Thromboembolism and thrombophilia in pregnancy

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Abstract

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 postpartum 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 recent increased interest in the thrombophilias and their link with recurrent miscarriage, pre-eclampsia, 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.

Keywords pregnancy; thromboembolism; thrombophilia

Introduction

One of the many early physiological adaptations of pregnancy involves changes in the coagulation system, which 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 to nonpregnant women. This risk is manifest from early in the first trimester until 4–6 weeks postpartum.

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 2003–2005, published in December 2007, there were 41 deaths from thrombosis – 33 were from pulmonary embolus and 8 from cerebral vein thrombosis. Without thromboprophylaxis, the incidence of non fatal pulmonary thromboembolism (PTE) and deep venous thrombosis (DVT) in pregnancy is about 0.1% in developed countries, this increases following delivery and the risk of DVT after caesarean section is around 1–2%, increasing further following emergency caesarean section. Venous Thromboembolism (VTE) is not just confined to late pregnancy and operative delivery though. In the Confidential Enquiry into Maternal Deaths two thirds of antenatal fatal PTE were in the first trimester, and over 50% of the postnatal VTE deaths were after vaginal delivery.

In the acute phase, DVT can lead to pulmonary embolus, while 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 is a major cause not only of maternal mortality but also of maternal morbidity.

Physiological changes in the coagulation system during pregnancy

Pregnancy is associated with a 6–10 fold increase in risk of VTE compared to the nonpregnant situation. The frequency of VTE is similar in all three trimesters, but the highest risk per day is during the postpartum period. Pregnancy is a hypercoagulable state. From Table 1 we can see that there is an increase in several procoagulant factors, a reduction in endogenous anticoagulant activity, suppression of fibrinolysis and venous stasis.

Changes in coagulation factors during pregnancy

Coagulation variable	Change
Factors: X, VIII, Von willebrand	Progressive increase throughout pregnancy
Fibrinogen	Increase, reaching a two folds increase over nonpregnant level at term
Antithrombin and protein C	No change
Protien S activity	Reduced
Plasminogen & Antiplasmin	Two fold increase over nonpregnant levels
Plasminogen activator inhibitor types 1 and 2	Increased
Plasminogen activator (t-PA)	Reduced
Venous flow velocity	Reduced reaching a nadir at 30 weeks gestation, and takes up to 6 weeks after delivery to return to nonpregnant values.

Table 1

Practice points

- Pregnancy is a hypercoagulable state
- The increased risk of thrombosis begins early in the first trimester and continues until 4–6 weeks postpartum
- The postpartum period is the time of highest risk

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Pre existing risk factors

Age >35
Obesity BMI > 30 kg/m^2
Parity >3
Previous thromboembolism
Thrombophilia (see below)
Gross varicose veins
Paraplegia
Sickle cell disease
Medical conditions e.g. inflammatory bowel disease, nephrotic syndrome

Box 1

Risk factors for venous thromboembolism in pregnancy

In some women the risks are increased further because they have one or more additional risk factors (Boxes 1 and 2). Of particular note is the association with obesity, which is an increasing problem.

Women should have a risk assessment for VTE performed at booking, to include the risk factors as listed above. However, this risk is 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.

Prevention of venous thromboembolism in pregnancy

Thromboprophylaxis during pregnancy

Women with a previous thrombotic event have an increased risk of recurrence in pregnancy (relative risk during pregnancy: 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, population screening of all pregnant women cannot 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 LMWH from early in the first trimester until 6 weeks postpartum. Low dose aspirin (75 mg daily) is of benefit in DVT prevention in surgical and medical patients, but there are no randomised control trials in pregnancy. Some clinicians will use aspirin if a woman is at increased risk of VTE but not high enough to justify LMWH, but this is still controversial.

Transient risk factors

Hyperemesis
OHSS (ovarian hyperstimulation syndrome)
Dehydration
Long-haul travel
Surgical procedure
Infection eg pyelonephritis
Immobility
Pre-eclampsia

Postpartum:
Prolonged labour
Operative delivery
Excessive blood loss

Box 2

The use of graduated elastic compression stockings (GCS) is recommended in all women with a previous VTE or thrombophilia during the pregnancy and for 6–12 weeks postpartum and these should be fitted according to patient size. These reduce venous stasis in the lower limb by reducing the diameter of the common femoral vein and increasing the rate of blood flow. There is evidence that below-knee GCS are as effective as full-length stockings and their use may increase compliance.

There are guidelines published by The Royal College of Obstetricians and Gynaecologists covering both pregnancy and the postpartum period (Table 2), and these are currently being updated.

Postpartum thromboprophylaxis

Further reassessment of risk factors for VTE should be performed before or during labour. Age over 35 and weight >80 kg (BMI >30 kg/m^2) are independent risk factors for postpartum VTE even after vaginal delivery. These risk factors in combination with any other risk factor (such as pre-eclampsia, 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 consideration of the use of low molecular weight heparin (LMWH) for 3–5 days postpartum or until fully mobile. There is emerging work that it may take several weeks for the hypercoagulable state of pregnancy to return to normal, and so for high risk patients the postnatal course is increased to 6 weeks. The 1995 RCOG guideline for the use of thromboprophylaxis following caesarean section has led to the almost universal adoption in protocols of thromboprophylaxis following emergency caesarean section and indeed in many units all women undergoing a caesarean section are given LMWH following delivery. Despite this, the recent UKOSS survey of antenatal PE, demonstrated that only 33% of those who should have received antenatal thromboprophylaxis actually did so, and 50% of those who had a PTE while receiving thromboprophylaxis were on an inadequate dose.

Diagnosis of acute venous thromboembolism

As clinical diagnosis of VTE is unreliable, women who are suspected of having a DVT or PTE should be investigated promptly using diagnostic imaging.

Deep vein thrombosis

Because of its high sensitivity and specificity in diagnosing proximal thrombosis in the nonpregnant woman, compression ultrasound should be the first investigation used in a suspected DVT. If the scan is negative and there is low clinical suspicion, treatment can be stopped. With high clinical suspicion and a negative scan, treatment should be continued and the scan repeated in one week.