocoumarol for 3 to 24 months showed that long-term exposure to treatment and prophylaxis of venous thromboembolism by LMWH causes a modest but progressive decrease in BMD [39]. A LMWH has recently been reported to induce a significant, dose-dependent inhibition of osteoblast proliferation and inhibition of protein synthesis in vitro [40]. It is thus unlikely that there is no risk of osteoporosis under long-term LMWH treatment. However, the prospective evaluation of BMD during pregnancy in women who have had recurrent miscarriage and antiphospholipid antibodies receiving prophylactic dalteparin failed to show a significantly different bone loss compared with physiologic losses in nontreated patients [41]. It may be that women who are inherently predisposed to pregnancy-related osteoporosis are more prone to enhanced bone loss if a LMWH is added during that period.

A combination of lifestyle behavior, genetic predisposition, and disease processes contributes to bone metabolism, but additive genetic effects are modest contributors [42]. The most significant factors affecting BMD and bone metabolism in pregnancy are the duration and frequency of lactation, the return of menses, and pre-pregnancy weight [43]. Prevention is based on calcium supplementation in pregnant women. Dual energy X-ray absorptiometry of lumbar spine and femoral neck is the gold standard for the diagnosis of osteoporosis and for the assessment of therapeutic effects. This widely available examination takes only a few minutes, and the dose of radiation is minimal, corresponding to a few days of background radiation. Some teams perform X-ray absorptiometry in high-risk women before and after a LMWH-treated pregnancy (eg, women who have a family history of osteoporosis) to discuss a specific treatment of osteoporosis in case of a significant bone loss. There is no consensus concerning when to perform the postpregnancy examination.

Management of bleeding complications

The use of antagonists, such as protamine sulfate for UFH (1 mg protamine/100 IU UFH), may be necessary in treating serious hemorrhagic events. However, it may worsen the thromboembolic event for which treatment was initially given, and adverse reactions can be encountered, including hypersensitivity reactions (hypotension, bronchospasm, and skin and mucous membrane reactions) and anaphylactoid shock. The severity of the adverse responses may vary from mild to severe and may cause death. Several potential risk factors for adverse reactions to protamine sulfate have been identified, including insulin-dependent diabetes mellitus, allergy to fish, prior exposure to protamine sulfate, and rate of infusion. The Heparin Removal Device constitutes an extracorporeal circuit that allows ex vivo deheparinization by means of a polycationic ligand that binds heparin molecules. This method may be useful in intensive care units as an alternative to protamine sulfate or when this drug is contraindicated. Its use during an acute bleeding complication is uncertain.

Protamine sulfate reverses only about 60% of antifactor Xa activity of LMWH and has negligible effects on danaparoid. The different commercially available LMWHs vary in their ability to be neutralized by protamine. This variability is correlated with the total sulfate content of the LMWH, whereby the reduced sulfate charge and no molecular mass is the principle reason that protamine sulfate is unable to fully inactivate LMWH.

Reports of spinal hematoma, occurring spontaneously and in association with regional anesthesia, have generated concern regarding the safety of spinal or epidural anesthesia in patients receiving LMWH [44]. European practice guidelines include a delay in needle placement of 12 hours after prophylactic-dose LMWH or UFH injection and 24 hours after an intermediate-dose or weight-adjusted LMWH injection. Subsequent administration

of prophylactic-dose LMWH is postponed for 6 to 12 hours for prophylactic UFH, 6 to 8 hours for prophylactic LMWH, and 24 hours for intermediate-dose or weight-adjusted LMWH after needle placement. Epidural catheter removal should be performed far from the last LMWH injection and 2 to 4 hours before the next LMWH dose. Traumatic needle placement might result in an additional delay in LMWH administration or the need for an alternate method of thromboprophylaxis. Formal guidelines for monitoring the patient's neurologic function were developed and seemed to be effective in reducing the frequency of spinal hematoma in patients receiving regional anesthesia and LMWH. Anti-Xa level is not predictive of the risk of bleeding and is therefore not useful in the management of women undergoing neuroaxial blockade. In patients receiving UFH and having neuroaxial anesthesia before the end of the 12-hour period after the last injection, a normal aPTT value should be obtained before needle placement. There are no clear data on danaparoid, which has a long (almost 20 hours) half-life.

Postpartum hemorrhage is defined as the loss of 500 mL or more of blood during the 24 hours after delivery (5% of deliveries), but maternal tolerance is threatened at losses of 1000 mL (approximately 1% of women). ''Life-threatening'' situations occur in approximately 1 out of 1000 patients, so obstetricians are rarely faced with this situation. For maternal morbidity or mortality, the risk factors of postpartum hemorrhage are nearly the same: maternal age, multiple pregnancies, uterine scars, abruptio placentae, cesarean section, poor social conditions, and absence of prenatal care. Postpartum hemorrhage is most commonly due to uterine atony, even in patients under UFH or LMWH treatments, and often responds to medical treatments such as the administration of uterotonic drugs alone or in combination with uterine massage or bimanual compression. In case of failure, newer therapies, such as arterial embolization, are aimed to avoid the need for emergency hysterectomy and to preserve reproductive function. The hemostatic agent recombinant human Factor VIIa is a potentially useful addition to the management of massive, life-threatening, obstetric hemorrhage, but its safety and efficacy remains untested in clinical trials.

Management of skin allergic reactions

Adverse skin reactions to LMWH are rare even though their true incidence is probably underestimated or under-reported. These reactions may occur as a maculopapular urticarial rash, presumably due to local histamine release, or may have the features of a classic type I immediate hypersensitivity reaction. Angioedema or bronchospasm are rare, and the diagnosis of hypersensitivity to heparin is reached by the clinical picture, positive skin tests (patch tests, prick tests, intradermal and subcutaneous tests with several UFH, LMWHs, and danaparoid sodium), and elevated serum tryptase levels.

Allergic reactions can also present as skin necrosis, often due to vasculitis (type III Arthus reaction) or HIT, which is sometimes associated with dermal necrosis. Heparin-induced antibodies are frequently observed. Local trauma may also be involved in the pathogenesis. Heparin-induced necrotic skin lesions are strongly associated with the formation of heparin-dependent IgG antibodies and should be considered as manifestations of the HIT syndrome even in the absence of the conventionally defined thrombocytopenia [45].

Erythematous, eczema-like, well circumscribed infiltrated lesions without necrosis are usually secondary to a delayed-type IV hypersensitivity reaction. Extensive cross-reactivity between different heparins and heparinoids often occurs. This reaction is relatively common after subcutaneous injections. In a recent prospective study performed on 28 patients who had proven reaction after subcutaneous injection, challenge with intravenous heparin was well tolerated in all the patients. Thus, a shift from subcutaneous to intravenous administration may be justified [46].

Although most LMWH-induced skin lesions are benign, treatment should be discontinued when they occur. In type I reactions or in the presence of skin necrosis with or without HIT, the LMWH should be replaced with an alternative medication, such as danaparoid sodium. Platelet counts should be monitored to diagnose HIT. In a type IV delayed hypersensitivity reaction, in the absence of severe, extensive, life-threatening mucocutaneous manifestations, a first-line pragmatic approach should consist of replacing one LMWH with another. If the skin symptoms do not improve, cutaneous tests may help detect the presence of cross-reactivity between the available preparations of LMWHs and danaparoid sodium. In the presence of a negative subcutaneous provocation test, the compound can be used with little risk. If all types of LMWH and danaparoid sodium are found positive in skin testing, mechanical prevention of venous thromboembolic disease or oral anticoagulants during the second trimester of pregnancy should be used, and intravenous injections of any kind of heparin should be avoided because of the potential risk of anaphylactic shock. Hirudin, which crosses the placenta, cannot be administered during pregnancy, and few preliminary data are available on the use of fondaparinux [47], which may have limited cross-reactivity with LMWHs and danaparoid sodium [48].

Management of heparin-induced thrombocytopenia

LMWHs are associated with a lower risk of type II HIT compared with UFH. HIT is a rare side effect of LMWH in pregnant women, probably due to pregnancy-related immune tolerance.

HIT should be considered as a clinicopathologic syndrome because the diagnosis is based on clinical and serologic grounds. Recognition of HIT is a challenge for which extensive recent evidence-based guidelines are available [49]. In these recommendations, it is suggested to perform platelet count monitoring in obstetric patients who receive UFH (risk range,

0.1–1%), but it is not recommended in obstetric patients receiving LMWHs only (estimated risk, <0.1%). Due to under-reporting of numerous treated and untreated cases, we do not agree with this recommendation and continue to monitor platelet counts. Moreover, it may be that a woman who has a past episode of HIT becomes pregnant and needs to be treated.

Treatment alternatives for pregnant patients who have HIT and a high risk of thrombosis or fetal demise are limited. Discontinuation of heparin is mandatory.

The heparinoid danaparoid sodium is a mixture of glycosaminoglycans with an average molecular weight of 6000 daltons that consists mainly of heparin sulfate, which contains dermatan sulfate. Danaparoid inhibits factor Xa via antithrombin and thrombin via antithrombin and heparin cofactor II, with a ratio of anti-Xa to anti-IIa activity of approximately 22:1. Danaparoid was used as an alternative anticoagulant in patients who had HIT who were enrolled in a compassionate-use program [50]. A recent review summarized 49 reported cases with heparin intolerance (51 pregnancies: 32 HIT, 19 heparin-induced skin rashes) [51]. In most cases, routine treatment regimens for thrombosis prophylaxis (35 cases: 750 U subcutaneously twice daily or three times daily in addition to the first subcutaneous dose, and an intravenous bolus of 750 U was usually applied) or for thrombosis treatment (16 cases, intravenous bolus of 2500 U followed by an infusion rate of 400 U/h for 4 hours, then 300 U/h for 4 hours, followed by a maintenance infusion rate of 150–200 U/h) were applied, and amidolytic anti-Xa plasma activity was monitored using specific danaparoid sodium references. Danaparoid crossreactivity was suspected in 4 of 32 patients who had HIT and in 5 of 19 non-HIT patients with skin reactions and was serologically confirmed in one of the two patients who had HIT. The possibility of a clinically significant antibody cross-reactivity may lead to systematic testing of danaparoid sodium in the case of HIT or skin reactions. Anti-Xa activity transfer was not observed in five samples of fetal cord blood and in three samples of maternal breast milk. Danaparoid sodium could be used as an alternative antithrombotic agent in a total of 42 pregnancies with contraindications to UFH and LMWHs. Between the 12th and 36th weeks of pregnancy, warfarin may be alternatively used after recovery of the platelet counts and is the postpartum treatment of choice in such a situation.

Summary

LMWHs are the major anticoagulant/antithrombotic treatment given to pregnant women to prevent and treat venous thromboembolism despite the absence of specific clinical trials. An emerging indication, the prevention of adverse pregnancy outcomes, is under investigation. During pregnancy, LMWHs seem to be safe and efficient. Some uncertainties remain about the management of rare potential side effects, particularly in the event of heparin intolerance and with cross-reactivity to danaparoid sodium.

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Thrombophilia and the Risk for Venous Thromboembolism during Pregnancy, Delivery, and Puerperium

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Thrombophilia has been defined as disorders of the hemostatic mechanisms that are likely to predispose to thrombosis. Heritable thrombophilias include deficiencies of the endogenous anticoagulants antithrombin, protein C, and protein S; genetic mutations in procoagulant factors such as Factor V Leiden (FVL) and the prothrombin G20210A and the thermolabile variant of the methylene tetrahydrofolate reductase (MTHFR) gene. Other common thrombophilias with a combination of heritable and acquired components include elevated plasma factor VIIIc, hyperhomocysteinemia, and acquired activated protein C resistance. In recent years there has been a rapid increase in the understanding of the contribution of these thrombophilic conditions to venous thromboembolism (VTE), with at least 50% of cases of VTE in pregnancy being associated with a known thrombophilia.

Pulmonary thromboembolism (PTE) remains a major cause of maternal mortality and is currently the most common direct cause of maternal death in the United Kingdom, with a twofold higher prevalence than the next most common cause, hemorrhage [1]. European studies have consistently calculated the pregnancy-related VTE mortality at 8.5 to 14 per million live births [2]. The UK Confidential Enquiries into Maternal Deaths have shown that most of these deaths are associated with substandard care, including a failure to recognize symptoms in women who already had obvious risk factors for VTE, delay in diagnosis, delayed or inadequate treatment for acute VTE, and inadequate thromboprophylaxis [1]. A key risk factor for pregnancy-related

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VTE is heritable thrombophilia, and it is important for obstetricians to understand the implications of these disorders with regard to VTE in pregnancy and the management of women who have thrombophilia.

Hereditary thrombophilia

Many of the inheritable thrombophilias exert their effects by disruption of the endogenous anticoagulant systems, the antithrombin and protein C/protein S system. Antithrombin is a member of the serpin (serpin proteinase inhibitor) gene family that inactivates serine proteases, including thrombin and factors Xa, IXa, XIa, and XIIa in the coagulation cascade. There is a reactive site at the amino terminus and a heparin-binding site. Thrombin cleaves the reactive site and this is followed by the formation of thrombin–antithrombin complexes, which are rapidly cleared from the circulation. When heparin binds to antithrombin the structure of the antithrombin molecule is altered, markedly enhancing the ability of antithrombin to bind activated coagulation factors, such as thrombin. The protein C/protein S system is regulated predominantly through thrombin generation. Protein C and its cofactor protein S are vitamin K-dependent proteins produced by the liver. Although protein C can be activated directly by thrombin, activation is more efficient when thrombin is bound to thrombomodulin on the vessel wall. Following activation, protein C, together with protein S, inactivates factors Va and VIIIa through proteolytic cleavage. Factor Va inactivation is brought about by an ordered series of cuts in the factor V molecule's heavy chain. Initially there is a rapid cut at Arg 506, then slower rates of cleavage at two more sites (Arg 306 and Arg 679). FVL occurs as a result of a single point mutation in the factor V gene at the cleavage site (Arg 506) where protein C acts. In laboratory testing it manifests as resistance to activated protein C, the endogenous anticoagulant directed against Factor Va. This results in a potentially hypercoagulable state caused by the failure of breakdown of Factor Va by the activated protein C.

The relative prevalence of these thrombophilias is variable (Table 1). Qualitative or quantitative deficiencies in antithrombin, protein C, and protein S are uncommon (Table 1), with a combined prevalence of less than 10 per 1,000 [3]. Collectively they present in less than 10% of cases with VTE.

Table 1
Prevalence rates for congenital thrombophilia in a European population

Thrombophilic defect	Prevalence (%)
Factor V Leiden heterozygous	2–7
Prothrombin G20210A heterozygous	2
Antithrombin deficiency	0.25–0.55
Protein C deficiency	0.20–0.33
Protein S deficiency	0.03–0.13
MTHFR C677T homozygous	10

In contrast, 2% to 7% of people in Western European populations are heterozygous for FVL [3]; however, it is uncommon in other populations, such as Taiwan Chinese, where only 0.2% are heterozygous for FVL [4]. FVL is usually identified in 20% to 40% of women who have a pregnancy-associated VTE [5]. Activated protein C resistance can also be caused by problems other than FVL, including antiphospholipid antibody syndrome and other genetic defects in the Factor V molecule, such as factor V Cambridge or the HR2 haplotype. Although factor V Cambridge is uncommon, the HR2 haplotype is common and has been reported to carry an excess risk for VTE in high-risk patients [6]. Activated protein C resistance may also be acquired in pregnancy, with 40% of pregnant women affected [7], possibly because of gestational increases in Factor V and Factor VIII. Such acquired changes are important, because in the nonpregnant state, high levels of factor VIII and activated protein C resistance are associated with an increased risk for VTE independent of the FVL status. Obviously this widely prevalent acquired thrombophilia may interact with an inherited thrombophilia to enhance risk further.

The prothrombin gene variant, prothrombin G20210A, is present in 2% of the Western European population [8]. Prothrombin G20210A can be found in approximately 6% of patients who have VTE, including gestational VTE [9], and it has been reported in almost 20% of those who have a strong family history of VTE [8]. Again, this thrombophilia is uncommon in the Taiwan Chinese community, in whom only approximately 0.2% are heterozygous for prothrombin G20210A [4].

Homozygosity for a variant of the methylene-tetrahydrofolate reductase gene (MTHFR C677T), sometimes known as the thermolabile variant, is associated with hyperhomocysteinemia. This genotype itself is not directly related to venous thrombosis but predisposes to arterial and venous thrombosis in which there is concomitant B vitamin deficiency [10]. In this situation the genotype interacts with the deficiency in B vitamins to provoke hyperhomocysteinemia. Approximately 10% of individuals in Western European populations are homozygous for this genetic variant. Such homozygotes, however, do not seem to be at increased risk for pregnancy-related VTE [10,11]. The reasons for this are unclear but may be attributable to the pregnancy-related physiologic reductions in homocysteine levels or the effects of folic acid supplementation in pregnancy [12].

Inherited thrombophilia and the risk for venous thromboembolism in pregnancy

Although in combination the described inherited thrombophilias are common (affecting 15% of Western populations) and underlie approximately 50% of VTE in pregnancy [13,14], VTE only complicates 0.1% of pregnancies [15]. The presence of a thrombophilia alone, even in the context

of the hypercoagulable state of pregnancy, therefore does not consistently result in a thrombotic event. This rarity of adverse events emphasizes that clinical thrombosis is a multifactorial disease resulting from the interaction between congenital and acquired risk factors [16], which include the changes in hemostasis and venous flow found in pregnancy. The risk for clinical thrombosis therefore depends on the type of thrombophilia, the number of thrombophilias present, whether previous VTE have occurred, and additional risk factors, such as obesity and immobility.

The level of risk for VTE in pregnancy in women who have thrombophilia is mainly derived from observational studies of symptomatic thrombophilic kindreds. These studies although originally criticized for historically overestimating the risks for previously asymptomatic women who have these defects and asymptomatic kindreds may actually be accurate in their risk calculations. For example, initial estimates for the risk for thromboembolism in pregnancy in women who have thrombophilia, in the absence of anticoagulant therapy, were approximately 60% for antithrombin-deficient women [3]. Other retrospective studies on symptomatic kindreds have produced similar estimates of risks ranging from 32% to 60% [17,18]. Several recent cohort and case-control studies have produced more accurate estimates for the risk for gestational thrombosis in the more common inherited thrombophilias, which support these original observations.

To collate the information on the contribution of thrombophilic abnormalities as risk factors for thromboembolism during pregnancy, Robertson and colleagues performed a systematic review [19]. Nine studies (n = 2,526 pregnancies) were included for assessment of the risk for VTE in pregnant women who had heritable thrombophilia. With the exception of homozygosity for MTHFR C677T, all heritable thrombophilias were found to be significantly associated with an increased risk for VTE (Table 2). In particular the odds ratio (OR) for VTE among FVL homozygous carriers during

Table 2
Risk for venous thromboembolism during pregnancy in women who have thrombophilia

Thrombophilic defect	odds ratio	(95% CI)
Factor V Leiden heterozygous	9.32	(5.44–12.70)
Factor V Leiden homozygous	34.40	(9.86–120.05)
Antithrombin deficiency	4.69	(1.30–16.96)
Protein C deficiency	4.76	(2.15–10.57)
Protein S deficiency	3.19	(1.48–6.86)
Prothrombin G20210A heterozygous	6.80	(2.46–19.77)
Prothrombin G20210A homozygous	26.36	(1.24–559.29)
MTHFR homozygous	0.74	(0.22–2.49)

Antithrombin deficiency odds ratio is an underestimate of risk for VTE, given 73% of affected individuals have a VTE (see text for full details).

Data from Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: a systematic review. Br J Haematol 2005;132:171–96.

pregnancy was as high as 34.4 (95% CI, 9.86–120.05). Antithrombin deficiency had an exceptionally low risk for VTE compared with previously identified cohorts, which suggested risks of approximately 33% for a quantitative deficiency in antithrombin. In the three articles studied, although 73% of individuals who had antithrombin deficiency (defined as less than 80% of control levels of antithrombin) had a VTE, a VTE prevalence of 29.7% in control subjects who had no known thrombophilia gave an OR for antithrombin deficiency of only 4.69 (95% CI, 1.30–16.96). It is clear, however, that despite the relative rarity of antithrombin deficiency, it is associated with a substantial risk for VTE. In support of this, the annual risk for asymptomatic family members who have an antithrombin deficiency has been estimated at 4%, a sixfold higher risk than observed in FVL families [20].

In this systematic review the data from MTHFR homozygous cases varied. This may have been caused by the women in one of these studies receiving folic acid supplements, because folic acid has potential confounding effects on the homocysteine levels and VTE effects [12]. Exclusion of this study, however, still failed to identify a significant risk for MTHFR homozygous women with an OR of 1.83 (95% CI, 0.95–3.51).

In one of the largest studies included and contributing 26% of patients to the meta-analysis, Gerhardt and colleagues assessed 119 women who had a history of venous thromboembolism during pregnancy and the puerperium and 233 age-matched normal women [11]. In addition to overall risks, they calculated the relative risks for a first episode of VTE in association with hereditary thrombophilias using multivariate modelling with correction for a body mass index of greater than 30 and the use of oral contraceptives. The presence of FVL was associated with a relative risk of 9.0 (95% CI, 4.7–117.4), the G20210A prothrombin-gene mutation had a relative risk of 10.8 (95% CI, 2.9–40.3), antithrombin deficiency (defined as greater than 80% of normal activity) had a relative risk of 6.2 (2.2–17.3) and protein S deficiency (less than 55% of normal activity) had a relative risk of 3.2 (95% CI, 1.3–8.0). Protein C deficiency (less than 70% of normal activity) was not associated with a significant increase in risk among women experiencing their first episode of VTE. The combination of FVL and G20210A prothrombin gene mutation had an estimated relative risk for first episode of VTE of 69, although only one woman in the study had this combined defect and she was in the recurrent thromboembolism group.

Martinelli and colleagues reported a case-control study with a first episode of VTE during pregnancy or the puerperium with similar estimates of risk for FVL 10.6 (95% CI, 5.6–20.4) but considerably lower for prothrombin G20210A heterozygotes 2.9 (95% CI, 1.0–8.6) [21]. It is unclear why there were such marked differences in these two studies given that both studied similar European populations.

In the study by Gerhardt, women who had recurrent thromboembolism had an increased prevalence of thrombophilia, with a twofold increase in

antithrombin deficiency and a threefold increase in protein C deficiency [11]. The combination of FVL and G20210A prothrombin gene mutation was observed in 12.8% of women who had recurrent thrombosis. An increase in the relative risks for each thrombophilia was also reported. Assuming an underlying rate of VTE of 0.66/1,000 pregnancies derived from Western populations [13], the actual risk of thrombosis for FVL is 1:500, 1:200 for prothrombin 20210A, and 4.6:100 for the combination of these defects. In support of these theoretical estimates of risk, the risk for thrombophilia-associated thrombosis was calculated using a large retrospective study of 72,000 pregnancies with 62 objectively confirmed VTE episodes in which assessment of thrombophilia in the VTE-positive women was performed [22]. The risk calculation was based on prevalence rates in a Western population and found that the risk for thrombosis was 1:437 for FVL, 1:113 for protein C deficiency, 1:2.8 for type 1 (quantitative) antithrombin deficiency, and 1:42 for type 2 (qualitative) antithrombin deficiency. Such data are invaluable in the management of pregnancies complicated by thrombophilia and facilitate stratification and individualization of risk for each woman and clinical scenario.

Risk factors for venous thromboembolism in pregnancy other than inherited thrombophilia

Virchow's classic triad for VTE—hypercoagulability, venous stasis, and vascular damage—all occur in the course of uncomplicated pregnancy and delivery. There are substantial increases in factor VIII and fibrinogen; acquisition of resistance to activated protein C in 40% of pregnancies; reduction in protein S levels; and impaired fibrinolysis [7]. There is substantial reduction in venous flow velocity in the lower limbs in pregnancy, with approximately a 50% reduction by 25 to 29 weeks' gestation, reaching a nadir at 36 weeks [23], and a delay of approximately 6 weeks after delivery before returning to normal nonpregnant flow velocity rates [24]. Furthermore, some degree of vascular endothelial damage or trauma to pelvic vessels seems inevitable in the course of vaginal or abdominal delivery.

An accurate assessment of maternal risk for VTE in a woman who has thrombophilia requires taking into account other independent risk factors that may be present and predispose to any of the three components of Virchow's triad. The most common risk factors for VTE in pregnancy, other than inherited thrombophilia, are age older than 35 years, obesity, and operative delivery (especially emergency caesarean section in labor) [22]. Other risk factors include prolonged labor, grand multiparity, gross varicose veins, immobility after delivery, prolonged bed rest, paraplegia, dehydration, infective and inflammatory conditions, pre-eclampsia, major obstetric hemorrhage, intravenous drug abuse, hyperemesis gravidarum, and medical conditions, such as nephrotic syndrome, sickle cell disease, myeloproliferative disease,

or ovarian hyperstimulation (OHSS). Although the overall rate of VTE in OHSS is low, when it occurs it usually involves the internal jugular vein presenting with neck pain and swelling [25,26]. In addition to these classic risks, increasingly long distance air travel is also seen as a risk factor for VTE [27,28]. Evidence for the importance of these physiologic and pathologic events predisposing to VTE in pregnancy has been substantiated by the studies of Pabinger and colleagues [29]. These investigators have shown that in a cohort of 109 women who had previous VTE, pregnancy was associated with a greater than threefold temporary increase in the risk for recurrent thrombotic events, even in the absence of a thrombophilia [29].

Screening for inherited thrombophilia in pregnancy

The rapid increase in the understanding of the contribution of thrombophilic defects to the occurrence of VTE has resulted in growing pressure to initiate laboratory studies on an increasing number of patients. Performance of a comprehensive laboratory screen for thrombophilia has become common practice in women presenting with deep vein thrombosis or pulmonary embolism. Thrombophilia screening is of limited value in women who have acute VTE in pregnancy, because it does not alter immediate clinical management; however, a family history of thrombosis should be taken. If a screen is to be performed, it should be performed before commencement of anticoagulation therapy; alternatively, it should be delayed until 1 month after anticoagulation has been discontinued. Thrombophilia screens taken during pregnancy need to be interpreted with caution, because protein S levels show a physiologic decrease in pregnancy, activated protein C resistance occurs in 40% of pregnancies without FVL, and antithrombin may be reduced in the presence of an acute thrombus. In addition, coexistent medical disease may alter plasma protein levels, because nephrotic syndrome is associated with lower antithrombin levels and liver disease is associated with a reduction in proteins C and S. Genotyping for FVL and prothrombin G20210A is not influenced by pregnancy or current thrombosis and can be interpreted safely.

Despite these limitations in the available data, there is consensus that women who have a personal history of VTE and an underlying thrombophilia should receive thromboprophylaxis with low-molecular weight heparin (LMWH) during pregnancy and with LMWH or a coumarin in the puerperium [30]. Screening is therefore required during early pregnancy if prepregnancy counselling and identification of a thrombophilia has not occurred. In addition, the recognition that thrombophilias may contribute to the pathophysiologic processes underpinning recurrent miscarriage, intrauterine death, severe or recurrent intrauterine growth restriction, and pre-eclampsia [13], suggests that screening for thrombophilia should be

undertaken in women who have a poor obstetric history, because not only are these women at increased risk for adverse perinatal outcome, but they are also at risk for VTE. Both may be amenable to treatment.

The association of thrombophilias with VTE in pregnancy and adverse perinatal outcome and the realization that treatment with anticoagulants may prevent some adverse events [31] has prompted calls for widespread screening of the antenatal population. We have previously demonstrated that universal screening for FVL in pregnancy is not cost effective in the management of VTE complications [32]. Similarly, even use of selective screening based on a personal or family (in a first-degree relative) history of VTE was not cost effective. This study did not address any of the maternal or neonatal costs associated with perinatal complications, however, instead concentrating on diagnosis and VTE treatment costs. Of the 967 women in the cohort, 30 had FVL, and of these, 6 (20%) had a vascular complication defined as miscarriage, stillbirth, VTE, intrauterine growth restriction, or pre-eclampsia. Only 1 woman of the 87 women identified within the overall cohort who had a vascular complication had a VTE; therefore, most vascular events were not related to VTE but rather to obstetric complications. Pre-eclampsia and intrauterine growth restriction are the leading causes of iatrogenic prematurity, and the care of the mother and the premature infant is associated with significant costs. In a subsequent study, some of these issues regarding maternal costs were addressed. Using a hypothetical population of 10,000 women and population-based prevalence figures for adverse pregnancy events and the following thrombophilias: FVL, prothrombin G20210A, antithrombin deficiencies, protein C, protein S, lupus anticoagulants, and anticardiolipin antibodies, Wu and colleagues calculated the cost effectiveness of universal prepregnancy screening [33]. They assumed that any intervention would have a 50% reduction in adverse vascular events, consistent with their previous study [32]. In this model, universal screening, enhanced antenatal care, and management of complications cost $9,887,851, in contrast to $965,734 if screening was not undertaken. Based on a reduction of adverse events from 2,921 to 2,861 this was associated with an incremental cost effectiveness ratio of £81,436.05. Based on these values, screening for thrombophilia would still seem not to be cost effective. Unfortunately this study did not take into account neonatal costs and the huge economic consequences of preterm delivery. For example, infants born before 28 weeks' gestation are associated with average inpatient health service costs of $40,403 (1998 costs) in the first 10 years of life alone and require further substantial investment in outpatient and educational and other support services [34]. Consideration of these neonatal costs and taking into account the reduction in psychologic morbidity may have altered the overall conclusion in favor of universal screening. This obviously depends on the assumption that aspirin and LMWH are an effective intervention for all of these vascular complications.

Thromboprophylaxis and inherited thrombophilia in pregnancy

Thromboprophylaxis in pregnancy centers on the use of unfractionated heparin (UFH) or LMWH because of the fetal hazards of coumarins [35]. Coumarin embryopathy is characterized by midface hypoplasia, stippled chondral calcification, scoliosis, short proximal limbs, and short phalanges; it affects 5% of fetuses exposed to the drug between 6 and 9 weeks' gestation. In addition, coumarin use has been associated with an increase in delayed neurodevelopment independent of the increased risk for hemorrhage in the mother and fetus [36]. Neither UFH [37] nor LMWH [38,39] cross the placenta, as determined by measuring anti-Xa activity in fetal blood, and thus there is no evidence of teratogenesis or risk for fetal hemorrhage. Although for many years UFH was the standard anticoagulant used during and beyond pregnancy, LMWH has now replaced UFH for the acute treatment of VTE in the nonpregnant population, and in Europe and Australasia LMWH is now the preferred choice for prevention and treatment of VTE in pregnancy [40]. The advantages of LMWH over UFH include an enhanced ratio of anti-Xa (antithrombotic) to anti-IIa (anticoagulant), resulting in a reduced risk for bleeding; stable and predictable pharmacokinetics with increased bioavailability and half-life, allowing less frequent fixed or weight-based dosing without the need for monitoring; subcutaneous administration; and less activation of platelets with less binding to platelet factor 4, substantially reducing the risk for heparin-induced thrombocytopenia (HIT) [41]. A major concern with the widespread use of UFH in pregnancy has been the 2% risk for symptomatic heparin-induced osteoporotic fracture in pregnancy [41]. LMWHs are associated with a lower risk for this complication.

The number of LMWH preparations available for use in pregnancy has continued to increase. Until recently, however, the data on the efficacy of LMWH as evidenced by incidence of recurrent or new VTE, and the safety of LMWHs, measured by the incidence of severe bleeding, allergic skin reaction, HIT, and osteoporosis, were limited to individual studies. To try and provide accurate quantification of risk for use of LMWH in pregnancy, Greer and colleagues performed a systematic review of 64 studies encompassing 2,777 pregnancies that reported outcomes, representing 79% of all studies, including case reports, detailing the use of LMWH in pregnancy [42]. In 174 patients the indication for LMWH was treatment of acute VTE, with 2 women (1.15%) experiencing recurrent VTE. This compares favorably with recurrence rates of 5% to 8% reported in trials performed in nonpregnant patients treated with LMWH or UFH followed by coumarin therapy who had a follow-up for 3 or 6 months. In 2,603 pregnancies, LMWH was used for thromboprophylaxis ($n = 1,348$), prevention of adverse pregnancy outcome ($n = 535$), or unspecified prophylaxis ($n = 720$). In the 2,603 women receiving thromboprophylactic doses, 0.54% experienced a DVT, 0.19% a pulmonary embolus, and 0.12% an unspecified VTE. The risk for VTE in pregnancy despite LMWH thromboprophylaxis

therefore seems to be 0.84%. This demonstrates that LMWHs provide effective thromboprophylaxis in pregnancy, and although not directly comparable, the risk for VTE was 2.4% in a cohort of women who had a single previous VTE subsequently managed during pregnancy without any specific thromboprophylaxis [43]. In addition to these venous thrombotic events, 0.54% of women experienced an arterial thrombosis. With respect to bleeding complications, significant antepartum hemorrhage occurred in 0.42%, postpartum hemorrhage in 0.92%, and a wound hematoma in 0.65%. It is reassuring therefore to observe that use of LMWH was not associated with an increased risk for bleeding peripartum, and the 1.99% risk for these combined bleeding episodes compares favorably with the rate of massive hemorrhage 0.7%, defined as greater than 1500 mL, as determined prospectively without the use of LMWH [44]. Allergy was observed in 1.84% of patients and an allergic skin reaction was more common with the use of dalteparin and nadroparin than with enoxaparin. A low platelet count defined as less than 100×10^9/L was only observed in 0.08% of women, and there were no cases of thrombosis associated with HIT. This is consistent with previous reports suggesting a lower incidence of HIT with LMWH use compared with UFH. This may represent under-reporting of thrombocytopenia or bias toward not attributing it to LMWH use, because it is likely that there were many more than the three reported cases of thrombocytopenia, as gestational thrombocytopenia can complicate up to 7% of pregnancies, and in pregnancy complications, such as pre-eclampsia [45]. The low rate of HIT in this study is consistent with the recent recommendation of the American College of Chest Physicians (ACCP) that there is no need to monitor platelet counts in pregnant patients treated exclusively with LMWH [46], because it is the use of UFH that often sensitizes women to heparin and the occurrence of HIT on subsequent LMWH exposure. With respect to osteoporosis, only one woman was affected, and this was derived from a single well-documented case of postpartum osteoporotic vertebral fracture in a woman who had received a high dose (15,000 IU daily) of dalteparin for a total of 36 weeks. A further study detailing three osteoporotic fractures secondary to tinzaparin use in pregnancy have also been reported recently [47]. At present it is unclear whether this is a problem related to specific patients, is tinzaparin-specific, is a dose-related effect, or whether this risk can be applied to the other LMWH preparations. In conclusion, this systematic review confirms that LMWH is safe in pregnancy and is an effective treatment strategy for acute thrombosis and provision of thromboprophylaxis. Given the widespread clinical use of enoxaparin and dalteparin, with accurate safety data these should be the first choice preparations, at least until more data on other LMWHs are available.

Graduated elastic compression stockings are effective for thromboprophylaxis in the nonpregnant population and are also likely to be effective in pregnancy. They may act by preventing overdistension of veins, thus preventing endothelial damage and exposure of subendothelial

collagen. They therefore can be combined safely with pharmacologic thromboprophylaxis.

The management of the woman who had a single previous VTE was not controversial until recently. Management was based on a prospective study of 125 pregnant women who had a single previous objectively diagnosed VTE to calculate accurate estimates of risk [43]. In this study no heparin was given antenatally, but anticoagulants, usually warfarin, following an initial short course of heparin or LMWH, was given for 4 to 6 weeks postpartum. The overall rate for recurrent antenatal VTE was 2.4% (95% CI, 0.2–6.9). None of the 44 women (95% CI, 0.0–8.0) who did not have an underlying thrombophilia and whose previous VTE had been associated with a temporary risk factor (pregnancy [35%], oral contraceptive pill [23%], surgery [18%], trauma [14%], immobility [4%], or chemotherapy [1%]) developed a VTE, whereas 5.9% (95% CI, 1.2%–16%) of the women who were found to have an underlying thrombophilia or whose previous VTE had been idiopathic (suggesting an underlying thrombophilia) had a recurrent event. Although pregnancy was considered a temporary risk factor in this report and because data are limited, many clinicians still prefer to provide thromboprophylaxis for patients in whom the previous VTE has been related to pregnancy or contraceptive pills. Further data challenging the concept of temporary risk factors and risk for recurrence have been produced in a study of 159 women with 293 pregnancies that calculated the overall rate for recurrent antenatal VTE as 6.2% (95% CI, 1.6%–10.6%) [48]. In this study, in 197 pregnancies without thromboprophylaxis, 8 had VTE during the pregnancy; of these, 4 did not have a known thrombophilia and all 8 were believed to have a temporary risk factor at the time of the original event. Admittedly, this study may have a higher detection rate than previous studies, because it included all women from conception [43], however, its conclusions regarding the usefulness of stratifying VTE risk based on temporary risk factors are valid. This study also highlights that the risk for recurrent VTE seems to be constant over the whole of gestation. Thrombophilias or hormonal changes that would be present immediately after conception, and not mechanical factors, therefore are mainly responsible for the increased risk for VTE in pregnancy. On the basis of the study by Brill-Edwards and colleagues, it has been widely accepted that in a woman who had a previous VTE that was not pregnancy-related and associated with a risk factor that is no longer present and with no additional risk factor or underlying thrombophilia, antenatal LMWH should not be routinely prescribed. The study by Pabinger and colleagues, however, questions this view, because women who did not have a thrombophilia and a temporary risk factor at time of first VTE still have an increased risk for VTE recurrence of 8.5% in subsequent pregnancies [48]. Even exclusion of women in whom the temporary risk factor was the use of contraceptive pills was associated with 2.7% risk for recurrence. At present, although the Seventh ACCP Consensus Conference on Antithrombotic Therapy [30] suggests

restricting thromboprophylaxis to women who have thrombophilia or spontaneous thrombosis, this large cohort study strongly suggests that all women who have previous VTE should receive antenatal thromboprophylaxis. Confirmation by intervention studies is now urgently required.

In those women who have had a single previous VTE and an underlying thrombophilia, or in whom the VTE was idiopathic or related to pregnancy or use of contraceptive pills, or in whom there are additional risk factors, such as obesity or nephrotic syndrome, there is a strong case for antenatal pharmacologic prophylaxis. Antenatally, these women should be considered for prophylactic doses of LMWH (eg, 40 mg enoxaparin or 5,000 IU dalteparin daily) plus graduated elastic compression stockings. This should be started as soon as possible following the diagnosis of pregnancy. More intense LMWH therapy is usually prescribed (eg, enoxaparin, 0.5–1 mg/kg every 12 hours or dalteparin, 50–100 IU/kg every 12 hours) in the presence of antithrombin deficiency, although many women who have had previous VTE and antithrombin deficiency are on long-term anticoagulant therapy. Postpartum anticoagulant therapy for at least 6 weeks (eg, 40 mg enoxaparin or 5,000 IU dalteparin daily or warfarin [target INR, 2–3] with LMWH overlap until the INR is ≥ 2.0) plus graduated elastic compression stockings is recommended. Consistent with previous reports, however, the study by Pabinger highlights that VTE can occur in the postnatal period despite thromboprophylaxis [43,48]. This therefore questions whether current thromboprophylaxis regimens are sufficient during this high-risk period; however, what appropriate modifications in either dose or preparation would be required are at present unknown. We are aware that when prophylactic doses of LMWH are used, the dose may require adjustment in women who have very low or very high body weight. At low body weight (less than 50 kg or BMI less than 20 kg/m^2), lower doses of LMWH may be required (eg, 20 mg enoxaparin daily or 2,500 IU dalteparin daily), whereas in obese patients (eg, BMI >30 in early pregnancy), higher doses of LMWH may be required. The same strategy of higher doses may be required in women who have previous VTE in the postpartum period.

The woman who has underlying thrombophilia and previous episodes of VTE receiving long-term anticoagulants should switch from oral anticoagulants to LMWH by 6 weeks' gestation and should be fitted with graduated elastic compression stockings. These women should be considered at very high risk for antenatal VTE and should receive anticoagulant prophylaxis throughout pregnancy. They should be advised, ideally before pregnancy, of the need to switch from warfarin to LMWH as soon as pregnancy is confirmed. The dose of LMWH given should be closer to that used for the treatment of VTE rather than that used for prophylaxis; for example, enoxaparin 0.5 to 1.0 mg/kg every 12 hours or dalteparin 50 to 100 IU/kg every 12 hours, based on the early pregnancy weight. Twelve-hourly dosing may be preferable to once-daily in view of the increased clearance of LMWH in pregnancy. Because previous exposure to UFH can sensitize to the

development of HIT, the platelet count should be checked before and 1 week after the introduction of LMWH and then approximately monthly. Postpartum, there should be resumption of long-term anticoagulants with LMWH overlap until the INR achieves the prepregnancy therapeutic range; in addition, graduated elastic compression stockings should be worn.

In the case of a woman who has a heritable thrombophilia confirmed on laboratory testing but no prior VTE, surveillance or prophylactic LMWH plus graduated elastic compression stockings can be used antenatally. The indication for pharmacologic prophylaxis in the antenatal period is stronger in antithrombin-deficient women (enoxaparin 0.5–1 mg/kg every 12 hours or dalteparin 50–100 IU/kg every 12 hours are usually used) than in the other thrombophilias and also in symptomatic kindred compared with asymptomatic kindred. The presence of additional risk factors, for example obesity or immobility, may also merit consideration for antenatal thromboprophylaxis with LMWH. Postpartum, these women should receive anticoagulant therapy for at least 6 weeks (eg, 40 mg enoxaparin or 5,000 IU dalteparin daily or warfarin [target, INR 2–3] with LMWH overlap until the INR is >2.0) plus graduated elastic compression stockings. These women usually require specialized and individualized advice from clinicians with expertise in the area.

Summary

The main inherited thrombophilias (antithrombin deficiency, protein C and S deficiency, FVL, the prothrombin gene variant, and MTHFR C677T homozygotes) have a combined prevalence in Western European populations of 15% to 20%. One or more of these inherited thrombophilias is usually found in approximately 50% of women who have a personal history of VTE. Obstetricians must therefore be aware of the interaction between thrombophilias and the procoagulant state of pregnancy and should have an understanding of additional risk factors that may act synergistically with thrombophilias to induce VTE. Such knowledge combined with the appropriate use of thromboprophylaxis and treatment in women who have objectively confirmed VTE continue to improve maternal and perinatal outcomes.

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Thrombophilia and Recurrent Pregnancy Loss

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Recurrent miscarriage is usually defined as three or more consecutive miscarriages before 20 weeks. The term recurrent pregnancy loss also includes later pregnancy losses. The cause may be fetal in origin because of an anomaly that is incompatible with life or may be caused by a hostile maternal environment. The embryonic causes of fetal demise include structural malformations and chromosomal aberrations. Between 19% and 60% of aborted embryos are chromosomally abnormal in women who have recurrent miscarriage [1–5]. Although fetal karyotyping is recommended by the British Royal College [6] and the American College of Obstetricians and Gynecologists [7], few centers attempt to karyotype the fetus to diagnose a maternal or fetal origin for pregnancy loss. A presumptive diagnosis is usually made after investigations for maternal causes only. Treatment is often offered for presumed maternal causes of pregnancy loss (eg, resection of uterine septa, anticoagulants and aspirin for antiphospholipid syndrome, and so on). The presence of a maternal cause of pregnancy loss, however, does not guarantee that the embryo has a normal chromosome complement. Ogasawara [2] and Takakkuwa and colleagues [8] have shown in two small series of 20 patients who have antiphospholipid syndrome, that 30% of lost embryos had chromosomal aberrations. Carp and colleagues [9] have found four chromosomal aberrations in the embryos of 16 patients who have hereditary thrombophilia (de novo balanced translocation, trisomy 16, trisomy 13, and 45XO).

There may also be structural malformations that are not caused by chromosomal aberrations. Philipp and colleagues [10] have assessed 233 missed abortions by embryoscopy. Of these, 75% had karyotypic aberrations, but 18% had a morphologic defect with no chromosomal aberrations. It is

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against this background that thrombogenic pregnancy loss, whether caused by hereditary thrombophilias or antiphospholipid syndrome, has been assessed and treated.

Evidence for pregnancy loss having a thrombogenic mechanism

The evidence for pregnancy loss having a thrombotic basis is the widely reported association between antiphospholipid antibodies (aPL) and recurrent pregnancy loss. APL antibodies are believed to cause pregnancy loss by thrombosis in decidual vessels, impairing the blood supply to the fetus and thus leading to fetal death. Because of the assumption that aPL induces thrombosis causing pregnancy loss, it has been assumed that any prothrombotic state may also increase the chance of pregnancy loss by a thrombotic mechanism, and that if this process recurs three or more times, there is recurrent miscarriage. The evidence for pregnancy loss having a thrombotic mechanism rests on three pillars, namely, increased prevalence of thrombophilias in recurrent pregnancy loss, a higher incidence of pregnancy loss in the presence of thrombophilias, and the demonstration of thrombosis in decidual vessels.

Prevalence

Opinions are divided whether thrombophilias are more prevalent in women who have pregnancy complications including recurrent miscarriage. Few studies have discriminated between early and late pregnancy losses, and none have taken embryonic structural malformations or chromosomal aberrations into account. As for late pregnancy complications, Kupferminc and colleagues [11] and a systematic review of 25 studies by Alfirevic and colleagues [12] have reported that various hereditary thrombophilias are more prevalent in pregnant women who have fetal growth retardation, pre-eclampsia, abruptio placentae, or stillbirth. Martinelli and colleagues [13] have reported that the risk for fetal loss (after 20 weeks of gestation) was thrice in carriers of the G20210A mutation or factor V Leiden (FVL). Preston and colleagues [14] were the first to distinguish between pregnancies before 27 and after 27 weeks. In the presence of antithrombin, protein C, protein S, or FVL, the odds ratios for fetal loss after 28 weeks of gestation has been reported to be 5.2, 2.3, 3.3, and 2.0, respectively; the odds ratio was 14.3 for women who had more than one type of inherited thrombophilia. The risk for developing complications was not significantly different before 27 weeks. There are reports that hereditary thrombophilias are associated with an increased risk for early fetal loss (less than 25 weeks) in women who have protein C, protein S, or antithrombin deficiencies [15] and with FVL [16]. Moreover, a meta-analysis of 31 studies by Rey and colleagues [17] has shown a significant association between hereditary thrombophilias and pregnancy loss.

Studies of the prevalence of thrombophilia in recurrent pregnancy loss or recurrent miscarriage have produced conflicting results. The author has not found an increased prevalence of FVL, G20210A, or MTHFR in women who have recurrent miscarriages [18]. The C46T polymorphism of the coagulation factor XII gene has not been found to be more prevalent in recurrent miscarriage [19]. Mtiraoui and colleagues [20] assessed the prevalence of FVL, G20210A, and aPL antibodies in 146 Tunisian women who had habitual abortions. APL antibodies and FVL were associated with recurrent pregnancy loss, but not G20210A. Krabbendam and colleagues [21] has reported a meta-analysis of 11 studies regarding the association between thrombophilia and recurrent miscarriage. There were significantly higher serum homocysteine levels among women who had a history of recurrent miscarriage, but no increased prevalence of the MTHFR C667T mutation. No relation was observed for the levels of antithrombin, protein C, or protein S. Seven studies showed that FVL or a pathologic activated protein C ratio (APCR) may play a role in second trimester losses, as do antiphospholipid antibodies. Studies on the prothrombin gene mutation yielded conflicting results.

Similar confusion has surrounded the results of prevalence studies in antiphospholipid syndrome (APS). The prevalence of APS varies according to the population assessed and how strict were the criteria used to assess the antibodies. aPL antibodies have been found in women who have normal pregnancies, but the prevalence is low [22–24]. Vinatier and colleagues [25] have reviewed 16 publications on the prevalence of aPL in women who have recurrent miscarriage. The prevalence of anticardiolipin antibody varied between 4.6% and 50.7%, with a mean of 15.5%. The prevalence of lupus anticoagulant varied between 0% and 14%, with a mean incidence of 8.3%. In women who had mid-trimester losses, however, the prevalence has been reported to be as high as 30% [26].

These studies leave the reader confused as to whether there is an increased prevalence of thrombophilia in recurrent miscarriage or recurrent pregnancy loss, and if so, which thrombophilia is important. The results might be more meaningful if the various studies were to have excluded patients losing chromosomally aberrant embryos, or restricted themselves to first trimester miscarriages alone, for example.

Subsequent pregnancies

After three miscarriages, the prognosis for a fourth miscarriage is approximately 40% [27]. If 60% of these 40% (24%) are chromosomally abnormal, any treatment of maternal causes of miscarriage can increase the live birth rate only from 60% to 76%. Any treatment effect is small, therefore, and a trial needs a large sample size to reach statistical significance. After five pregnancy losses, the chance of a live birth is only 29% [27]. If 50% are chromosomally abnormal, treatment could increase the live birth rate by 35%, making it easier to show a treatment effect. Most trials, however, have

not accounted for the predictive factors mentioned or for fetal chromosomal aberrations.

There are two studies examining the subsequent live birth rate in women who have recurrent miscarriage and hereditary thrombophilia. In the report of Ogasawara and colleagues [28], the subsequent miscarriage rate was not different for patients who had decreased protein C or S activity or antithrombin. Carp and colleagues [29] found the live birth rate to be similar to that expected in recurrent miscarriage, whether the patient had FVL, G20210A, MTHFR, protein C or S, or antithrombin deficiencies.

There is also disagreement as to the incidence of pregnancy loss in the presence of aPL. In patients who have APS, Rai and colleagues [30], in a small series of 20 patients, reported the incidence of pregnancy loss to be as high as 90%. In a meta-analysis of three articles comparing the use of aspirin to placebo [31], 52 of 61 pregnancies developed normally in the placebo group. None of these trials, however, assessed β2GP1 (which is now known to be the antigen for aPL's action [32]). It is thus difficult to draw any conclusions about the incidence of pregnancy loss in the presence of aPL.

Women who have recurrent pregnancy loss are at a higher risk for obstetric complications, such as preterm deliveries, perinatal deaths, and intrauterine growth restriction [33,34] and possibly gestational diabetes and pregnancy-induced hypertension [35]. It remains to be determined whether the late pregnancy complications associated with recurrent pregnancy loss are associated with thrombophilia. Although there are cohort studies in low risk populations that assess the risk for late obstetric complications [36–38], there are no studies on recurrent abortions. In the author's series of 21 pregnancies in women who had recurrent miscarriage with FVL and which were followed prospectively, there was one case of HELLP syndrome, but no other obstetric complications and no deep vein thrombosis or pulmonary embolus [Author's series, manuscript in preparation].

Placental changes

Rushton [39] found thrombosis in 12.1% of 1,486 abortion materials examined. There were no thromboses in blighted ova, which account for 71% of recurrent miscarriages [40]. Thrombosis was found, however, in 27% of macerated and in 17% of fresh abortions. No group has assessed the placenta in recurrent miscarriage with hereditary thrombophilia. Many and colleagues [41] compared the placental findings in women who had severe pregnancy complications with and without thrombophilia. The number of women who had villous and multiple infarcts was significantly higher in women who had thrombophilia. The number of placentas with fibrinoid necrosis of the decidual vessels was also significantly higher in women who had thrombophilia. The study of Mousa and Alfirevic [42] could not confirm these results, however, but found a high incidence of placental infarcts (50%) and thrombosis in women with and without thrombophilia. Arias

and colleagues [43] evaluated 13 placentas of women who had pre-eclampsia, preterm labor, intrauterine growth restriction, or stillbirth. Ten of 13 women (77%) had thrombophilia, including aPL, protein C, protein S, and antithrombin deficiencies, APCR, and FVL. Rather than decidual thrombosis, however, a fetal thrombotic vasculopathy was found with fibrotic villi or stem villi obliterated by fibrous tissue. There was also fetal stem vessel thrombosis, infarcts, hypoplasia, spiral artery thrombosis, and perivillous fibrin deposition.

The placenta has not been assessed in recurrent miscarriage with APS. The syndrome has been associated with placental vascular thrombosis, decidual vasculopathy, intervillous fibrin deposition, and placental infarction caused by disruption of the annexin shield [44]. Lyden and colleagues [45] have examined stained placental sections after treatment with monoclonal antiphospholipid antibody. Most reactivity was localized in the cytotrophoblast, suggesting that the trophoblast may be directly damaged by mechanisms unrelated to thrombosis. Out and colleagues [46] found decreased vasculo-syncytial membranes, increased syncytial knots, fibrosis, hypovascular villi, and infarcts in women who had APS compared with women who did not have APS. These histologic changes are on the fetal side of the placenta.

The maternal spiral arteries become remodeled by pregnancy hormones and trophoblast into uteroplacental arteries toward the end of the first trimester. In the uteroplacental arteries, the lumen is larger and the media is replaced by endovascular trophoblast cells. If there is thrombosis of the maternal uteroplacental arteries, it is by no means certain that thrombosis can also occur in first trimester arteries. No study has assessed the placenta in first trimester pregnancy loss in the presence of thrombophilia, nor has any study assessed the placenta in the presence of genetic pregnancy loss compared with pregnancy losses with a normal karyotype.

Thrombophilia, including APS, hence may require a second messenger to make thrombosis become apparent or to cause a fetal villous vasculopathy independent of thrombosis.

Possible second messengers

There are various possible second messengers that may induce thrombosis, some of which are listed here and summarized in Fig. 1.

Cytokines

Cytokines are low molecular weight peptides or glycopeptides produced by lymphocytes, monocytes/macrophages, mast cells, eosinophils, and blood vessel endothelial cells that can exert their effect in an endocrine, paracrine, or autocrine fashion [47]. Two cytokines have been associated with initiation of coagulation in infections; TNFα and IL-6 upregulate the expression of tissue factor [48,49], which initiates the extrinsic phase of the coagulation cascade and subsequent thrombin generation.

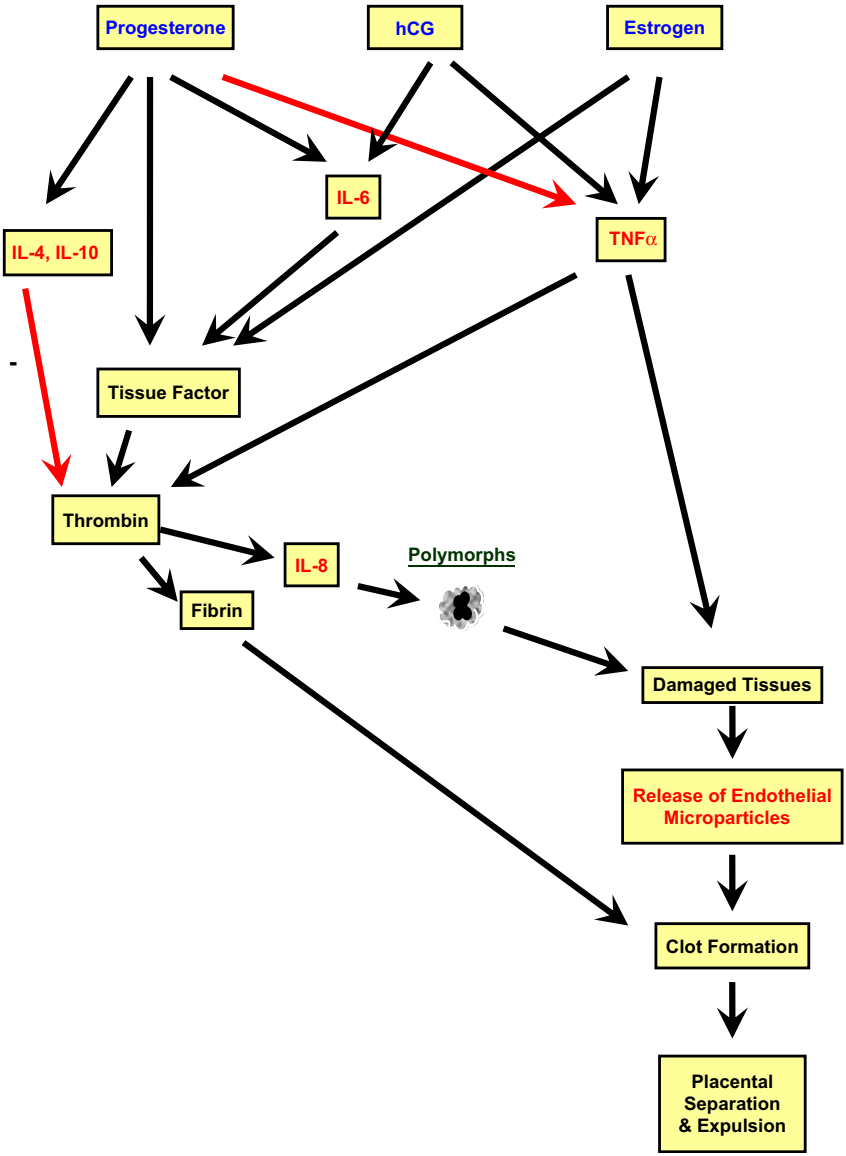

Fig. 1. Hormones and cytokines acting on thrombosis. In this diagram, the hormones estrogen, progesterone, and hCG are seen to affect the prothrombotic cytokines TNFα and IL-6 and the anti-inflammatory cytokine IL-4. The cytokines likewise affect tissue factor and thrombin generation and subsequent thrombosis. It can be seen that these pathways may be more likely to result in thrombosis in genetically susceptible individuals in whom thrombin generation is more likely because of antiphospholipid antibodies or the hereditary thrombophilias. Inhibitory pathways are shown in red.

Cytokine imbalance has been described in recurrent pregnancy loss [50], antiphospholipid syndrome [51–53], pre-eclampsia [54–56], preterm births [57,58], and intrauterine growth restriction [59–61]. The predominance of prothrombotic cytokines may lead to placental thrombosis in genetically susceptible individuals.

Microparticles

Apoptosis within the placenta is a feature of recurrent pregnancy loss [62]. Following apoptosis and cell activation, microparticles are released, with remodeling of the membrane leading to externalization of procoagulant phospholipids, such as phosphatidylserine. Microparticles in turn lead to increased expression of adhesion molecules [63], thus amplifying the procoagulant or inflammatory response on the endothelial cell surface. Microparticles have been found in increased numbers in normal pregnancy [64], when there is constant deportation of trophoblast into the maternal circulation. Microparticles have been associated with several prothrombotic conditions, such as thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia, myocardial infarction, sepsis, and even pre-eclampsia [64,65]. Laude and colleagues [66] and Carp and colleagues [67] have found increased levels of circulating microparticles in women who have recurrent pregnancy loss. The question arises, however, whether endothelial microparticles are the cause of pregnancy loss or are a product of embryonic demise. As stated, in first trimester miscarriage 29% to 60% of recurrent pregnancy losses are caused by chromosomal aberrations that invariably cause abortion, regardless of the presence of microparticles or other associations or causes of pregnancy loss. Even in missed abortion caused by chromosomal aberrations, the trophoblast undergoes apoptosis with subsequent microparticle formation and thrombosis. In some patients, however, circulating endothelial microparticles may themselves induce thrombosis and subsequent loss of an apparently normal pregnancy.

Hormones and thrombosis

The hormones of pregnancy, estrogen, progesterone, and hCG, all affect thrombosis. During pregnancy, estradiol and estriol increase in concentration. Estrogen may alter the concentrations of clotting factors to a prothrombotic profile, thus promoting factor XII gene transcription [68], raising factors VII [69] and plasminogen activator (PAI-1) [70], and reducing antithrombin III [70,71]. In mice, estrogen sulfotransferase, (a cytosolic enzyme that catalyzes the sulfo-conjugation of estrogens) has a critical role in modulating estrogen activity in the placenta during mid-gestation [72]. Inactivation of estrogen sulfotransferase causes local and systemic estrogen excess and an increase in tissue factor, leading to placental thrombosis and fetal loss. In addition, estrogen can stimulate or inhibit the production of IL-1 and TNF cytokines [73–75].

The literature is divided on the effect of progesterone. Progesterone has been shown to upregulate the expression of tissue factor [76]. Progesterone can induce the production of cytokines such as IL-4, however, which is believed to inhibit coagulation [77]. The progestogen dydrogesterone inhibits production of TNFα (prothrombotic), but increases the levels of IL-4 (antithrombotic) and IL-6 (prothrombotic) [78].

In addition to its endocrine luteotrophic role, hCG could also have a local role within the uterine environment [79]. Specific binding sites for hCG have been shown in various cells of the endometrium and decidua. The local function of hCG in the endometrium has not been fully elucidated. Uzumcu and colleagues [80] assessed endometrial production of cytokines following stimulation by hCG. Increasing doses of hCG caused a dose-dependent increase in TNFα and IL-6 secretion, both of which have been reported to be thrombogenic.

Fetal thrombophilia

As placental histology usually shows fetal vasculopathy rather than maternal thrombosis, fetal thrombophilia may explain (some of) the pathologic changes. The hemostatic balance in the placenta may be determined by maternal and fetal factors cooperatively regulating coagulation at the fetomaternal interface [81]. The author has seen fetal deaths in utero in which sonograms showed complete occlusion of the umbilical blood vessels. It is impossible to say, however, whether the thromboses caused fetal death or whether the changes occurred postmortem.

Treatment

If thrombophilia is responsible for recurrent pregnancy losses, the question arises as to whether treatment with anticoagulants is warranted. In APS, treatment with heparin and low-dose aspirin is widely used. There are isolated reports [82,83] that the presence of hereditary thrombophilia warrants thromboprophylaxis. The role of treatment, however, can only be determined in well-designed, randomized trials in which the effect of treatment is compared with untreated or placebo-treated patients. As yet, there are no randomized placebo-controlled trials assessing treatment with anticoagulants in hereditary thrombophilia.

In APS, there have been no trials comparing heparin and aspirin to no treatment or placebo. A meta-analysis of three trials comparing aspirin to aspirin plus heparin [84] showed a common odds ratio of 2.63 (95% CI, 1.46, 4.75) in favor of heparin and aspirin compared with aspirin alone. Aspirin has been assessed in placebo-controlled trials. The summary in a meta-analysis [31] found that aspirin had no beneficial effect over placebo.

In hereditary thrombophilia, a recent prospective study by Gris and colleagues [85] compared enoxaparin to aspirin in patients who had thrombophilia and one pregnancy loss. Enoxaparin was found to be superior to

low-dose aspirin. This study did not distinguish between early and late pregnancy losses, however, nor did it correct for early losses caused by genetic or other factors known to affect the subsequent live birth rate. Carp and colleagues [9] reported a comparative cohort study between enoxaparin to no treatment in women who had hereditary thrombophilia and recurrent miscarriage. The primary outcome measure was the incidence of subsequent live births. A total of 26 of the 37 pregnancies in treated patients (70.2%) ended in live births, compared with 21 of 48 (43.8%) of untreated patients (OR 3.03, 95% CI, 1.12, 8.36). The beneficial effect was mainly seen in women who had primary abortions, ie, women who had no previous live births (OR 9.75, 95% CI, 1.59, 52.48). This benefit was also found in patients who had a poor prognosis for a live birth (five or more miscarriages), in whom the live birth rate was increased from 18.2% to 61.6%. Although this trial was not randomized or blinded, it is the only trial comparing the effect of treatment to a cohort of untreated patients who had hereditary thrombophilias.

There is no trial of anticoagulants comparing the effects of treatment to untreated patients regarding late obstetric complications. Although as yet there is no definite evidence of effect of anticoagulants in recurrent pregnancy loss [6], the American College of Chest Physicians recommended in its guidelines [86] that anticoagulants may be used in patients who have pregnancy complications and hereditary thrombophilia. The optimal dose of anticoagulants has not yet been determined. In a randomized prospective study, no difference was found between 40 mg or 80 mg of enoxaparin in women who had thrombophilia and pregnancy loss [87].

It seems that more basic work is required to adequately assess the place of treatment. Although such trials can be designed and assessed in the case of hereditary thrombophilia, it is doubtful if a trial can be initiated in the case of APS, in which treatment is so widespread.

The mode of action of treatment also requires clarification. It has been assumed that thrombophilia act by way of thrombosis. Anticoagulants, however, also have anti-inflammatory effects. Heparin protects against systemic harmful manifestations of TNF by increasing serum TNF binding protein [88]. Similarly, low molecular weight heparins inhibit TNFα production [89].

Heparin and low molecular weight heparins limit the anti-inflammatory response, and because thrombosis results in an inflammatory response in the vein wall [90], including neutrophil extravasation and decreasing vein wall permeability, the anti-inflammatory effects of heparins may be as relevant, if not more relevant, than its anticoagulant effects.

Summary

Many unanswered questions regarding thrombophilia and recurrent pregnancy loss exist. For example, does a true association exist? Are thrombotic mechanisms relevant? Is a second messenger necessary to cause the manifestation of thrombosis?

At present it seems that thrombophilia are associated with and may even cause some cases of pregnancy loss. The role of treatment remains to be determined. Although the aim of physicians working in this field is entirely laudable, to allow childless couples to have children, it is necessary to have good evidence of effect before treatment is given to all patients. A serious ethical dilemma remains, however, namely should treatment that may be effective be denied to patients who have prior pregnancy losses? Denial of treatment is extremely distressing for the patient and the physician. The author's own practice is to offer treatment after a full explanation, particularly because treatment is generally prescribed in the antiphospholipid syndrome and justified in hereditary thrombophilias according to the report of Carp and colleagues [12], showing a 25% improvement in live birth rates in treated patients. When treatment fails, however, the embryo should be karyotyped to exclude chromosomal aberrations.

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Thrombophilia and Adverse Pregnancy Outcome

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Women who have thrombophilia may have an increased risk for placental vascular complications, including pregnancy loss, pre-eclampsia, intrauterine growth restriction, and placental abruption. Accumulating data suggest that maternal antithrombotic prophylaxis may result in improved gestational outcome. Randomized trials are underway and, it is hoped, will optimize maternal and neonatal outcome.

Thrombophilic risk factors are common and can be found in 15% to 25% of Caucasian populations. Because pregnancy is an acquired hypercoagulable state, women having thrombophilia may present with clinical symptoms of vascular complications for the first time during gestation or at the postpartum period [1].

Hemostatic changes in pregnancy

During normal pregnancy there is a marked increase in the procoagulant activity characterized by an elevation of coagulation factors VII, X, and VIII, fibrinogen, and von Willebrand factor [2] and associated with an increase in prothrombin fragment 1 and 2 and thrombin–antithrombin complexes [3]. This increase is maximal around term. In parallel, there is a decrease in physiologic anticoagulants manifested by significant reduction in protein S activity [4] and by acquired activated protein C (APC) resistance [5]. Finally, the overall fibrinolytic activity is impaired during pregnancy but returns rapidly to normal following delivery [6]. This is largely caused by the placenta-derived plasminogen activator inhibitor type 2 that is present in substantial quantities during pregnancy [7]. D-dimer, a specific marker of fibrinolysis resulting from breakdown of cross-linked fibrin polymer by plasmin, increases as pregnancy progresses [8].

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Recent studies have focused on local placental hemostasis during pregnancy. Trophoblast expresses vascular cell characteristics. Of note, syncytiotrophoblast expresses abundant tissue factor (TF) and low levels of TF pathway inhibitor (TFPI), with the opposite findings in umbilical vein endothelial cells [9]. Taken together, these findings may be relevant to the hemostatic phenotype (bleeding or thrombosis).

Thrombophilia and fetal loss

A growing body of evidence suggests that hereditary thrombophilia is common in women who experience fetal loss. For example, a case-control study in women who have inherited thrombophilia, protein C, protein S, and antithrombin deficiencies documented an increased risk for fetal loss. In 60 women who have thrombophilia, 42 (22%) of 188 pregnancies were lost, compared with 23 (11%) of 202 control pregnancies (odds ratio [OR] 2.0, 95% confidence interval [CI], 1.2, 3.3) [10]. In addition, a high incidence of gestational abnormalities was reported in 15 women who had dysfibrinogenemia associated with thrombosis. Of 64 pregnancies, 39% ended by miscarriage and 9% ended by intrauterine fetal death [11]. In a recent study, at least one thrombophilic defect was found in 96 (66%) of 145 women who had fetal loss, compared with 41 (28%) of 145 in control subjects (OR, 5.0; 95% CI, 3.0–8.5) [12].

The association of factor V Leiden (FVL) mutation with pregnancy loss has been recently analyzed by the College of American Pathologists Consensus Conference on Thrombophilia [13,14] and at least 16 case-control studies found a high prevalence of FVL in women who had unexplained recurrent fetal loss (up to 30%) compared with 1% to 10% of control subjects (ORs ranging from 2 to 5). Despite differences in study populations and selection criteria, the results were consistent. No association between FVL and fetal loss was found by six other case-control studies. These latter studies were smaller and mostly included women who had early first-trimester fetal losses (which often are caused by non–thrombophilia-related factors). There were three retrospective cohort studies that also found that FVL carriers have a significantly increased risk for recurrent fetal loss. The risk for fetal loss is greater in homozygotes than in heterozygotes with FVL and in female siblings of thrombophilic women who have FVL [15]. Women who have thrombophilia have an increased percentage of losses at later stages of gestation [12]. Activated protein C resistance in the absence of FVL has also been associated with pregnancy loss [12,16].

A recent meta-analysis demonstrated that FVL is associated with early (OR 2.01, 95% CI, 1.13, 3.58) and late (OR 7.83, 95% CI, 2.83, 21.67) recurrent fetal loss [17]. Exclusion of women who had other pathologies associated with fetal loss strengthens the association with FVL. In this meta-analysis, APC resistance (APCR) was also associated with early recurrent fetal loss (OR 3.48, 95%, CI 1.58, 7.69).

Fetal loss has also been associated with factor II 20210G > A but not with the methylenetetrahydrofolate reductase (MTHFR) TT polymorphisms [12,18].

Differences in type of pregnancy loss (ie, primary or secondary, isolated or recurrent, consecutive or nonconsecutive) and timing (ie, first, second, or third trimester) may also influence the magnitude of these associations [19–21].

Recently, Lissalde-Lavigne and colleagues [22] reported findings from the NOHA First study, a large and carefully designed case-control study, nested in a cohort of nearly 32,700 women, 18% of which had pregnancy loss during the first gestation. After analyzing the characteristics of 3,496 pairs of women who had an unexplained pregnancy loss and normal pregnancy control subjects, the investigators describe the incidence of FVL and factor II G20210A in these groups. Notably in this study, the great majority (85%) of losses were after 10 weeks' gestation, partly because of careful exclusion of other causes of pregnancy loss. The findings of the multivariate analysis clearly demonstrate an overall association between unexplained first pregnancy loss and the two thrombophilic risks factors (OR, 3.09 and OR, 2.34, respectively). The association results from the 3,065 women who had losses after 10 weeks of gestation (OR, 3.46 and OR, 2.60, respectively) but were not found in women who had losses between 3 and 9 weeks of gestation. As unexplained first pregnancy loss occurred in approximately 10% of gestations, the findings of this study may have significant clinical impact, because it is now clear that women who had first unexplained pregnancy loss after 10 weeks of gestation should be screened for thrombophilia.

Until recently studies on treatment of women who have inherited thrombophilia and pregnancy loss were predominantly uncontrolled and included small series of patients treated mostly with low molecular-weight heparin (LMWH). A recent collaborative study demonstrated the safety of using LMWH during 486 gestations [23]. A successful outcome was reported in 83 (89%) of 93 gestations in women who had a history of recurrent pregnancy loss and in all 28 gestations in women who experienced pre-eclampsia during a previous pregnancy. A retrospective French study on use of enoxaparin during 624 pregnancies revealed a good safety profile [24]. More recently a review of close to 2,800 treated pregnancies evaluated safety and efficacy of LMWH in pregnancy [25]. The main indications were prophylaxis of VTE and prevention of pregnancy loss. Rate of bleeding complications was low (<2%) and thrombocytopenia was rare, with no cases of heparin-induced thrombocytopenia. Likewise, clinically significant osteoporosis was extremely rare. Live birth rate was 85% to 96%, depending on the indication for treatment.

The author's group has treated 61 pregnancies in 50 women who had thrombophilia and who presented with recurrent fetal loss with the LMWH enoxaparin throughout gestation and 4 to 6 weeks into the postpartum period. Enoxaparin dosage was 40 mg/d, except for patients who had combined thrombophilia or in the case of abnormal Doppler velocimetry

suggesting decreased placental perfusion, in which case the dosage was increased to 40 mg twice a day. Of the 61 pregnancies, 46 (75%) resulted in live birth, compared with a success rate of only 20% in these 50 women in prior gestations without antithrombotic therapy [26].

Carp and colleagues [27] reported a cohort study undertaken to assess the effect of enoxaparin on subsequent live birth rate in women who had three or more consecutive pregnancy losses and hereditary thrombophilia. Live birth rate was higher in women treated with enoxaparin: 26 (70.2%) of 37, compared with 21 (43.8%) of 48 in untreated patients. The beneficial effect was mainly in women who had primary abortions and in those who had five or more miscarriages.

The optimal dosage of LMWH is yet unknown and should be determined by prospective randomized trials. Ideally large placebo-controlled trials should be advocated. Logistic and ethical difficulties, however, limit such an approach. A recent study by Gris and colleagues [28] demonstrated that in women who had thrombophilia and previous one pregnancy loss after 10 weeks' gestation, enoxaparin at a dose of 40 mg daily resulted in a significantly better live birth rate compared with low-dose aspirin (86% versus 29%, respectively). The differences were found in women who had FVL and factor II G20210A and in women who had protein S deficiency.

LIVE-ENOX is a multicenter, prospective, randomized study recently conducted in Israel comparing two doses of enoxaparin, 40 mg/d and 40 mg/every 12 hours, starting at 5 to 10 weeks of gestation, throughout pregnancy, and for 6 weeks postpartum to women who had thrombophilia and pregnancy loss [29] (defined as three or more first trimester, two or more second trimester, and at least one third trimester loss). The primary efficacy endpoint was the delivery of a healthy infant. Other efficacy endpoints were duration of gestation, birth weight, and incidence of gestational thrombosis and gestational vascular complications (pre-eclampsia, placental abruption, and IUGR). Safety endpoints were infant and maternal bleeding episodes, maternal thrombocytopenia, infant health (weight, gestational age, Apgar score at 5 minutes), and any drug-related adverse events. In the LIVE-ENOX study, the incidence of pre-eclampsia in the enoxaparin 40 mg/day and 80 mg/day groups was 6.7% and 14.3%, respectively, and the incidence of placental abruption was 13.5% and 8.8%, respectively. Approximately one quarter of the women in both groups had IUGR in previous gestations (22.5% and 24.2%, respectively). Of the 180 women enrolled, live birth rate before the study was only 28%, but during the study, live birth rates were 84% for the 40 mg/d group and 78% for the 80 mg/d group. Late gestational complications decreased after enoxaparin treatment. The incidence of pre-eclampsia in the enoxaparin 40 mg/day and 80 mg/day groups was 3.4% and 4.4%, respectively. Similarly, the incidence of placental abruption in the enoxaparin 40 mg/day and 80 mg/day groups was 4.5% and 3.3%, respectively [30]. Both doses of enoxaparin seemed to be safe and well tolerated. The gestation period was greater than 36 weeks in more than 80% of

patients in each group. Preterm delivery, however, occurred in 10% and 18.5% of women in the enoxaparin 40 mg/day and 80 mg/day groups, respectively. Postpartum bleeding (1.1% of women in each group) and enoxaparin-related allergic local skin reactions at the injection sites were observed in a small number of women (2.2% and 3.3% of those receiving 40 mg/day and 80 mg/day, respectively). Prophylaxis with enoxaparin (40 mg/day or 80 mg/day) is thus safe and effective for improving pregnancy outcome and reducing late pregnancy complications in thrombophilic women who have a history of pregnancy loss.

Thrombophilia and intrauterine growth restriction

Risk factors for IUGR are of maternal, fetal, or placental origin. Maternal causes include chronic vascular diseases and inherited or acquired thrombophilia. Chronic abruption and extensive infraction are among the placental abnormalities. The association of IUGR and thrombophilia is controversial, however. Such an association was demonstrated in women who had severe IUGR but not in milder cases. Martinelli and colleagues [31] studied 63 women who had a history of IUGR defined as birth weight under the tenth percentile, and 93 parous women with uneventful pregnancies. Among women who had IUGR, 13% had FVL compared with 2.2% in control subjects (OR 6.9, 95% CI, 1.4, 33.5), and 12% had prothrombin mutation compared with 2.2% in control subjects (OR 5.9, 95% CI, 1.2, 29.4). In a regression analysis model these thrombophilia factors were independently associated with IUGR. A later report from the same group [32] tested these mutations in neonates weighing less than 2,500 g. Neonates delivered by mothers who had FVL or prothrombin mutations accounted for 30% of newborns weighing less than 1,000 g, 18.7% weighed between 1,001 to 2,499 g, and only 9.5% weighed 2,500 g or more. Overall, 27.6% of neonates of mothers who had the mutations weighed less than 2,500 g, compared with 13.9% of the neonates born to mothers who did not have mutations (OR, 2.4; 95% CI, 1.5–3.7). Recently, Infante-Rivard and colleagues [33] did not find an association between thrombophilic mutations and IUGR of less than the tenth percentile. In this study the prevalence of thrombophilia in mothers of 493 newborns who had IUGR and 472 control subjects did not differ significantly. One third of the studied population, however, was non-Caucasian and the degree of IUGR was mild, with a mean birth weight of 2,393 $\pm$ 606 g, and 83% of the newborns were delivered at 36 to 40 weeks' gestation. In contrast, in the study by Kupferminc and colleagues [34] the mean birth weight and gestational week were much lower: 1387 $\pm$ 616 g and 33 $\pm$ 4.0, respectively.

Data on antithrombotic prophylaxis for IUGR at an index pregnancy and on subsequent gestations in women who have thrombophilia are limited. In the LIVE-ENOX study, IUGR was uncommon, occurring in 7 of 65 (10.8%) infants and in 5 of 63 (7.9%) infants in the 40 mg/day and

80 mg/day enoxaparin groups, respectively. The IUGR was mild in all but one case in both treatment groups (1.5%). Regression analysis showed that birth weight correlated well with gestational week of delivery ($r = .82$ and $r = .84$ for the 40 mg/day and 80 mg/day enoxaparin groups, respectively) [30]. In view of the risk for recurrences of other gestational complications, including IUGR, and the results of the LIVE-ENOX study [30], antithrombotic prophylaxis might be considered in this setting.

Thrombophilia and pre-eclampsia

Pre-eclampsia is found in 3% to 7% of pregnancies and is a leading cause of maternal and fetal life-threatening complications. In pre-eclampsia, the placental vasculature fails to become a high-volume, low-pressure system, which is the earliest difference that can be detected between pre-eclamptic and normal pregnancies. Widespread deposition of fibrin and vascular damage normally occur in hypertensive disorders of pregnancy, suggesting an activation of the coagulation cascade in this condition [35]. Recent reports suggest that vascular endothelial growth factor is decreased in pre-eclampsia [36,37] and this fact may be relevant for novel therapeutic modalities for this disorder.

The association of pre-eclampsia and thrombophilia is controversial. Several case-control studies have demonstrated an association, whereas other studies failed to support this occurrence. Hemolysis, elevated liver enzymes low platelet count (HELLP) syndrome is a severe form of pre-eclampsia manifesting disseminated platelet aggregation and liver dysfunction and necessitating early emergent termination of pregnancy. This syndrome may be associated with thrombophilia, particularly with the FVL mutation [38].

Kupferminc and colleagues [34] found that the prevalence of thrombophilia in 110 women who had severe obstetric complications was 65% compared with 18% in 110 control subjects. Women who had obstetric complications also had a significantly higher incidence of combined thrombophilia. The results showed a higher prevalence of the thrombophilic polymorphisms, FVL, factor II 20210G > A, and MTHFR 677TT in women presenting with pre-eclampsia. In a sample of 140 Italian women who had a history of gestational hypertension with or without significant proteinuria, a higher prevalence of thrombophilic risk factors was documented regardless of the presence of proteinuria [39]. Logistic regression showed that FVL and factor II 20210G > A mutations were independently associated with occurrence of gestational hypertension.

Other studies failed to find an association between a common genetic risk factor for thrombosis and the occurrence of pre-eclampsia [40]. These studies seem to differ, however, in selection of control subjects and in ethnic backgrounds. A recent meta-analysis demonstrated an association with FVL and factor II 20210G > A only in women who have severe early onset of pre-eclampsia [41]. More recently, an Italian case-controlled study

evaluated for inherited and acquired thrombophilia a total of 808 Caucasian patients who developed pre-eclampsia (cases) and 808 women who had previous uneventful pregnancies (control subjects), match for age and parity [42]. Women who had severe pre-eclampsia (406 cases) had a higher risk (OR 4.9, 95% CI, 3.5, 6.9) of being carriers of an inherited or acquired thrombophilic factor, except for protein S, protein C, and antithrombin deficiency. In women who had mild pre-eclampsia (402 cases), only prothrombin and homozygous MTHFR gene mutations were significantly more prevalent than in the control subjects. Thrombophilic patients who have severe pre-eclampsia are at increased risk for acute renal failure (OR 1.8, 95% CI, 1.5, 2.2), disseminated intravascular coagulation (OR 2.7, 95% CI, 1.1–6.4), abruptio placentae (OR 2.6, 95% CI, 1.2, 6.0), and perinatal mortality (OR 1.7, 95% CI, 1.5, 2.2) compared with non-thrombophilic pre-eclamptic patients. This study demonstrated a significant association between maternal thrombophilia and severe pre-eclampsia in Caucasian women. Thrombophilia also augments the risk for life-threatening maternal complications and adverse perinatal outcomes in pre-eclamptic patients.

In the 1980s, the potential benefit of aspirin in prevention of pre-eclampsia was raised and refuted. To date there are no placebo-controlled trials on prevention of pre-eclampsia at subsequent gestation with LMWH. Several small studies, however, have suggested a benefit in outcome of subsequent gestations after antithrombotic prophylaxis [43,44]. The results of these studies and the LIVE-ENOX trial [30] suggest that LMWH may be of benefit in this setting, but randomized controlled trials are warranted.

Hyperhomocysteinemia and MTHFR 677

Homocysteine levels decrease in pregnancy by 50%. Gestational vascular complications can be associated with hyperhomocysteinemia documented in 26% of women who had placental abruption, in 11% of cases with intrauterine fetal death, and in 38% of women delivering infants whose birth weight was less than the fifth percentile compared with an estimated 2% to 3% in control subjects [45]. In the Hordaland Homocysteine Study, the largest performed to date, plasma homocysteine levels were evaluated in 5,883 women with 14,492 pregnancies [46]. When comparing the upper with the lower quartile of plasma homocysteine levels, the adjusted risk for pre-eclampsia was 1.32 (95% CI, 0.98, 1.77), for prematurity it was 1.38 (95% CI, 1.09, 1.75), for very low birth weight it was 2.01 (95% CI, 1.23, 3.27), and for stillbirth it was 2.03 (95% CI, 0.98, 4.21).

In a recent meta-analysis, Nelen and colleagues [47] reviewed 10 case-control studies that examined the association of fetal loss and hyperhomocysteinemia and reported a three- to fourfold increased risk, whereas in six other studies the odds ratios for homozygosity for MTHFR were not significant. These data suggest that although hyperhomocysteinemia is a risk factor for recurrent fetal loss, homozygosity for MTHFR as a solitary

thrombophilic defect is not. Testing for MTHFR 677TT, however, may be of value in women who have relative decreased folate and vitamin B12 levels commonly acquired during pregnancy and for identifying women who have a combination of MTHFR 677TT with other thrombophilic factors who may be at higher risk during gestation [48].

Combined thrombophilic risk factors

Thrombophilic risk factors can be found in up to 25% of certain populations. Combinations of thrombophilic risk factors thus are not uncommon and, in fact, can be found in up to 5% of Israeli women who have pregnancy loss [12]. Women who have combined thrombophilia may be at a particularly high risk for gestational vascular complications, and therefore require close management and may need higher doses of LMWH. Because homozygosity for MTHFR is common worldwide, with an estimated prevalence of 10% to 25% among various ethnic groups, combinations of other thrombophilic risk factors with homozygosity for MTHFR are common. Indeed, combinations of thrombophilic risk factors may further increase the risk for recurrent fetal loss. The European Prospective Cohort on Thrombophilia (EPCOT) study documented the highest odds ratio for stillbirth (OR,14.3; 95% CI, 2.4, 86) in patients who had combined thrombophilic defects [19].

Combined thrombophilic defects were documented in 31 (21%) of 145 women who experienced pregnancy loss, compared with 8 (5.5%) of 145 in control subjects (OR, 5.0; 95% CI, 2.0, 11.5) [12]. In the Nimes Obstetricians and Haematologists Study 5 (NOHA5), placental pathologic vascular findings were documented in 88% of women who had combined thrombophilia and in 100% of those who had a combination of any thrombophilia and MTHFR 677TT [48].

Inherited thrombophilias and abruptio placentae

Placental abruption is an uncommon clinical presentation occurring in 0.5% of gestations, but one that carries a high fetal mortality and significant maternal risk. Risk factors for placental abruption include pre-eclampsia, prior abruption, sudden uterine decompression, chemical teratogens, external trauma, and uterine malformations. A potential association with thrombophilia is suggested by several studies. Wiener-Megnagi and colleagues [49] studied 27 women who had abruptio placentae and 29 control subjects matched for age, parity, and ethnic origin. Of the case patients, 63% had an activated protein C ratio of 2.5 or less, compared with 17% of control subjects, with an OR of 8.16. Of 15 patients, 8 were found to have FVL, compared with 1 heterozygote in the control subjects (3.4%). In another study, thrombophilia was found in 70% of 20 women who had abruptio placentae [50], and the OR for factor II 20210G > A mutation was 8.9 (95%

CI, 1.8, 43.6), whereas the OR for FVL was 4.9 (95% CI, 1.0, 17.4). An increased prevalence in first-degree relatives for venous thrombosis in women who had placental abruption indicates a higher prevalence of thrombophilia. Based on these data and in the absence of prospective clinical trials on subsequent gestation, these women may be offered prophylaxis with LMWH.

Unresolved issues

Fetal genotype

Although there are reports that fetal thrombophilia is important for the outcome of pregnancy [51], there are several reasons to suggest that this may not be the case. First, most thrombophilic polymorphisms are mild risk factors for gestational vascular complications and gestational VTE. Second, thrombotic changes are noted mainly on the maternal side of the uteroplacental unit. Third, LMWH that does not cross the placenta is beneficial. Unless there is a severe thrombophilic defect (ie, homozygous protein C deficiency), fetal thrombophilic state is thus probably not a major contributor to gestational vascular complications or VTE.

Local hemostatic mechanisms

A recent study evaluated TF-TFPI balance in placental sections [52]. The study revealed a decrease of TFPI levels in women who had gestational vascular complications and its normalization in women who had a history of recurrent fetal loss and thrombophilia who were treated with enoxaparin during the index gestation. LMWH stimulates expression, synthesis, and release of TFPI in endothelial cells. As LMWH does not cross the placenta to the fetus, we hypothesize that enoxaparin exerts its effect in pregnant women who have thrombophilia by modulating local hemostasis on the placental syncytiotrophoblast surface.

Monitoring of low molecular-weight heparin therapy

A recent study investigated the modulation of systemic hemostatic parameters by enoxaparin in women who have recurrent pregnancy loss and evaluated plasmatic parameters that would potentially enable monitoring LMWH prophylaxis effect during pregnancy [53]. Plasma Anti-Xa levels at 10 to 15 weeks of gestation were higher (0.39 ± 0.38 U/mL in the successful pregnancy outcome group compared with the abortion group). Prophylactic anti-Xa activity levels (0.28 ± 0.13 U/mL) were documented from 15 weeks of gestation until delivery in the successful pregnancy outcome group. D-dimer antiprothrombin 1 plus 2 levels seemed to be significantly

increased, whereas APC-SR and free protein S levels gradually decreased during pregnancy, with no difference between study groups. LMWH prophylaxis during pregnancy thus enables modulation of systemic hemostatic parameters by way of inhibition of factor Xa and increases in plasmatic total and free TFPI levels.

Does aspirin have a role?

The role of aspirin, if any, in the setting of thrombophilia and vascular gestational abnormalities remains to be confirmed. Currently, as an extrapolation to studies with unfractionated heparin (UFH) [54] in patients who have antiphospholipid syndrome, aspirin is prescribed, together with LMWH. Whether aspirin has an added value to UFH or LMWH alone, however, has not been evaluated.

Women who have unexplained pregnancy complications

When evaluation for current known thrombophilia factors is negative, one of the possibilities is that a yet-undiscovered thrombophilia factor may be present and may be implicated in the placental thrombotic changes that can be found in women who have severe gestational vascular complications without thrombophilia. Following preliminary experience with antithrombotic therapy in these women, prospective randomized multicenter trials are currently underway in these settings.

Future perspectives

There are several issues in this field that probably need to be addressed in the coming years. First, as of now 30% to 50% of vascular gestational pathologies cannot be accounted for by currently available tests for thrombophilia. Whether other genetic or acquired thrombophilia will be found remains to be determined. Polymorphisms at the thrombomodulin and endothelial protein C receptor genes [55] may be associated with recurrent fetal loss. Circulating microparticles identified by flow cytometry have recently been suggested to play a role in women who have recurrent fetal loss [56]. Although the involved mechanism has not been established, it is intriguing to speculate whether antithrombotic strategies will be of value in this setting [57].

Second, in view of the potential association of thrombophilia and recurrent fetal loss and the high prevalence of thrombophilia in the Caucasian populations, issues of screening are raised. As complete thrombophilia work-up is currently elaborate and costly, screening tests are highly warranted. One such potential assay is the protein C global test, which in a preliminary study was found to be abnormal in most women who had recurrent fetal loss and could also identify women who have recurrent fetal loss who do not have any other thrombophilic defect [58].

Third, the pathogenetic mechanisms responsible for placental vascular pathologies in women who have thrombophilia have not been elucidated, and it is yet unknown why certain women who have thrombophilia express vascular gestational pathologies and others do not. It is possible that this may relate to local factors affecting coagulation, fibrinolysis, and vascular tone at the level of placental vessels. A recent study demonstrates that a fetomaternal cross-talk in the placental vascular bed may result in control of coagulation by trophoblast cells [59]. Spontaneous differentiation of trophoblast stem cells is associated with the acquisition of an endothelial cell-like thromboregulatory gene expression program and is developmentally regulated and conserved between mice and humans. These observations define candidate fetal genes that are potential risk modifiers of maternal thrombophilia-associated pregnancy complications. In addition, they provide evidence that coagulation activation at the fetomaternal interface can affect trophoblast physiology, altering placental function.

Finally, the role of antithrombotic modalities deserves prospective clinical trials to improve results in a large population of women who currently experience poor gestational outcome. Future trials should focus on efficacy and safety of tailored therapy for specific thrombophilic polymorphisms in a particular gestational complications setup.

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Fetal and Neonatal Thrombophilia

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The incidence of thromboembolic events among children is much lower than among adults [1–3]. Among children, neonates exhibit the highest risk, with a reported incidence of 0.24 to 0.51 per 10,000 births for venous thrombosis [3–5].

The pathogenesis of any vascular thrombosis stems from acquired and inherited causes; the latter are defined as inherited thrombophilia [6]. The most common genetic thrombophilias include the substitution of arginine by glutamine at amino acid residue 506 in the coagulation factor V (Factor V Leiden [FVL]) [7] and a glutamine-to-arginine transition at position 20,210 of the 3′ untranslated region of the factor II gene (FIIG20210A) [8]. In addition, the homozygous state of the cytosine-to-thymine transition at position 677 polymorphism of 5,10-methylenetetrahydrofolate reductase (MTHFR) gene may be associated with vascular disease, possibly due to increased plasma homocysteine levels [9]. Genetic prothrombotic risk factors play an important role in the pathogenesis of infantile thrombosis [1–5]. Occurrence of thrombosis is often triggered by additional predisposing factors, such as sepsis, cancer, or the presence of central lines [10–12].

The dynamic hemostatic process begins in-utero. Coagulation factors are synthesized by the fetus by 10 weeks gestational age, and their concentrations gradually increase, being physiologically lower in premature infants as compared with full-term babies or healthy children [1,13,14]. In the neonate, plasma concentrations of vitamin-K–dependent coagulation factors (II, VII, IX, X) and contact factors (XI, XII, prekallikrein, and high-molecular-weight kininogen) are about 50% of adult values [13,14]. Furthermore, the capacity of newborns to generate thrombin, dependent upon plasma concentrations of procoagulants, is reduced [1,14,15]. These facts, theoretically increasing the risk of severe bleeding, are balanced by the protective

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effects of physiologic deficiencies of the inhibitors of coagulation and by the decreased fibrinolytic capacity in infants [14,16,17], whereas the latter factors may account for the higher prothrombotic risk of neonates as compared with older children.

Premature infants confer a unique subgroup and thus deserve special attention. Prematurity is associated with increased risk of neonatal complications, and among the potential factors affecting the prevalence of these conditions are those influencing blood flow and perfusion pressure, thus promoting vascular insufficiency and vessel occlusion. The relations between maternal and fetal thrombophilia and their potential influence upon pregnancy outcome have not been clarified. Inherited maternal thrombophilia increases the risk for venous thrombosis during pregnancy [18]. Recently, it has been reported to increase the risk of fetal loss [19] and other pregnancy complications, including fetal (intrauterine) growth restriction (IUGR), abruptio-placenta, stillbirth, and pre-eclampsia [20,21]. Thrombotic vasculopathy of the placenta may be associated with maternal thrombophilia and neonatal thrombosis [22]. The association between thrombophilia of the neonate and perinatal complications, such as IUGR, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and other conditions, remains to be elucidated. This article discusses the available data regarding the potential role of thrombophilic risk factors and their association with various types of perinatal thrombosis and other fetal and perinatal complications.

Perinatal arterial stroke and cerebral palsy

Perinatal arterial ischemic stroke (PAS) occurs between 28 weeks gestation and 7 days of age [23], although studies of PAS often refer to cerebrovascular events occurring up to 28 days of life. Its prevalence is 1 in 4000 live births [23,24]. Newborns who have arterial infarction may present acutely during the neonatal period with neurologic symptoms such as seizures [23,24] or may be clinically asymptomatic until several months of age, when signs of motor impairment or seizures are first noted, leading to a delayed diagnosis of PAS [25–28]. Whether the infants presenting with acute or delayed clinical signs of PAS differ regarding the timing of injury, underlying pathogenesis, and neurologic outcome is unknown.

Perinatal arterial stroke has received increased attention as an important cause of cerebral palsy (CP) and other neurologic disabilities, including epilepsy and cognitive impairment [29–36]. Although PAS is diagnosed primarily in neonates who are born at term and is responsible for at least 22% to 70% of congenital hemiplegic CP in this population [23,24,32], CP prevalence is about 1 in 500 live births and occurs mostly in preterm babies, being sometimes associated with PAS.

The cause of PAS is poorly understood. Investigators have reported a number of obstetric and neonatal complications in the setting of perinatal

stroke. The clinical diagnosis of ''birth asphyxia'' has been considered a risk factor for PAS but may represent signs of the consequences of cerebral infarction unrelated to the underlying causal mechanism [24,32]. Other conditions include maternal pre-eclampsia, chorioamnionitis, fetal cardiac anomalies, polycythemia, and systemic infection [29,35,37–42]. Due to the paucity of data, more controlled studies are required to establish a significant difference in the frequency of perinatal complications between infants with PAS as compared with healthy control subjects.

The role of genetic thrombophilias in the pathogenesis of PAS and CP is yet to be defined. Factor V Leiden (FVL) mutation, the prothrombin mutation (FIIG20210A), hyperhomocystinemia, and elevated lipoprotein (a) levels have been described with increased frequency in infants who have PAS when compared with healthy control subjects [43–51]. Nonetheless, most studies describe only a small number of children or lack an adequate comparison group to assess the significance of potential risk factors. In a recent case-controlled study, nonstroke CP was not associated with a higher prevalence of genetic thrombophilic markers as compared with control subjects [52]. Because PAS is a serious thrombotic event that may stem from maternal and fetal risk factors, we recommend a full thrombophilia assessment to be performed for all infants presenting who have PAS or stroke-associated CP. Selected maternal populations (eg, mothers of ''thrombophilic'' families or mothers with pregnancy complications) may benefit from such screening tests. Further studies are required to better define the potential role of infantile and maternal thrombophilia in the pathogenesis and outcome of PAS and CP.

Cerebral sinus venous thrombosis

Cerebral sinus vein thrombosis (CSVT) is a serious and rare disorder with a reported annual incidence of 0.67 per 100,000 children, with a peak incidence noted among neonates [53]. The etiology and pathophysiology of CSVT in the pediatric population is poorly understood, and the role of thrombophilic risk factors remains to be elucidated [53–58]. Most information about childhood and perinatal CSVT derives from two large studies. The Canadian pediatric stroke registry reported 160 consecutive pediatric and neonatal CSVT patients, recruited from 16 tertiary referral centers since 1992 [53], and the German childhood stroke study group reported on 149 pediatric patients (median age, 6 years) who had CSVT whose data were collected between 1995 and 2002 [58]. Children presented with focal or diffuse neurologic manifestations, and the neurologic deficits persisted in 38% of the Canadian patients. Comorbid risk factors, such as head and neck disorders and acute and chronic illnesses, were demonstrated in 29% to 54% of the Canadian cases, whereas 70% of German patients presented with underlying clinical conditions. The prevalence of prothrombotic risk factors was

41% and 56.4% of patients in the Canadian and German studies, respectively. Most patients (50% and 87% of the Canadian and German patients, respectively) were treated by anticoagulants. The impact of this treatment on the long-term prognosis has not been determined. Controlled studies addressing the role of thrombophilia in this rare disorder at the perinatal period only are not available. Nonetheless, testing is recommended for all infants diagnosed to define future prothrombotic risks and potentially affect decisions regarding the length of anticoagulant therapy required.

Renal vein thrombosis

Renal venous thrombosis (RVT), although rare in adults, is a well recognized and potentially fatal entity in children and neonates [4,5,59]. RVT is by far the most common manifestation of neonatal thrombosis: the overall incidence of thromboembolic events in the neonatal period is 5 per 100 000 births. More than 40% of all thrombotic manifestations in this age group are symptomatic RVTs [5]. The incidence decreases significantly after the first year of life. Persisting impairment of kidney function and the need for renal replacement therapy are serious and common complications in patients who have RVT [61]. RVT may present with a clinically palpable enlargement of the kidney in association with hematuria, proteinuria, renal failure and oliguria, hypertension, or thrombocytopenia. Long-term functional impairments include hypertension and renal insufficiency [60–62]. Ultrasound and color Doppler ultrasound are the diagnostic techniques most commonly used in the evaluation of neonates who have suspected RVT [61].

The etiology of RVT is not fully understood. Predisposing factors for neonatal RVT include dehydration, sepsis, birth asphyxia, polycythemia, maternal diabetes, traumatic delivery, congenital renal vein defects, and an indwelling umbilical venous catheter [59–62].

Little is known of the role of inherited prothrombotic risk factors in the development of spontaneous or exogenously triggered RVTs in children. FVL mutation and other hereditary prothrombotic risk factors are strong determinants of thromboembolic complications in pediatric patients [63,64]. Their role in the pathogenesis of neonatal renal venous thrombosis is not clear. Moreover, the published studies on this disease are few, and follow-up data on the functional outcome after neonatal RVT in larger numbers of patients are lacking [65–69]. In a recent case-controlled study comparing 59 consecutively recruited white neonates who had RVT and 118 control subjects in Germany, 32 (54.2%) of the cases showed underlying clinical conditions; 40 (67.8%) of these infants and 23 (85.2%) of the 27 infants with idiopathic RVT showed at least one thrombophilic risk factor. Univariate analysis revealed significantly elevated odds ratios (OR) 95% confidence intervals (CI) for FVL and Lp(a). Deficiencies of protein C, antithrombin, and anticardiolipin antibodies were also more prevalent in the

patient group. Multivariate analysis calculated significant OR and 95% CI only for FV (OR, 9.4; 95% CI, 3.3–26.6) and elevated Lp(a) (OR, 7.6; 95% CI, 2.4–23.8), implying that these thrombophilic risk factors may play a significant role in the pathogenesis of neonatal RVT [68]. Another retrospective cohort study by a Canadian group reported on thrombophilic risk factors in 43% of 28 patients studied [69]. Further studies are required to define the efficacy of anticoagulant or thrombolysis for treatment of RVT and the optimal therapy length in infants with or without thrombophilia.

Other neonatal complications

The relations between thrombophilia of the full-term or premature neonate and low birth weight are controversial [70,71]. Some case reports and small case series have noted an increased incidence of thrombophilic risk factors in selective cohorts of neonates who have vascular complications, such as intraventricular hemorrhage [72], retinopathy of prematurity, and necrotizing enterocolitis. Hypercoagulability may also be associated with neonatal morbidity [74] and late neurologic sequelae [46]. Infants who have low birth weight may be born to mothers who have thrombophilia, resulting in placental infarction and intrauterine growth retardation [19,21,22].

Fetal thrombophilia may result from low birth weight. In a retrospective analysis, von-Kries and colleagues [70] stated that a higher odds ratio for birth weight in the lowest quartile was observed among children carrying prothrombotic risk factors. This conclusion was not supported by Rivard and colleagues [71] in a recent large case-controlled study.

Prematurity may be associated with vascular complications. NEC is frequently accompanied by hematologic abnormalities, including evidence for intravascular coagulation [74]. Nonetheless, whether thrombophilic risk factors promote the occurrence of NEC or its severity remains to be proven.

Retinopathy of prematurity (ROP) is considered as a multifactorial disease and was reported to be associated with low birth weight, prematurity, perinatal morbidity, and prolonged mechanical ventilation [75,76]. The suggested mechanism for ROP is of hypoxia-induced angiogenesis [77]. Low levels of insulin-like growth factor I were shown to suppress vascular endothelial growth factor signaling in retinal endothelial cells, promoting formation of avascular, hypoxic retina [78]. Vasculogenesis may be influenced by the presence of thrombophilic risk factors [79]; however, this could not be supported by a recent single-center prospective Israeli study because the incidence and severity (grade) of ROP was similar among premature infants who had thrombophilia as compared with nonthrombophilic infants of the study group [80]. In this study, the association of thrombophilia and neonatal complications was evaluated. The prevalence of genetic prothrombotic markers (FVL, MTHFR, FII20210A) and plasma homocysteine levels were assayed in 166 premature (mean gestational age, 30.9 $\pm$ 2.3 weeks) and

low-birth-weight (mean weight, 1327 ± 319 g) infants. The occurrence of any neonatal complications was compared between infants with and without thrombophilia. The prevalence of perinatal complications and the severity of diseases were similar among infants with or without thrombophilia [80], although the numbers of patients within any subgroup of complications was small. Larger studies are required to assess these findings.

It has been suggested recently that IVH may be triggered by thrombophilia, especially by the presence of FVL [72]. The possible pathogenesis may be vessel occlusion triggering high-pressure bleeding. The incidence of FVL was increased among infants reported in two case-series with IVH and as hydrocephalus [73,81]; however, the occurrence of periventricular leukomalacia (PVL) in patients who had IVH was not increased among FVL-heterozygous patients [73]. In the Israeli study [80], neither the occurrence of IVH nor the severity of IVH were associated with thrombophilia, and similar findings were shown for the occurrence of PVL, although most of the cases diagnosed with PVL in this study group did not stem from IVH.

Summary

Thrombophilia of the fetus and neonate may contribute to higher prevalence of perinatal thrombosis. Due to the potential interaction between thrombophilic risk factors of the neonate and maternal thrombophilia and placental vasculopathy, we recommend thrombophilia assessment be performed in any child and in the mother in case of perinatal thrombosis. Further attention and larger prospective studies are required to establish the role of thrombophilic risk factors in the pathogenesis of any other perinatal complications.

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Exogenous Sex Hormones and Thrombophilia

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Worldwide, hundreds of millions of women use exogenous estrogens in contraceptives or for postmenopausal hormone replacement [1]. Exogenous estrogens increase the risk for venous and arterial thrombosis. Since 1961, when a woman who had used a compound containing 100 μg of mestranol for the treatment of endometriosis presented with a pulmonary embolism, it has been evident that the use of female sex hormones may be associated with an increased risk for venous thrombosis [2]. Shortly after the first case of pill-related venous thrombosis was reported, a case of myocardial infarction in a woman using an oral contraceptive was described [2,3].

Effects of contraceptive or hormone replacement therapy on hemostasis

Use of combined oral contraceptives (COCs) or hormone replacement therapy (HRT) has many effects on hemostasis, lipids, and inflammatory markers [4–11]. With increased levels of coagulation factors VII, IX, X, XII, and XIII and reduced levels of the natural anticoagulants protein S and antithrombin, the overall effect is a prothrombotic shift in the hemostatic balance. The effects on the levels of procoagulant, anticoagulant, and fibrinolytic factors are more marked with COCs containing third generation progestogens than with those containing second generation progestogens [12–15]. Compared with women not using COCs, plasma from COC users has significantly increased resistance to activated protein C (APC) [7,9] and plasma from women who use third generation COCs has significantly greater APC resistance than plasma from users of second generation COCs [12,16].

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The changes that HRT induces in hemostasis are similar in direction but lesser in magnitude than those associated with COC—a trend toward increased thrombin generation with a slight reduction in the levels of antithrombin and protein S [17–19] and increased acquired APC resistance [20]. Several studies have demonstrated that, in general, the effects on hemostasis of estrogen only and estrogen plus progestogen preparations are similar [21–23], although the increase in clotting factor VII levels demonstrated in the women taking unopposed estrogen is not seen in women using estrogen plus progestogen preparations [21,23]. The effects of oral HRT preparations on hemostasis seem to be greater than the effects of nonoral preparations, reflecting that oral preparations undergo "first pass" hepatic metabolism [24,25].

Oral contraceptives

COCs contain an estrogen and a progestogen. The progestogen prevents ovulation and the estrogen minimizes the risk for breakthrough bleeding. Since COCs were first licensed in 1959, the dose of estrogen has been reduced. The earliest COCs contained 150 μg of mestranol. Nowadays some contain as little as 15 to 20 μg of ethinyl-estradiol. In addition to changes in estrogen dose, the chemical composition of the progestogen content has been successively altered. Early COCs contained so-called first generation progestogens—norethisterone, norethynodrel, lynestrenol, or ethynodiol acetate. In the 1970s, these were replaced by COCs containing second generation progestogens—norgestrel, levonorgestrel, or norgestrione. COCs containing third generation progestogens—gestodene, desogestrel or norgestimate—were introduced in the 1980s. The newest COCs contain cyproterone acetate or drospirenone.

Oral contraceptives and venous thrombosis

A case control study published in 1967 reported a threefold increased risk for venous thrombosis in COC users compared with nonusers [26]. Later studies confirmed this increased risk [27–33]. There is little evidence that decreasing the estrogen content has significantly reduced the incidence of venous thrombotic events caused by COCs [1]. A meta-analysis published in 2005 reported an overall odds of developing venous thrombosis among COC users approximately three times greater than that of nonusers (Table 1) [34]. The increased risk is effective from commencement of COC use, is not incremental with duration of use, and disappears when COC use ceases. The increased risk is most pronounced in the first year of use [35].

In late 1995 a series of articles was published that reported that COCs containing third generation progestogens are associated with a higher relative risk for venous thrombosis than are second generation COCs [36–38]. These findings were unexpected and attracted a great deal of attention.

Table 1
Odds ratios for venous thrombosis associated with thrombophilia and oral contraceptive use

	Odds ratio	95% CI
Oral contraceptive users without thrombophilia	3.10	2.17–4.42
Oral contraceptive nonusers with thrombophilia		
Factor V Leiden	3.78	2.22–6.42
Prothrombin 20210A	1.34	0.81–2.23
Factor V Leiden+prothrombin 20210A	4.03	1.01–16.01
Protein S deficiency	5.31	2.48–11.37
Oral contraceptive users with thrombophilia		
Factor V Leiden	15.62	8.66–28.15
Prothrombin 20210A	6.09	0.81–45.64
Factor V Leiden+prothrombin 20210A	7.85	1.65–37.41
Protein S deficiency	4.88	1.39–17.10
Protein C deficiency	6.33	1.68–23.87
Antithrombin deficiency	12.60	1.37–115.79

Data from Wu O, Robertson L, Langhorne P, et al. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophila Screening (TREATS) Study. Thromb Haemost 2005;94(1):17–25.

Most subsequent studies have confirmed that third generation COCs are associated with a greater risk for venous thrombosis than are second generation COCs [35,39–44] but some have not [45–47]. A meta-analysis found an overall 1.7-fold increased risk for venous thrombosis in third generation COC users compared with second generation COC users [48].

Venous thrombosis risk in oral contraceptive users who have additional risk factors

Several studies have described an increased risk for venous thrombosis in antithrombin-deficient COC users [43,49], the overall odds of venous thrombosis in antithrombin-deficient COC users being 12.6 (Table 1) [34]. Oral contraceptive users with protein C or protein S deficiency have an increased risk for venous thrombosis [43,49], the overall odds being 6.33 and 4.88, respectively (Table 1) [34].

Vandenbroucke and colleagues reported that, compared with COC nonusers who have wild type Factor V, the relative risk for venous thrombosis for COC users who have Factor V Leiden is 34.7, significantly higher than the sum of the relative risks for COC use and for Factor V Leiden [50]. Positive associations between Factor V Leiden and the risk for venous thrombosis in COC users have been reported from several subsequent studies [43,49–53], overall odds 15.62 (Table 1) [34]. Despite the approximately 35-fold increased risk for venous thrombosis in COC users who have Factor V Leiden, the absolute incidence of venous thromboembolism even in this higher risk group is only 28.5 per 10,000 women per year [50]. This figure would not support a policy of routine screening of women before

prescribing a COC [54]. The interaction between Factor V Leiden and COC use is greater for third generation COCs than for second generation COCs [38].

Increased risk for venous thrombosis in COC users who have the prothrombin 20210A mutation has also been reported [49,51,53], overall odds 6.09 (Table 1) [34]. As with COC use and Factor V Leiden, a synergistic effect has been described for prothrombin 20210A and COC use [51,55]. As may be expected, COC users who are heterozygous for Factor V Leiden and prothrombin 20210A also have an increased risk for venous thrombosis [49,53], overall odds 7.85 (Table 1) [34].

Timing of first venous thrombosis and risk for recurrence in oral contraceptive users who have thrombophilia

The increased risk for venous thrombosis during the first year of COC use is particularly pronounced in women who have thrombophilia [56,57]. There are few firm data on the risk for recurrent venous thrombosis in COC users. In one study, recurrent thrombosis occurred in 11 of 58 women who chose to use a COC during follow-up after a first venous thrombosis, a recurrence rate of 28.0 per 1,000 patient-years (95% CI, 15.9, 49.4) compared with 12.9 per 1,000 patient-years (95% CI, 7.9, 21.2) in the women who did not use a COC during the follow-up period [58]. Fifteen of 58 women who used COCs during follow-up had Factor V Leiden, but only one thrombotic event recurrence occurred in this group.

Oral contraceptives and the risk for arterial thrombosis

Early reports suggested that COC use may be associated with increased risk for myocardial infarction [3] or stroke [59,60]. A multicenter study reported that current COC users have a fivefold increased risk for myocardial infarction [61], a threefold increased risk for ischemic stroke [62], and a one and a half- to twofold increased risk for hemorrhagic stroke [63]. Oral contraceptives also increase the risk for peripheral arterial disease [64].

Oral contraceptive users who have additional cardiovascular risk factors such as smoking or hypertension [65–67] are at particular risk for myocardial infarction, and those who have no major cardiovascular risk factors have a low excess risk [68]. Several small studies that compared the risk for myocardial infarction associated with second and third generation COCs produced conflicting results [61,67,69,70]. Larger studies, however, failed to demonstrate a lower risk for myocardial infarction in users of third generation COCs than in those using COCs containing levonorgestrel [71–73].

Heritable thrombophilia may mildly increase the risk for myocardial infarction, but the increased risk seems to be confined to women who have major cardiovascular risk factors, in particular smoking [74–77]. Overall in users of modern COCs, the presence of a heritable thrombophilia does

not seem to influence the risk for myocardial infarction [76]. The association between thrombophilia and ischemic stroke remains controversial, particularly in young adults. In one study, prothrombin 20220A but not Factor V Leiden was shown to be a risk factor for cryptogenic stroke in young adults [78]. In another study, COC-using carriers of Factor V Leiden had an 11-fold higher risk for ischemic stroke than did women without either risk factor. Women who had the thermolabile variant of methylenetetrahydrofolate reductase (MTHFR 677TT) using COCs had a 5.5 higher risk than did women without these risk factors [79].

Hormone replacement therapy

Post- or perimenopausal estrogen replacement may be administered orally or by nonoral routes, such as transdermal or intravaginal. In the United States, conjugated equine estrogens are widely used. These estrogens are called ''natural'' but are of nonhuman origin and are a mixture of different estrogen derivatives. Esterified estrogens are also occasionally used in the United States. In Europe, synthetic estradiol is more frequently used. A progestogen is usually given in addition (in combination or in sequence) to reduce the risk for cystic hyperplasia of the endometrium (or endometriotic foci in women who have had a hysterectomy).

Hormone replacement therapy and the risk for venous thrombosis

An early study suggested that HRT increased the risk for venous thrombosis [80], but two studies published shortly thereafter failed to confirm this observation [81,82]. Even in the early 1990s, the association between HRT and venous thrombosis risk was disputed [83,84]. From the mid 1990s, however, many studies reported convincing evidence that HRT is associated with a two- to fourfold increased risk for venous thrombosis [85–93]. As with COC users, the risk for venous thrombosis associated with HRT is greatest in the first year [86,89–91].

Increased risk has been shown for conjugated equine estrogens and estradiol [91,93], but in a recently published report, women using high- or low-dose oral esterified estrogen did not seem to have an increased risk for venous thrombosis [94]. There is no clear evidence that venous thrombosis risk is related to estrogen dose in HRT [86,89]. Early studies demonstrated no significant difference in venous thrombosis risk between users of unopposed estrogen and combined estrogen plus progestogen regimens [85,90], but it has since been reported that, compared with users of unopposed estrogen, users of estrogen plus progestogen regimens have an increased risk for venous thrombosis (OR 1.6; 95% CI, 1.13, 2.26) [94]. Although it was initially reported that there was no difference in venous thrombosis risk between oral and transdermal HRT [86,90], in a multicenter case-control study [95] the odds ratios for venous thrombosis in current users of oral

and transdermal HRT compared with nonusers were 3.5 (95% CI, 1.8, 6.8) and 0.9 (95% CI, 0.5, 1.6), respectively, and the estimated risk for venous thrombosis in current users of oral HRT compared with transdermal HRT users was 4.0 (95% CI, 1.9–8.3).

Effect of patient-related factors

Increasing age is associated with increasing risk for HRT-associated venous thrombosis [96]. Other additional risk factors, including lower limb fractures, recent surgery, obesity, cancer, or medical illness, have been shown to further increase the risk for HRT-related venous thrombosis [87,96]. Hormone replacement therapy users who have a history of previous venous thrombosis are at increased risk for a recurrent thrombotic event [97].

There is little published information on the risk for venous thrombosis in HRT users who have an underlying identifiable thrombophilic abnormality, but Rosendaal and colleagues reported that HRT users who have Factor V Leiden have a 15-fold increased risk (95% CI, 3.1, 77) [98], similar to the odds described by Herrington [99]. The overall odds of venous thrombosis in users who have Factor V Leiden is 13.16 (Table 2) [34], exceeding the expected combined odds ratio if the risks were merely additive. Other prothrombotic genetic variants have not been shown to modify the risk for HRT-associated venous thrombosis.

Hormone replacement therapy and arterial disease

Randomized placebo-controlled trials have failed to confirm a beneficial effect of hormone replacement therapy with respect to arterial disease in primary [99] or secondary [101–103] prevention. The Women's Health Initiative and European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) studies confirmed an increased risk for ischemic stroke in

Table 2
Odds ratios for venous thrombosis associated with thrombophilia and hormone replacement therapy use

	Odds ratio	95% CI
Hormone replacement users without thrombophilia	3.16	1.90–5.23
Hormone replacement nonusers with thrombophilia Factor V Leiden	3.58	1.43–8.97
Hormone replacement users with thrombophilia Factor V Leiden	13.16	4.28–40.47

Data from Wu O, Robertson L, Langhorne P, et al. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophila Screening (TREATS) Study. Thromb Haemost 2005;94(1):17–25.

hormone replacement therapy users, but no difference was noted in the Heart and Estrogen/progestin Replacement Study (HERS) [100,103–105]. In a case control study, the prothrombin 20210A mutation was shown to increase the risk for myocardial infarction in hypertensive women [105]. In women who have hypertension, compared with hormone replacement therapy nonusers who have wild-type prothrombin genotype, current hormone replacement therapy users who have prothrombin 20210A had an almost 11-fold increased risk for nonfatal myocardial infarction (95% CI, 2.15, 55.2) [105]. No excess risk for nonfatal myocardial infarction has been found in hormone replacement therapy users who have Factor V Leiden [105]. In women who have either Factor V Leiden or prothrombin 20210A, compared with nonusers, current hormone replacement therapy users have been shown to have a twofold increased risk for nonfatal ischemic stroke [104].

Assisted conception therapy

In vitro fertilization (IVF) procedures involve ovarian stimulation using gonadotrophin releasing hormone analogs and exogenous gonadotrophins. Severe ovarian hyperstimulation characterized by ovarian enlargement, pleural effusion, ascites, and a reduction in intravascular volume, complicates 1% to 2% of IVF treatment cycles [106]. Ovarian hyperstimulation is associated with a trend to hypercoagulability [107] and an increased risk for venous and arterial thrombosis [108]. With increasing availability of IVF, the numbers of reported cases of thrombosis in patients undergoing ovarian stimulation increased. Most cases are associated with the ovarian hyperstimulation syndrome [109–111], but in some cases other risk factors for venous thrombosis, including thrombophilia, have been reported [106,112,113]. It has been suggested that thrombophilia may increase the risk not only of thrombosis in ovarian hyperstimulation syndrome but also that for developing ovarian hyperstimulation syndrome itself [106].

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The Obstetrical Patient with a Prosthetic Heart Valve

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The management of a pregnant woman who has a prosthetic heart valve requires important considerations in deciding how to maintain anticoagulation. Because there are little prospective data, one cannot make definitive recommendations for each patient. Therapy must be individualized because there are known risks to the mother and her fetus regardless of whether warfarin, unfractionated heparin, or low-molecular-weight heparin (LMWH), or some combination of the three, is used. Although initially seen as a possible advance in preventing thromboembolism, the use of LMWH in this clinical setting has not been definitively evaluated. In this article, the historical controversies over the use of warfarin and subcutaneous unfractionated heparin and the most recent evolution of the debate concerning the use of LMWH in this setting are discussed in detail. An understanding of the most current data is critical in helping the patient and the clinician decide on the appropriate strategy for anticoagulation.

Hemostatic changes during normal pregnancy and the risk of thrombosis

Throughout a normal pregnancy, there is an increase in von Willebrand factor, fibrinogen, and factors VII, VIII, and X [1,2]. Levels of protein S decrease [3,4], and the activity of tissue plasminogen activator is depressed [5] (contributing to the diminished activity of the fibrinolytic system until after delivery of the fetus [6]). Because of the pronounced vasodilatory state of pregnancy, there is an increase in arterial and venous capacity, which may affect the integrity of the vessel wall [7]. Local or systemic trauma to the vasculature may contribute to the increased incidence of thrombosis during this

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time [8–11]. The risk of venous thrombosis in pregnant women has been estimated to be up to five times greater than in nonpregnant women of the same age [12]. One study found that the risk for venous and arterial thrombosis may be up to 10 times greater [13].

Thrombosis of prosthetic heart valves during pregnancy

In general, the risk of thomboembolism is greater for older-generation prosthetic valves in the mitral position, such as the Bjork-Shiley tilting-disc prosthesis as compared with the St. Jude valve [14]. The risk of thromboembolism, miscarriage, and premature birth is felt to be higher in patients who have prosthetic heart valves requiring anticoagulation [15]. The greatest risk is the potential for valve thrombosis; resultant mortality rates are as high as 10% to 40% [16–20]. When thrombosis does occur, surgery may be needed, especially if thrombolysis is contraindicated [21,22]. The high risk of fetal loss during surgery has prompted the use of thrombolysis in such circumstances [23–26].

The use of warfarin throughout pregnancy

The effects of warfarin (coumadin) on the developing fetus during the first trimester have been well described by ''coumadin embryopathy'' and include facial abnormalities, optic atrophy, digital abnormalities, epithelial changes, and mental impairment [27–29]. The incidence of this syndrome has been estimated at 5% to 30% when warfarin has been used during the first trimester [30,31]. Because the fetus' synthetic function of the vitamin K–dependent clotting factors is diminished in the first trimester, its exposure to warfarin results in substantially higher levels than that of the pregnant woman [32]. The ability of the developing fetus to generate significant levels of these clotting factors increases after the first trimester until birth [33].

There has been much debate over the true incidence of the effects of warfarin on the developing fetus, but its use during the first trimester has been discouraged. The teratogenicity is not in question, but uncertainty has persisted in the literature as to whether there is a danger to the pregnant mother in avoiding warfarin in trying to prevent any adverse effects to the fetus. One such controversy arose when a study proposed that the effects of warfarin may be dose related [34]. In a study of 43 women receiving this drug throughout pregnancy for having a prosthetic valve, all 43 women agreed to hold warfarin 2 days before an elective cesarian section at week 38. The target international normalized ratio (INR) was 2.8. The study population was divided into one group of women who required greater than 5 mg of warfarin to maintain the target INR and one group who required 5 mg or less. A total of 58 pregnancies resulted in 31 healthy neonates (30 full-term and 1 preterm). There were 27 fetal complications (22 spontaneous abortions, 2 warfarin embryopathies, 1 stillbirth, 1 ventricular septal defect, and 1 growth restriction). Twenty-two of the 27 fetal complications occurred

in women who required more than 5 mg of warfarin. The two cases of warfarin embryopathies (incidence of 3.4%) occurred in women who required more than 5 mg of the drug. Because there were little data to suggest that subcutaneous heparin was superior to warfarin during the first trimester of pregnancy, the authors suggested that the use of warfarin at doses less than 5 mg to achieve a therapeutic INR may be considered during the first trimester. They also proposed that for women requiring larger doses, the option of using warfarin or subcutaneous heparin should be offered with the knowledge of the greater risks of teratogenicity existing with warfarin at higher doses compared with lower doses. The rate of spontaneous abortion was 37.5%.

The resulting editorial comment by Elkayam [35] cautioned against the widespread incorporation of the use of warfarin during the first trimester. In addition to the small number of patients in the study, which made definitive conclusions impossible, he stated that most women would not take warfarin during the first trimester when given the option of doing so. He suggested that women at particularly high risk of thrombosis, such as those with first-generation valves in the mitral position, be given all options, including warfarin, because the use of subcutaneous heparin instead of warfarin may result in a higher incidence of thromboembolism. In addition, higher doses of heparin should be administered to this subset of women who have increased risk of valve thrombosis.

Can subcutaneous unfractionated heparin be substituted for warfarin?

The use of heparin presents an attractive alternative to warfarin because it does not cross the placenta [36]. At first glance, studies that have reported on the use of subcutaneous unfractionated heparin (UFH) during pregnancy seem to raise the concern of an increased incidence of maternal risk in the form of valve thrombosis without any significant reduction in the incidence of spontaneous miscarriage as compared with warfarin [37–39]. However, the dosages of heparin administered ranged from 5000 U every 12 hours to a partial thromboplastin time (PTT) of 1.5 to 2.5 of the control level. The incidents of valve thrombosis occurred in the older-generation valves (Bjork-Shiley prosthesis), particularly in the mitral position. There are data to suggest that increased dosing of heparin during pregnancy is required to achieve the desired levels of PTT, thus highlighting the hypercoagulability during this physiologic state [40,41].

The largest review of the use of anticoagulation in pregnant women included 976 women with 1234 pregnancies in various studies conducted from 1966 to 1997 [42]. The rate of ''coumadin embryopathy'' occurred in 6.4% of live births. Substitution of heparin for warfarin during weeks 6 to 12 of gestation nearly eliminated its occurrence. However, the incidence of valve thrombosis occurred in 3.9% of pregnancies when warfarin was used throughout pregnancy, as compared with 9.2% when heparin was

substituted for warfarin in weeks 6 to 12. This occurrence was reflected in a maternal risk of death of 4.2% when heparin was substituted for warfarin in the first trimester, as compared with 1.8% when warfarin was used throughout pregnancy. The authors concluded that the risk of thrombosis was least when warfarin was used, but this was at the expense of coumadin embryopathy. The use of heparin in the first trimester can prevent warfarin's teratogenic effects on the fetus, but it may expose the mother to an increased risk of valve thrombosis and death.

These findings have been criticized because of the possibility of too-low target PTT for heparin dosing, especially for patients with high-risk prosthesis in the mitral position [43], in whom a minimum PTT of 2.5 times control is likely needed. Finally, the claim that lower incidence of fetal malformation with warfarin in these studies concluding that heparin offers no advantages over warfarin may have under-represented the true incidence of coumadin embryopathy syndrome [44].

The controversy over low-molecular-weight heparin

The use of LMWH as a substitute for warfarin for various procedures was seized by clinicians as an easy and cost-effective method of treating pregnant patients with and without prosthetic heart valves. Because it could achieve anticoagulation more reliably than unfractionated heparin, it could be safer, as opposed to the many reports of thromboembolism with unfractionated heparin. The first uses of LMWH for "bridging" nonpregnant patients who have prosthetic heart valves who need to discontinue their warfarin for procedures seemed to support this assumption. Warfarin was discontinued while anticoagulation was maintained with LMWH, the last dose of which was usually given 12 hours before the anticipated procedure. Afterward, LMWH was administered concomitantly with warfarin until desired INR levels were reached. In August 2002, a report concluded that in a cohort of 1082 patients who were prophylactically "bridged" from oral anticoagulation as outpatients, periprocedural management with LMWH was found to be safe and effective (A.G.G. Turpie, personal communication, 2002). This group included 401 patients who had and 681 patients who did not have prosthetic valves but who had other indications for anticoagulation (eg, atrial fibrillation, recurrent venous thrombosis, cerebral emboli, and transient ischemic attacks).

Thus, although not approved for such uses, LMWH had rapidly evolved as "standard of care." In the summer of 2002, however, the pharmaceutical company producing enoxaparin (a LMWH) issued a warning to health care providers discouraging the use of enoxaparin to prevent thromboembolic events in any patient who has prosthetic heart valves due to case reports of adverse outcomes in pregnant women who have valve prosthesis. Physicians responded to this warning with disbelief because no comprehensive data exist to suggest that this use of LMWH poses any more risk than

unfractionated heparin does. Such a restrictive labeling prompted clinicians to worry that although the company was seeking to protect itself, it was potentially shifting all legal liability to the practitioner. In the summer of 2003, the company mailed letters to physicians stating that LMWH had not been adequately studied in pregnant women who have mechanical prosthetic heart valves, thus amending their previous recommendation to avoid its use in all patients who have prosthetic heart valves. A critical analysis of the history of LMWH and its use in pregnant women who have and those who do not have prosthetic heart valves is presented.

Low-molecular-weight heparin in pregnant women who do not have prosthetic heart valves

The use of LMWH in the prevention or treatment of deep-vein thrombosis in pregnant women who do not have prosthetic heart valves was reported in a review of 624 patients [45] and in the results of several serial case studies [46–49]. These studies concluded that its use was safe and effective and that there was no evidence of adverse outcomes directly related to its administration. A recent analysis of the use of LMWH in the acute treatment of 174 pregnancies with venous thromboembolism, for routine prophylaxis in 1348 pregnancies, for prophylaxis of 447 pregnancies with a history of recurrent pregnancy loss, and in an additional 720 pregnancies for ''unspecified prophylaxis'' was reported [50]. In this cumulative review of 2777 pregnancies, the overall rate of venous and arterial thrombosis was 1.38%. Although the authors admitted that this retrospective analysis included a heterogeneous patient population, they concluded that LMWH is safe and effective for treating and preventing thrombosis in pregnancy.

Low-molecular-weight heparin in pregnant women who have prosthetic heart valves

The labeling change made by the pharmaceutical company was based on early results from a study that was supposed to enroll 110 patients in a randomized, open-label fashion to compare enoxaparin with warfarin and unfractionated heparin in pregnant women who had prosthetic heart valves [51]. The safety committee terminated the study after only 12 patients were enrolled due to two deaths from prosthetic valve thrombosis in the enoxaparin group. This catastrophic event occurred in one patient who had a prosthetic mitral valve and in another patient who had prosthetic valves in the mitral and aortic positions. Careful review of the data showed that just before death or at the time of death, both women had levels of Factor Xa below the recommended therapeutic ranges of 0.6 to 1.0 IU/mL [52]. These subtherapeutic levels may be due to the alteration of the pharmacokinetics of LMWH during pregnancy, suggesting that higher doses of the

drug and measurement of Factor Xa levels rather than usual weight-based dosing may be required to achieve the therapeutic range [53–55].

Little information has been published on the use of LMWH in pregnant women who have prosthetic heart valves. There are case reports or small case series on the use of LMWH in such circumstances that detail incidences of valve thrombosis [56–59]. A recent review reported a valve thrombosis rate of 8.64% in 81 pregnancies of 75 women treated with LMWH [60]. Of the seven episodes of valve thrombosis, six were on fixed doses; only one event occurred in 51 pregnancies when factor Xa levels were monitored. Based on these results, critics contended that most cases of thrombosis were a result of inadequate dosing; this deficiency can be amended by monitoring of factor Xa levels and adjusting the dosage accordingly. A target trough level of 0.6 to 0.7 U/ml would be more appropriate for such a high-risk group of patients [61]. The American College of Chest Physicians has recommended LMWH as a reasonable alternative to unfractionated heparin with a desired a 4-hour postinjection anti-Xa heparin level of approximately 1.0 to 1.2 U/mL [62].

Current guidelines: European Society of Cardiology and American College of Cardiology/American Heart Association

The most recent guidelines by the European Society of Cardiology [63] and the American College of Cardiology/American Heart Association (ACC/AHA) [64] are from 1998. They are summarized as follows:

- Both societies recommend the use of warfarin as the anticoagulation of choice for pregnant women who have mechanical prosthetic heart valves for the first 35 weeks of pregnancy.
- If the patient does not wish to use warfarin in the first trimester, then the ACC/AHA report has tailored therapy depending on the risk profile of the patient. (a) For women at particularly high risk for thromboembolism, including those with a previous history of such an event or an older-generation mechanical valve in the mitral position, the ACC/AHA report recommends that unfractionated heparin be given continuously intravenously, with a target of activated PTT (aPTT) of 2 to 3 times control. (b) Women at low risk for thromboembolism who choose not to take warfarin should receive adjusted-dose subcutaneous heparin to achieve a desired aPTT 2 to 3 times control.
- Unfractionated heparin should replace warfarin after the 36th week of pregnancy; if warfarin is continued until the time of delivery, then a cesarean section should be undertaken.
- Once hemostasis has been achieved after delivery, heparin should be resumed 4 to 6 hours after delivery with resumption of warfarin. If warfarin is not used during the first trimester, a thorough discussion with the patient must be undertaken to clarify that unfractionated heparin is less

safe for the patient and the fetus, with higher risks of thrombosis and bleeding, than warfarin and that any risk to the mother puts the health of the baby at risk.

- Because no data exist concerning the use of LMWH, there were no recommendations on its use in this setting.

Recent updates

The incorporation of LMWH in the management strategy has yet to be defined in terms of feasibility and timing. However, at the European Society of Cardiology in September 2005, an updated list of proposed recommendations was presented by Elkayam [65]. Although not officially endorsed by the European Society of Cardiology, ACC, or AHA, it will influence the next set of guidelines. Given that many women in the United States will not take warfarin during the first trimester, Elkayam has developed a strategy based on the literature and his experience. The patient is defined as high- or low risk according to the ACC/AHA guidelines (Table 1). For the high-risk patient, Elkayam recommends warfarin (target INR of 2.5–3.5) for the first 35 weeks followed by UFH (target aPTT of 2.5–3.5 times control) with low-dose aspirin. If the patient does not wish to take warfarin during the first trimester, subcutaneous UFH (target aPTT of $>$ 2.5 times control) or LMWH (target trough level of Factor Xa of $\sim$0.7) are proposed

Table 1
Anticoagulation prophylaxis in pregnant women who have a prosthetic heart valve

Higher risk	Lower risk
First-generation PHV (eg, Starr-Edwards, Bjork Shiley) in the mitral position, atrial fibrillation, history of TE on anticoagulation	Second-generation PHV (eg, St. Jude Medical, Medtronic-Hall) and any mechanical PHV in the aortic position
Warfarin (INR 2.5–3.5) for 35 wk followed by intravenous UFH (aPTT of 2.5–3.5) + ASA 80–100 mg qd	SC UFH (midinterval aPTT 2.0–3.0) or LMWH (predose anti-Xa $\sim$0.6) for 12 wk followed by warfarin (INR 2.5–3.0) to 35th week, then SC UFH (midinterval aPTT 2.0–3.0) or LMWH (predose anti-Xa level $\sim$0.6)
OR	OR
SC UFH (aPTT $>$2.5) or LMWH (predose anti-Xa $\sim$0.7) for 12 wk followed by warfarin (INR 2.5–3.5) to 35 wk, then IV UFH (aPTT $>$2.5) or LMWH (predose anti-Xa $\sim$0.7) + ASA 80–100 mg qd	SC UFH (midinterval aPTT 2.0–3.0) or LMWH (predose anti-Xa $\sim$0.6) throughout pregnancy

Abbreviations: APTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PHV, prosthetic heart valve; SC, subcutaneous; TE, thromboembolism; UFH, unfractionated heparin.

From Westminster Publications and Elkayam U, Singh H, Irani A, Akhter MW. Anticoagulation in pregnant women with prosthetic heart valve. J Cardiovasc Pharmacol Therapeut 2004;9:107–15.

as alternatives. After 12 weeks, warfarin should be resumed, with cessation after 35 weeks and substitution with UFH or LMWH and the addition of low-dose aspirin.

For the lower-risk patient, UFH or LMWH with lower target levels can be used for the first 12 weeks, followed by warfarin. After 35 weeks, warfarin should be stopped, and UFH or LMWH should be resumed. If the lower-risk patient is unwilling to take warfarin, UFH or LMWH can be used throughout pregnancy. Most importantly, Elkayam has stressed the importance of properly maintaining adequate levels of anticoagulation with frequent monitoring because failure to do so is associated with the greatest risk for thromboembolism.

Summary

Definitive recommendations on anticoagulation strategy in pregnant women who have prosthetic heart valves are lacking because of the paucity of prospectively collected data. The use of warfarin, UFH, LMWH, or any combination of these choices has potentially adverse outcomes for the mother and fetus. Although there is no treatment option that has proven to be completely satisfactory, there is agreement that failures are most often due to underdosing and the lack of intensive monitoring of anticoagulation. A careful discussion with the patient must be undertaken so that she and the clinician can come to a decision about the most appropriate protocol.

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Peripartum and Perioperative Management of the Anticoagulated Patient

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Management of the pregnant patient requiring anticoagulation in the peripartum period represents a significant clinical challenge. The peripartum period includes the most thrombogenic pregnancy-associated state [1] and the intrapartum and immediate postpartum periods, when hemorrhage is an important concern. Clinical decisions depend on the type of antepartum anticoagulation, obstetric factors, risk of hemorrhage, and the risk and implications of thrombosis.

Antepartum anticoagulation

Unfractionated heparin

In patients being expectantly managed at or near term, unfractionated heparin can usually be safely continued. The half-life of unfractionated heparin is short, with an anticoagulant effect of approximately 8 to 12 hours [2]. Heparin is partially reversible with protamine sulfate [3]. Recent administration is not a contraindication to regional analgesia if the partial thromboplastin time (PTT) is not prolonged [4].

Low-molecular-weight heparin

The half-life of low-molecular-weight heparin (LMWH) is longer than that of unfractionated heparin and cannot be reversed with protamine sulfate [5]. In addition, regional analgesia within 18 to 24 hours of LMWH administration may be associated with epidural hematoma [4]. For these

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reasons, patients being expectantly managed at or near term should be switched from LMWH to unfractionated heparin. If cesarean delivery or induction of labor is planned, LMWH can be continued until the day before the scheduled delivery [6]. Patients should be made aware of the risks of hemorrhage and the possibility of not receiving regional analgesia should spontaneous labor occur before the day of scheduled delivery.

Warfarin

The half-life of warfarin is long; the production of vitamin K–dependent clotting factors is inhibited for 36 to 48 hours. Warfarin should be discontinued near term and replaced with unfractionated heparin. Because warfarin is typically used in pregnancy only in women who have mechanical heart valves, it is important to minimize the duration of time in which a patient is not receiving anticoagulation or is not therapeutically anticoagulated [7]. To minimize the risk of stroke, intravenous heparin, which has a half-life of 1 to 2 hours, can be administered until active labor.

If delivery is anticipated soon after warfarin administration, vitamin K can hasten the production of the vitamin K–dependent clotting factors. If prothrombin time is prolonged in the laboring patient or in the patient who requires cesarean delivery, clotting factor replacement with fresh frozen plasma may be warranted.

Delivery

Induction of labor versus expectant management

The main benefit of scheduling labor induction is to avoid presenting in labor in a state of anticoagulation. This is of particular concern in women taking LMWH because they may not be candidates for regional analgesia [4]. Women who present for scheduled induction of labor should not take LMWH less than 24 hours before admission.

Although labor induction may eliminate the need to switch patients from LMWH to unfractionated heparin, the spontaneous onset of labor is associated with lower rates of cesarean delivery, particularly in nulliparous women [8]. Cesarean delivery is associated with higher rates of peripartum thrombosis compared with vaginal delivery [9]. Induction of labor is most appropriate when it is unlikely to significantly increase the risk of cesarean delivery. Multiparous patients and those with a favorable cervix are the best candidates for labor induction.

Patients on anticoagulants who are expectantly managed should be counseled to present to the hospital with the earliest signs or symptoms of labor and to withhold anticoagulants until labor is ruled out. In the patient who has been taking unfractionated heparin, coagulation studies should be performed promptly. If the PTT is not prolonged, the risk of hemorrhage is low.

Route of delivery

Because cesarean delivery is associated with a higher risk of thromboembolism hemorrhage, vaginal delivery is preferable in most cases. In patients who are at highest risk of thrombosis, one objective may be to minimize the duration of time in which anticoagulation is withheld. If there is a maternal or fetal indication mandating delivery, cesarean delivery should be considered in some cases if labor induction may be prolonged or relatively unlikely to result in vaginal birth.

Intrapartum management

Prophylactic doses of unfractionated heparin or LMWH are unlikely to cause intrapartum hemorrhage [10]; there is evidence that certain forms of thrombophilia may prevent hemorrhage [11]. Nevertheless, it is generally recommended that anticoagulation be withheld during labor [12]. In patients who have had a recent acute venous thromboembolic event or who are otherwise considered at high risk of pulmonary embolism, intravenous heparin until active labor can be considered [12]. Alternatively, placement of an inferior vena caval filter should be considered [13].

To avoid prolonged immobilization, ambulation should be encouraged early in labor. Although the use of pneumatic compression boots during labor has not been evaluated in a clinical trial, it is reasonable to use them in high-risk patients [14]. Pneumatic compression boots should also be used before elective cesarean delivery [15].

It is crucial to ensure hemostasis at the time of resuming anticoagulation in the postpartum period. Placement of a closed drainage device after cesarean delivery may provide early evidence of hemorrhage when anticoagulation is resumed.

Regional analgesia

Low-dose subcutaneous heparin (5000 units every 12 hours) is not associated with an increased risk of spinal or epidural hematoma [4]. In the patient who has been receiving subcutaneous heparin for prophylactic or therapeutic anticoagulation, neuraxial anesthesia may be administered when the PTT returns to normal [4].

According to the second American Society of Regional Anesthesia Consensus Conference on Neuraxial Anesthesia and Anticoagulation, in patients receiving LMWH, spinal or epidural placement should not be performed until at least 12 hours after the last dose of prophylactic (once-daily dosed) LMWH and not until at least 24 hours after the last dose in patients receiving therapeutic dosing of LMWH [4]. When continuous epidural analgesia is used, the removal of the epidural catheter is postponed at least 6 hours postpartum.

Postpartum

There are no clinical trials evaluating the optimal time to begin postpartum anticoagulation. It is reasonable to resume prophylactic anticoagulation 4 to 8 hours after vaginal delivery and 8 to 12 hours after cesarean delivery in the absence of any evidence of hemorrhage [12]. According to the American Society of Regional Anesthesia, if postoperative LMWH is to be used in a patient who had spinal or epidural analgesia, the first dose should not be administered before 24 hours postoperatively if a twice-daily (therapeutic) dosing regimen is planned. A once-daily (prophylactic) dosing regimen can be resumed 6 to 8 hours postoperatively [4].

In patients requiring prophylactic anticoagulation, resumption of the regimen used in the antepartum period is reasonable. Because warfarin blocks formation of the antithrombotic factors protein S and protein C before inhibiting clotting factors, heparin should be used concurrently until prothrombin time produces an international normalized ratio level in the desired range. Warfarin is compatible with breast feeding [16].

Postpartum anticoagulation should be continued throughout the 6-week postpartum period. In patients being treated for thromboembolism during pregnancy, anticoagulation may need to be continued for a longer duration.

To minimize the risk of thromboembolism, early ambulation is important in any postpartum patient. Ambulation should be encouraged in patients who have thrombophilia. Sequential compression boots can be discontinued upon ambulation.

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The Seventh American College of Chest Physicians Guidelines for the Antenatal and Peripartum Management of Thrombophilia: A Tutorial

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The latest guidelines for the prevention of venous thromboembolism (VTE) were published by the American College of Chest Physicians (ACCP) in September 2004 [1]. This set of updated guidelines represents a discussion of treatments of venous thrombosis, thromboprophylaxis, and a revision of those published in 2001. These guidelines propose some ''official'' recommendations for health-care providers for women during the peripartum period.

The ACCP guidelines are based on a new approach that assesses and grades the quality of evidence and strength of recommendations. The panel of scholars who developed the guidelines recommended the distribution educational material to facilitate guideline implementation. Of special note is the grading system. If the experts are certain that benefits do, or do not, outweigh risks, burdens, and costs, the recommendation is defined as Grade 1. If the experts are less certain, a weaker recommendation is defined as Grade 2. Consistent results from randomized clinical trials (RCTs) generate Grade A recommendations, whereas observational studies with strong effects or secure generalizations from RCTs generate Grade C+ recommendations. Inconsistent results from RCTs generate Grade B recommendations, and observational studies generate Grade C recommendations. One substantive change to the grading system was added in the 2004 revision, namely the downgrading of methodologic quality in favor of treatments that carry greater risk, inconvenience, and cost than the alternatives, if sample size is small or event rates are low [1]. If the results were not statistically significant or if the addition of a small number of adverse events to the treatment arm would render

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a result nonsignificant, the recommendation was downgraded from Grade A to Grade B. In addition, the panel expressed the strength of the recommendation by using "we recommend" for strong recommendations (Grades 1A, 1C+, 1B, and 1C) and "we suggest" for weaker recommendations (Grades 2A, 2C+, 2B, and 2C) [1]. These nuances enable clinical judgment and "tailored" medicine in cases where clear-cut evidence does not exist.

Despite the detailed recommendations, physicians may find them somewhat intimidating and consequently are inconsistent when applying the ACCP antithrombotic guidelines. In fact, as far as peripartum events are concerned, seven scenarios were described. The purpose of this article is to settle some ambiguity and to present these recommendations in a clinical format. The treatment options are summarized in Table 1. Compression stockings are invariably recommended.

Scenario I

Example 1

A 17-year-old female student had patellar fractured after a car accident. After orthopedic treatment, the patient developed deep vein thrombosis (DVT) in her left femoral vein. Now she is 23 years old and 6 weeks pregnant.

Example 2

A 17-year-old female student was started on oral contraception. After 4 months she had patellar fractured after a car accident. After orthopedic treatment, the patient developed DVT in her left femoral vein. Now she is 23 years old and 6 weeks pregnant (Box 1).

Table 1
Treatment options

Regimen	Dosage
Mini-dose UFH	SC, 5000 U q 12 h
Moderate-dose UFH	SC, q 12 h, anti-Xa adjusted
Adjusted-dose UFH	SC, q 12 h, PTT adjusted
Prophylactic LMWH	SC, dalteparin, 5000 U/d
	SC, enoxaparin, 40 mg/d
Intermediate-dose LMWH	SC, dalteparin, 5000 U/12 h
	SC, enoxaparin, 40 mg/12 h
Adjusted dose LMWH	SC, weight adjusted
	Enoxaparin, 1 mg/kg/12 h
	Dalteparin, 100 U/kg/12 h
Postpartum	Warfarin (INR 2–3)

The two LMWHs mentioned in the table are two examples of several preparations. It is suggested to check the availability of the LMWH preparation in each country and the approval for the use during pregnancy of each preparation.

Abbreviations: LMWH, low-molecular-weight heparin; SC, subcutaneous; UFH, unfractionated heparin.

Box 1. Recommendation I: VTE + transient risk factor

- Close observation
- In estrogen-related/pregnancy/risk factors → antenatal anticoagulants (2C)
- Postpartum anticoagulants (1C)

Comment

The ACCP recommendations distinguish between the natures of the transient event that caused the DVT. If the cause was unrelated to estrogen (eg, surgery or trauma), close observation during pregnancy may be sufficient. If the event can be related to a previous pregnancy or to estrogen, an anticoagulant may be given in the antenatal period (grade 2C recommendation). Finally, there is a strong recommendation for postpartum anticoagulation (6 weeks) (grade 1C recommendation).

Scenario II

Example 1

A 25-year-old nulligravid woman had DVT in her left calf. Meticulous history and complete thrombophilia work-up did not reveal any etiology for DVT. Familial history suggestive of thrombophilia was negative. Three years later, the patient becomes pregnant.

Example 2

A 25-year-old nulligravid woman had DVT in her left ilio-femoral vein. Meticulous history and complete thrombophilia work-up did not reveal etiology for DVT. Familial history suggestive of thrombophilia was negative. Three years later, the patient becomes pregnant (Box 2).

Comment

In this scenario, the DVT is considered idiopathic (or better put, idiopathic until our understanding and the availability of laboratory methodology improves). Despite the fact that every year new thrombophilic factors

Box 2. Recommendation II: single episode of idiopathic VTE

- Close observation
- Mini- to moderate-dose unfractionated heparin
- Prophylactic LMWH
- Postpartum anticoagulants

are identified and available for clinical testing, the approach to such a patient without an identifiable cause for the DVT varies (grade 2C recommendations). The minimum is close observation and for postpartum anticoagulation (6 weeks). Some clinicians would consider DVT in a large vein (example 2) as more risky than calf DVT and would treat with mini- to moderate-dose unfractionated heparin (UFH) or prophylactic LMWH.

Scenario III

Example 1

A 20-year-old nulligravid woman had DVT in her left leg. The thrombophilia work-up revealed a heterozygous state of FVL. Two years later, the patient becomes pregnant.

Example 2

A 25-year-old nulligravid woman had DVT in her left leg. Her mother had pulmonary embolism 3 days postpartum. A complete thrombophilia work-up did not reveal etiology for DVT. Two years later, the patient becomes pregnant (Box 3).

Comment

This patient has VTE and proven thrombophilia or a strong familial history. This combination puts her at a higher risk for recurrent VTE compared with case scenario II. The ACCP panel considers a strong familial history as important as a proven thrombophilia. Thus, close observation may not be enough, and the clinician should anticoagulate (grade 2C recommendations) the patient with mini- to moderate-dose UFH or prophylactic or intermediate LMWH. These patients should be given postpartum anticoagulants (6 weeks).

Scenario IV

Example 1

A 20-year-old nulligravid woman had DVT in her left leg. The thrombophilia work-up revealed antithrombin deficiency. Three years later, the patient becomes pregnant (Box 4).

Box 3. Recommendation III: single episode of VTE + thrombophilia/strong family history

- Mini- to moderate-dose UFH
- Prophylactic or intermediate LMWH
- Postpartum anticoagulants

Box 4. Recommendation IV: single episode of VTE + high-risk thrombophilia

- Moderate-dose UFH
- Intermediate-dose LMWH
- Postpartum anticoagulants

Comment

This patient is identical in her case presentation to the patient in example 1 in scenario III, except for a different thrombophilia. This recommendation (grade 2C) takes into consideration the observation that some thrombophilias carry a higher risk than others. The ACCP panel pointed out ATIII, a combination of FII + FVL mutations, and a combination of homozygous state to FII or FVL. Thus, the level of anticoagulation is higher and includes moderate-dose UFH or intermediate-dose LMWH. The need for postpartum anticoagulants (6 weeks) remains the same.

Scenario V

Example 1

An 18-year-old patient was found to be heterozygous for Factor II mutation by her physician before prescribing oral contraception. No personal or familial history of VTE could be elicited. Three years later, the patient becomes pregnant (Box 5).

Comment

This scenario is the other side of the coin presented in scenario III, but in this case, the patient carries a thrombophilia but is otherwise healthy. The ACCP panel does not ignore this risk, but the assigned risk does not necessarily translate to anticoagulation. Thus, close observation only is an option, as is minimal anticoagulation (grade 2C recommendation). Postpartum anticoagulants (6 weeks) are recommended.

Box 5. Recommendation V: no prior VTE + thrombophilia

- Close observation
- Mini-dose UFH
- Prophylactic LMWH
- Postpartum anticoagulants

Scenario VI

Example 1

A 18-year-old patient was found to be double heterozygous for FII + FVL mutations by her physician before prescribing oral contraception. No personal or familial history of VTE could be elicited. Three years later, the patient becomes pregnant (Box 6).

Comment

This case differs from case V in the thrombophilic factor involved. As was the case in scenario IV, the recommendations (grade 2C) take into consideration the different risk assigned to different thrombophilias and their combination. Consequently, a higher level of anticoagulation is required. The need for postpartum anticoagulants (6 weeks) remains the same.

Scenario VII

Example 1

A 30-year-old para 2 had recurrent VTE in each of her pregnancies. Since the last birth nearly 3 years ago, she was kept under oral anticoagulation. The patient becomes pregnant for the third time (Box 7).

Comment

Such a patient as described in scenario VII is at risk for a recurrent VTE. Irrespective of long-term anticoagulation, the patient needs careful ante- and postpartum anticoagulation. Anticoagulation (grade 2C recommendation) is tailored by the PTT (for intravenous UFH) for a value of $\times 1.5$ to 2.0 of baseline PTT or by adjustments in subcutaneous LMWH dosing according to weight gain during pregnancy (1 mg/kg twice daily) and puerperium. The twice-daily dosing is related to drug kinetics. The current practice is to adjust LMWH by the anti-Xa level (0.5–1.2 U/mL). Oral

Box 6. Recommendation VI: no prior VTE + high-risk thrombophilia

- Moderate-dose UFH
- Intermediate-dose LMWH
- Postpartum anticoagulants

Box 7. Recommendation VII: multiple episodes of VTE and/or long-term anticoagulation

- PTT-adjusted UFH
- Weight-adjusted LMWH
- Postpartum anticoagulants

anticoagulants, monitored by international normalized ratio, should be resumed after delivery.

Reference

[1] Hirsh J, Guyatt G, Albers GW, et al. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Evidence-based guidelines. Chest 2004;126:172S–3S.