Thromboembolism and thrombophilia in pregnancy

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Thrombosis; Thrombophilia; Pregnancy; Maternal health

Summary
Venous thromboembolism (VTE) is one of the leading causes of maternal mortality worldwide and is also the cause of significant maternal morbidity. This article discusses the risk factors for VTE in pregnancy, the management of the pregnant woman at risk both antenatally and post-partum, and the acute management of VTE when it occurs during pregnancy.

The thrombophilias, both heritable and acquired, are becoming increasingly recognised as a cause of morbidity and mortality both within and outside pregnancy. There has been a recent increased interest in the thrombophilias and their link with recurrent miscarriage, preeclampsia, abruption and intrauterine growth restriction. The relationship between the thrombophilias and adverse pregnancy outcome is addressed in detail, with reference to the current literature available on this evolving subject.

Introduction
One of the many early physiological adaptations of pregnancy involves changes in the coagulation system that promote coagulation and impair fibrinolysis. The physiological goal is to prepare for the haemostatic challenge of delivery. A 'side effect' of this change is an increased risk of thrombosis. All pregnant women are therefore at risk of thrombosis compared with non-pregnant women. This risk is manifest from early in the first trimester until at least 6 weeks post-partum.

The scale of the problem
Thromboembolism is the leading cause of maternal mortality in the UK. In the most recent Confidential Enquiry into Maternal Deaths 2000–2002, published in November 2004, there were 30 deaths from thrombosis: 25 from pulmonary embolus and five from cerebral vein thrombosis. Without thromboprophylaxis, the incidence of non-fatal pulmonary embolism and deep venous thrombosis (DVT) in pregnancy is about 0.1% in developed countries. The risk increases following delivery, and the risk of DVT after caesarean section is around 1–2%. This risk is increased further following emergency caesarean section.

In the acute phase, DVT can lead to pulmonary embolus, whereas in the longer term, post-phlebitic syndrome and deep venous insufficiency will affect almost 70% of patients with a previous DVT within 5 years. This is manifest in various ways, ranging from leg swelling and varicose veins to trophic changes and ultimately skin ulceration in a proportion of these women. Thus, venous thromboembolism (VTE) is a major cause of not only maternal mortality, but also maternal morbidity.

Physiological changes in the coagulation system during pregnancy
Pregnancy is associated with a 6–10-fold increase in risk of VTE compared with the non-pregnant situation.
The frequency of VTE is similar in all three trimesters, but the highest risk occurs during the post-partum period.

Pregnancy is a hypercoagulable state. There is an increase in several procoagulant factors, a reduction in endogenous anticoagulant activity and a suppression of fibrinolysis. For example, the amount of factors X and VIII and von Willebrand factor increase progressively as pregnancy advances. Furthermore, fibrinogen increases substantially during pregnancy, with an almost 2-fold increase over non-pregnant levels by term. There is thus a marked increase in the coagulation potential, which is maximal by term.

Although antithrombin and protein C levels remain constant, there is a significant reduction in protein S activity in normal pregnancy, which in 15% of women remains low 8 weeks post-partum. Fibrinolytic activity is impaired during pregnancy but returns rapidly to normal following delivery. This impairment of fibrinolysis is due to increased circulating concentrations of plasminogen activator inhibitor type 2, derived exclusively from the placenta, and also endothelial-derived plasminogen activator inhibitor type 1. The additional changes in the fibrinolytic system include an increase in plasminogen and antiplasmin levels, a 2-fold increase in the concentration of tissue plasminogen activator, derived from the endothelium, and a reduction in the fibrinolytic response to stimulation by venous occlusion in which total tissue plasminogen activator and free tissue plasminogen activator release are significantly reduced compared with the non-pregnant situation. This may be clinically relevant as impaired fibrinolysis can be found in some patients with a history of DVT, and thus the physiological impairment of fibrinolysis seen in pregnancy may contribute to the increased thrombotic risk associated with pregnancy. The physiological purpose of these changes is thought to be preparation for the haemostatic challenge of delivery.

An additional risk factor for thrombosis is venous stasis in the lower limbs. Venous flow velocity is reduced during pregnancy, with a significant reduction in flow velocity being seen by 18–20 weeks’ gestation. This reaches a nadir at 30 weeks’ gestation and takes at least 6 weeks after delivery to return to non-pregnant values. The reduction in flow is thought to reflect a decrease in venous tone. Trauma to the pelvic veins at the time of delivery as the head passes through the pelvis or at caesarean section can also contribute. Thus, all factors of Virchow’s triad of venous stasis, hypercoagulability and endothelial injury are present in the course of pregnancy and delivery.

Practice points
- Pregnancy is a hypercoagulable state.
- The increased risk of thrombosis begins early in the first trimester and continues until at least 6 weeks post-partum.
- The post-partum period is the time of highest risk.

Risk factors for VTE in pregnancy

In some women, the risks are increased further because they have one or more additional risk factors (Boxes 1 and 2).

Women should have a risk assessment for VTE performed at booking, including the risk factors listed in the boxes. This risk is, however, not static and should be reconsidered if, for example, the woman is admitted to hospital or has an intercurrent illness. A careful history should also be taken from the woman of any prior or family history of thromboembolic events.

Post-partum thromboprophylaxis

Further reassessment of risk factors for VTE should be performed before or during labour. Age over 35 and weight greater than 80 kg (body mass index > 30 kg/m²) are independent risk factors for post-partum VTE even after vaginal delivery. These risk factors in combination with any other risk factor (such as preeclampsia, prolonged labour, instrumental delivery or excessive blood loss) or two other persisting risk factors for VTE as outlined in Boxes 1 and 2 should lead to a consideration of the use of low-molecular weight heparin (LMWH) for 3–5 days post-partum or until the woman is fully mobile. The 1995 Royal College of Obstetricians and Gynaecologists guideline for the use of thromboprophylaxis after caesarean section has led to the almost universal adoption of thromboprophylaxis following high-risk caesarean section, and indeed, in many units, all women undergoing a caesarean section are given LMWH following delivery.

Practice points
- Women should have their risk of VTE assessed at booking, and this risk should be reviewed when they are admitted antenatally, in labour and post-natally.
Thromboprophylaxis must be considered in the light of these risk factors in all women if they are admitted antenatally and after delivery. The greatest number of deaths from VTE now occurs following vaginal delivery as thromboprophylaxis following caesarean section is now routine.

Prevention of VTE in pregnancy: thromboprophylaxis during pregnancy

Women with a previous thrombotic event have an increased risk of recurrence in pregnancy (the relative risk during pregnancy being 3.5). Screening is recommended for inherited and acquired thrombophilia in women with a personal or strong family history of VTE within or outside pregnancy, particularly if there is a history of unprovoked or idiopathic thromboembolism. However, given the overall low incidence of these disorders, the population screening of all pregnant women cannot currently be justified financially. Even without an abnormal thrombophilia screen, the presence of an unprovoked VTE with a family history and in the presence of the other known risk factors, as described in Boxes 1 and 2, should lead to the consideration of treatment with low-dose (75 mg) aspirin alone or LMWH from early in the first trimester until 6 weeks post-partum.

The use of graduated elastic compression stockings is recommended in all women with a previous VTE or thrombophilia during the pregnancy and for 6–12 weeks post-partum; stockings should be fitted according to patient size. There is evidence that there is no major benefit of full-length graduated elastic compression stockings over the below-knee variety, and using below-knee stockings may increase compliance.

Excellent guidelines were published by the Royal College of Obstetricians and Gynaecologists in 2004 outlining recommendations for thromboprophylaxis during pregnancy, labour and following vaginal delivery (Table 1).

<table>
<thead>
<tr>
<th>Recommended treatment</th>
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<tr>
<td>Antenatal high prophylactic or therapeutic dose LMWH and 6 weeks post-natal warfarin</td>
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<tr>
<td>Antenatal and 6 weeks postnatal prophylactic LMWH</td>
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<td>Post-natal prophylactic LMWH ± antenatal low-dose aspirin</td>
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LMWH, low molecular weight heparin; VTE, venous thromboembolism.

Diagnosis and management of acute VTE

As the clinical diagnosis of VTE is unreliable, women who are suspected of having a DVT or pulmonary embolism should be investigated promptly using diagnostic imaging. In the case of suspected DVT, ultrasound (compression or duplex) is the first-line diagnostic tool.

If pulmonary embolism is suspected, an initial electrocardiogram, chest X-ray and arterial blood gases should be performed along with ventilation–perfusion lung scanning and bilateral duplex ultrasound leg examinations. If the ventilation–perfusion scan reports a low risk of pulmonary embolism, yet there is high clinical suspicion, anticoagulant treatment should be continued, with repeat testing in 1 week. Alternative imaging techniques should be considered if the clinical suspicion is high, even if the ventilation–perfusion scan shows low probability and leg ultrasound examination is negative; or if the chest X-ray is abnormal. These techniques include pulmonary angiography, magnetic resonance imaging and helical computed tomography.

Low-dose perfusion scanning (omitting ventilation scanning) gives a fetal radiation dose of less than 0.012 rad. There have been concerns regarding the fetal radiation dose associated with helical computed tomography scanning, but recent studies conclude that the average fetal radiation dose with this technique is less than that with ventilation–perfusion scanning (0.58 rad). The maternal breast tissue is, however, especially sensitive to radiation exposure during pregnancy.

D-dimer levels can be elevated in pregnancy due to the physiological changes in the coagulation system and if there is another problem such as preeclampsia, threatened miscarriage or antepartum haemorrhage. A 'positive' D-dimer test in pregnancy cannot therefore be used as a diagnostic tool, but a low level of D-dimer in pregnancy is likely, as in the non-pregnant patient, to suggest that there is no VTE. Once the suspicion of VTE in pregnancy has been raised, treatment should be commenced while diagnostic tests are awaited.
Warfarin is rarely recommended for use in pregnancy (exceptions include women with prosthetic heart valves) as it crosses the placenta and is teratogenic in the first trimester. There is a 6% risk of warfarin embryopathy if it is taken between 6 and 12 weeks' gestation. The risk of miscarriage and stillbirth is also increased. There is also a significant risk of fetal intracerebral haemorrhage when warfarin is used in the third trimester.

LMWHs are now the treatment of choice. They do not cross the placenta and have been shown to be at least as safe and effective as unfractionated heparin in the treatment of VTE, with fewer haemorrhagic complications in the initial treatment of subjects who are not pregnant. LMWH is safe and easy to administer. Women are taught to inject themselves and can continue on this treatment for the remainder of their pregnancy.

Intravenous unfractionated heparin can be used for initial treatment, followed by 6 months of LMWH in therapeutic doses or adjusted-dose subcutaneous unfractionated heparin. Unfractionated heparin treatment is, however, associated with heparin-induced thrombocytopenia and is much more difficult to monitor than LMWH.

Following delivery, women can choose to convert to warfarin, with the need for initial stabilisation of the dose and frequent checks of the international normalised ratio, or to remain on LMWH. Both heparin and warfarin are safe for use in women who are breast-feeding.

Graduated elastic compression stockings should be used for the initial treatment of DVT and should be worn for 2 years following a DVT to prevent post-phlebitic syndrome. The RCOG has a guideline on the management of acute VTE in pregnancy and the postnatal period.

**Practice points**

- Rapid treatment of suspected VTE in pregnancy should be commenced while awaiting diagnosis.
- LMWHs are now the treatment of choice.
- Graduated compression stockings should be properly fitted and worn for 2 years.

**Thrombophilia in pregnancy**

There is growing evidence that both heritable and acquired thrombophilias are associated with several adverse pregnancy outcomes—pregnancy loss, preeclampsia, abruptio and intrauterine growth restriction (IUGR). All these conditions are associated with thrombotic damage in the placental bed. The major hereditary forms of thrombophilia currently recognised include deficiencies of the endogenous anticoagulants—antithrombin, protein C and protein S; abnormalities of procoagulant factors—factor V Leiden and the prothrombin gene mutation G20210A; and homozygosity for methylene-tetrahydrofolate reductase C677T, which in conjunction with an insufficient dietary intake of B vitamins, is associated with hyperhomocystinaemia and, in turn, increased vascular risk. Heritable thrombophilias are present in at least 15% of Western populations.

If thrombophilic disorders are taken together, more than 50% of women with pregnancy-related VTE will have a thrombophilia identified on testing. The most commonly found is factor V Leiden. This in found primarily in Caucasian individuals (in approximately 5–8% of Europeans, Jews, Arabs and Indians), in 5.2% of American whites and in 1.2% of African Americans, whereas it is rare in Asian and African populations. Approximately 20% of those with the factor V Leiden mutation will be heterozygous and 1.5% homozygous for factor V Leiden.

Women with a known thrombophilia should ideally be seen for prepregnancy counselling. Screening should be undertaken outside pregnancy, the risks discussed and a plan made to commence thromboprophylaxis in early pregnancy if appropriate. Advice should be taken on how to interpret an abnormal thrombophilia screen result sampled within pregnancy or while the patient is being treated with heparin or warfarin.

**Thrombophilia and adverse pregnancy outcome**

In the first trimester, in a healthy pregnancy, the trophoblast invades the uterine decidua and reaches the inner layer of the myometrium. This trophoblast migration transforms the small, musculoelastic spiral arteries into large (a 4-fold increase in diameter) sinusoidal vessels, resulting in a high-capacitance, low-resistance blood supply to the intervillous space. Although it starts in the first trimester, the change is completed in the second trimester when a second wave of trophoblast migration alters the myometrial segments of the arteries. Inadequate invasion of the maternal circulation by the trophoblast and damage to the spiral arteries supplying the placenta lead to impaired flow and thrombotic changes in the vessel wall, which are implicated in adverse pregnancy outcomes including miscarriage, IUGR, preeclampsia with fetal compromise and stillbirth.

**Recurrent fetal loss**

Around 25% of human conceptions end in miscarriage, and in the majority of these cases no identifiable cause is found. It is considered that the causes are heterogeneous, particularly with regard to very early losses. Recurrent fetal loss (three or more successive losses) affects 1–2% of women of reproductive age, and two or more successive losses affect around 5%. Investigations will reveal anatomical, chromosomal, endocrinological or immunological problems in the mother or the fetus in a small number of cases.

A recent systematic review by Robertson et al. has been the first to present the overall relationship between all major thrombophilias and VTE and the adverse outcomes of pregnancy loss, preeclampsia, IUGR and abruptio. The data for early pregnancy loss appear to be easier to interpret than those on recurrent early pregnancy loss and non-recurrent pregnancy loss in the second trimester. Significant associations with early pregnancy loss are observed in carriers of homozygous factor V Leiden (odds ratio (OR) 2.71, 95% confidence interval (CI) 1.32–5.58), heterozygous factor V Leiden (OR 1.68, 95% CI 1.09–2.58), prothrombin heterozygosity (OR 2.49; 95% CI 1.24–5.00), anticardiolipin antibodies (OR 3.40; 95% CI 1.33–8.68), lupus anticoagulant
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(OR 2.97, 95% CI 1.03–8.56), acquired activated protein C resistance (OR 4.04, 95% CI 1.67–9.76) and hyperhomocysteinaemia (OR 6.25, 95% CI 1.37–28.42). Women with the factor V Leiden mutation (homozygotes and heterozygotes) are at higher risk of pregnancy loss in the second trimester compared with the first (OR 4.12, 95% CI 1.93–8.81 and OR 1.91, 95% CI 1.01–3.61, respectively). In women with prothrombin heterozygosity, the risk of non-recurrent second trimester loss was increased more than 3-fold (OR 8.60, 95% CI 2.18–33.95) compared with recurrent first trimester loss (OR 2.70, 95% CI 1.37–5.35).

Not all studies in the literature demonstrate an association between thrombophilia and late pregnancy loss. In Robertson et al.’s9 systematic review, significant associations were observed in carriers of heterozygous factor V Leiden (OR 2.06, 95% CI 1.01–3.86), heterozygous prothrombin (OR 2.66, 95% CI 1.28–5.53), protein S deficiency (OR 20.09, 95% CI 3.70–109.15) and anticardiolipin antibodies (OR 3.30, 95% CI 1.62–6.70).

Preeclampsia

Preeclampsia is associated with widespread endothelial damage and dysfunction, with activation of the coagulation system and microvascular fibrin deposition. This can affect multiple organs, including the liver, kidney, brain and placenta. Despite the association with coagulation activation, the role of heritable thrombophilias in preeclampsia has been controversial. There are conflicting results from different studies, which may reflect the varying definitions of these complications, different selection criteria and the small number of cases included. The most common heritable thrombophilia—factor V Leiden—was identified in 4.5–26% of women with severe preeclampsia, eclampsia or HELLP syndrome (haemolysis, elevated liver enzymes and low platelets). When restricting the analysis to severe preeclampsia only in the Glasgow systematic review, an OR of 2.04 (95% CI 1.23–3.36) was found in women heterozygous for the factor V Leiden mutation.

Placental abruption

It is more difficult to ascertain the relationship between thrombophilias and abruptio placentae as there are many confounding variables such as chronic or acute hypertensive problems and cigarette smoking. Abruption is often found in the context of other pregnancy complications such as preeclampsia. Small studies have examined the prevalence of thrombophilia in women with abruption. Overall, thrombophilia was associated with an increased risk of placental abruption, but significant associations were only observed with heterozygous factor V Leiden (OR 4.70, 5% CI 1.13–19.59) and heterozygous prothrombin (OR 7.71, 95% CI 3.01–19.76).

IUGR

Just as with preeclampsia, recent studies have produced conflicting evidence on the association between the thrombophilias and IUGR. Meta-analyses have also varied. For example, Alferivc et al.10 did not report an association between factor V Leiden and IUGR, whereas the more recent analysis by Dudding and Attia11 did (OR 4.8, 95% CI 2.4–9.4). This may reflect additional pregnancy complications associated with factor V Leiden in the women with IUGR in the later meta-analysis. In Robertson et al.’s12 systematic review, there was a general trend of increased IUGR risk in women with thrombophilia, but a significant association was observed only with the presence of anticardiolipin antibodies (OR 6.91, 95% CI 2.70–17.68).

Practice points

• Screening for the thrombophilias should be carried out in pregnant women with a strong personal or family history of VTE.
• The prevalence of thrombophilia in the population does not justify universal screening of the pregnant population.
• There is evidence in some studies of links between the thrombophilias and adverse pregnancy outcome such as recurrent pregnancy loss, preeclampsia, abruption and IUGR.

Research directions

• Further studies are needed on the relationship between thrombophilia and adverse pregnancy outcome.
• Randomised trials of antithrombotic treatment in women with a known thrombophilia and previous adverse pregnancy outcome are required.

The incidence of VTE in pregnancy and its role in maternal morbidity and mortality makes it an important issue for all obstetricians. The Confidential Enquiry into Maternal Deaths in the UK13 makes it clear that there is still work to be done to improve recognition of the risk factors and thus prevention, as well as in the acute treatment of VTE when it occurs in pregnancy.

The true incidence of the contribution of the thrombophilias is not yet fully known but is the subject of current research. Women with a known thrombophilia are at increased risk of personal VTE during pregnancy, and their management during pregnancy must reflect this. Some are also at risk of adverse pregnancy outcome, but the optimal management for these women still needs to be subjected to randomised controlled trials.

References


