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The diagnosis and treatment of thromboembolic disease in pregnancy

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ABSTRACT Pulmonary thromboembolism remains the most common direct cause of maternal death in the UK (see *Why Mothers Die* by J Drife; http://www.rcpe.ac.uk/fellows/CME/maternal/drife/drife_1.html). Pregnancy is associated with prothrombotic changes in the coagulation system, and therefore the risk of VTE disease is increased at any time during the pregnancy but is highest in the puerperium and greatest in women who have undergone caesarean section.

KEYWORDS Diagnosis, pregnancy, thromboprophylaxis, treatment, venus thromboembolism

LIST OF ABBREVIATIONS Activated partial antithromboplastin time (APTT), activated protein C (aPC), acute coronary syndromes (ACS), antithromboplastin time (APTT), central nervous system (CNS), chest X-ray (CXR), computed tomographic pulmonary angiography (CTPA), deep vein thrombosis (DVT), heparin-induced thrombocytopenia (HIT), international normalised rate (INR) low molecular weight heparin (LMWH), magnetic resonance imaging (MRI), pulmonary thromboembolism (PTE), transthoracic echocardiogram (TTE), unfractionated heparin (UH), venous thromboembolic (VTE), lung scan (V/Q)

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SUMMARY

Pregnancy is a prothrombotic condition, but despite advances in the prophylaxis and treatment of VTE disease, PTE remains the most common direct cause of maternal death in the UK. Diagnosis is difficult because many of the symptoms of VTE disease occur in normal women, so in order to avoid unnecessary anticoagulation, women with signs or symptoms of VTE should undergo objective testing. Anticoagulant treatment should be started immediately and a CXR, V/Q scan (for PTE), and bilateral Doppler ultrasound leg studies (for DVT) performed. Measurement of D-dimer is unhelpful as it is often raised in normal pregnancy, while echocardiography can help in patients who are haemodynamically unstable.

Treatment can be either with UH or LMWH; however, as experience grows, LMWH is emerging as the preferred formulation. Dosing is easier with LMWH since activated partial APTT monitoring is problematic even in the non-pregnant woman, and apparent heparin resistance in pregnancy can interfere with the APTT test and result in unnecessarily high doses being used. Low molecular weight heparin also allows women to self-medicate and is associated with a lower risk of osteoporosis, bone fractures, and HIT than is UH. Warfarin use in pregnancy carries many risks, including embryopathy, miscarriage, and stillbirth. The risks are increased in women requiring greater than 5 mg warfarin and the risk of teratogenesis can probably be eliminated if warfarin is avoided between 6 and 12 weeks' gestation.

Treatment should be continued throughout pregnancy. Where VTE occurs early in pregnancy, after six months the anticoagulation may be reduced for the remainder of the pregnancy. It is recommended that anticoagulant treatment be continued for 6–12 weeks postpartum, depending upon circumstances.

Pre-pregnancy assessment of thromboembolic risk is the ideal and, failing this, risk factor assessment should occur in all women at booking. Those with a prior history of VTE should be screened for both acquired and inherited thrombophilias, and antenatal thromboprophylaxis offered, dependent upon risk.

THE DIAGNOSIS OF VTE IN PREGNANCY

Pregnancy provides difficulties for the physician in both the diagnosis and treatment of VTE because of concerns that intervention may affect the fetus. The diagnosis of both DVT and PTE provides the clinician with challenges, since leg swelling and discomfort and breathlessness are common symptoms in normal pregnancy. Less than half of patients with a suspected diagnosis of VTE are confirmed with objective testing. In order to avoid the risks, inconvenience, and costs of inappropriate anticoagulation, any woman with signs and symptoms suggestive of VTE should undergo objective testing. In cases of suspected VTE, treatment should be commenced

immediately and a CXR, V/Q scan (for PTE), and bilateral leg Doppler ultrasound leg studies (for DVT) should be performed. In the case of suspected PTE, initially, a perfusion scan alone can be performed, with a ventilation scan only being carried out if the perfusion scan is abnormal. Chest X-ray and V/Q are associated with negligible radiation to the fetus. Treatment should be continued if the V/Q reports either a 'medium' or 'high' probability of PTE and, in the case of a 'low' probability, if the Dopplers are also positive. In a case where there is a high degree of suspicion of PTE but the V/Q is reported as low probability and Dopplers are negative, then anticoagulation should be continued and the tests repeated one week later. Computed tomographic pulmonary angiography and MRI are safe during pregnancy. The radiation dose to the fetus of a CTPA is minimal although there is significant radiation of the maternal breast. However, this investigation may be indicated if proximal PTE is suspected or if CTPA is the standard diagnostic tool for PTE in an individual hospital. Diagnosis of DVT is best achieved with ultrasound.

D-dimer is often elevated in pregnancy owing to the normal physiological changes in the coagulation system, and this is exacerbated in states such as pre-eclampsia. Therefore, measurement of D-dimer is not usually helpful in the setting of pregnancy.

In cases where the patient is haemodynamically unstable a bedside TTE may aid in the diagnosis, though this is not a very sensitive test. Large PTE may be associated with a number of abnormal echo findings, including right ventricular dilation, abnormal septal motion, loss of right ventricular contractility, elevated pulmonary artery or right ventricular pressures, moderate to severe tricuspid regurgitation, pulmonary regurgitation, and occasionally visualisation of clot in the right ventricle or pulmonary artery. The presence of these findings on TTE is not unique and, whilst their presence raises the suspicion of PTE, this may not be the optimal diagnostic tool.

TREATMENT OF ACUTE THROMBOEMBOLISM IN PREGNANCY

In clinically suspected VTE, treatment with either UH or LMWH should be given until the diagnosis is excluded by objective testing, or unless treatment is strongly contraindicated (e.g. active bleeding). Intravenous UH is the traditional method of administering heparin in acute VTE and remains the preferred treatment in massive PTE because of its rapid effect and extensive use in this situation. There is, however, increasing realisation in clinical practice that the APTT monitoring of UH that is required is poorly performed and technically problematic. During pregnancy, an apparent heparin resistance occurs due to increased fibrinogen and Factor VIII levels which affect the APTT results. As a consequence, unnecessarily high doses of heparin may be administered with haemorrhagic sequelae. The pharmacokinetic properties of LMWH allow fixed dose subcutaneous regimens and thus minimise or avoid the need for monitoring. If, however, UH is required, then measurement of the anti-Xa level as a measure of anticoagulation avoids these overdosing concerns.

Low molecular weight heparins are as effective as UH in the treatment of PTE, and are more effective in the treatment of DVT in non-pregnant women. Whilst no randomised clinical trials have been carried out in pregnant women, and there is no specific license for use of these agents in pregnancy, systematic reviews have concluded that LMWH is a safe alternative to UH as an anticoagulant during pregnancy and, specifically, is associated with a lower risk of HIT and osteoporosis than is UH. Monitoring anti-Xa activity does not appear to be necessary, except possibly at the extremes of weight. LMWHs can be reversed with protamine sulphate but repeated doses may be necessary in view of the long half-life of LMWH. The treatment doses of LMWH vary depending upon the specific LMWH but are higher than those used in the non-pregnant woman. Essentially, the dose is the same as that for ACS and so, in the example of enoxaparin, is 1 mg/kg bd instead of 1·5 mg/kg od. The appropriate doses of LMWH for thromboprophylaxis and treatment of VTE in pregnancy are shown in Table 1. In the postpartum period the dose is the same as in the non-pregnant woman.

Inferior vena cava filters are only indicated in the case of documented inferior vena cava or ileofemoral DVT with recurrent PTE, despite adequate anticoagulation.

THROMBOPHILIA SCREEN

Ideally, before anticoagulation is commenced, a thrombophilia screen should be taken, as well as the usual full blood count, coagulation screen, urea and electrolytes, and liver function tests. A thrombophilia screen will not influence the immediate management of a suspected or confirmed VTE, but it may provide information for the

TABLE 1 Antenatal prophylactic and therapeutic doses of different LMWHs for an average (50–90 kg) sized woman. (Adapted from Royal College of Obstetricians and Gynaecologists. *Thromboprophylaxis During Pregnancy, Labour and After Vaginal Delivery. Guideline no. 37.* London: RCOG Press; 2004.)

	Enoxaparin	Dalteparin	Tinzaparin
Prophylaxis	40 mg daily	5,000 units daily	4,500 units daily
High prophylactic dose	40 mg 12 hourly	5,000 units 12 hourly	4,500 units 12 hourly
Treatment dose	1 mg/kg 12 hourly	90 units/kg 12 hourly	90 units/kg 12 hourly or 175 units/kg daily

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duration and intensity of anticoagulation (for example, if antithrombin deficiency is identified). Thrombophilia screens, however, need to be interpreted by clinicians with specific expertise in the area since both pregnancy and acute thrombus may affect the results. Protein S levels fall in pregnancy, making a deficiency difficult to diagnose, whilst aPC resistance is found in 40% of pregnancies. Anticardiolipin antibodies can influence the aPC result, and antithrombin may be reduced when extensive thrombus is present. Clearly, genotyping for Factor V Leiden and prothrombin G20210A will not be influenced by pregnancy or acute VTE.

MAINTENANCE TREATMENT OF DVT OR PTE

Warfarin is normally avoided during pregnancy. Oral anticoagulants readily cross the placenta and are associated with a characteristic embryopathy in the first trimester, CNS abnormalities, fetal haemorrhage, miscarriage, and stillbirth. The embryopathy occurs in 5–6% of patients taking warfarin throughout pregnancy and it is probable that the risk can be eliminated if the drug is avoided between the sixth and twelfth weeks of gestation. The risk is greater when patients require more than 5 mg per day to maintain a therapeutic INR. Central nervous system abnormalities and intracerebral haemorrhage can occur at any time during the pregnancy, and the concern regarding haemorrhagic problems in the neonate from a combination of the anticoagulant effect in the fetus and traumatic delivery means that warfarin use is avoided in the two weeks prior to delivery.

Low molecular weight heparin is the anticoagulant of choice. As well as the advantages of LMWH discussed earlier, women can be taught to self-administer and can be managed as outpatients until delivery. Long-term use of LMWH is associated with a lower risk of osteoporosis and bone fractures than UH.

Anticoagulant treatment should be continued throughout pregnancy, but if the VTE occurs early in pregnancy it may be appropriate to decrease doses to a high prophylactic level after six months. Regional anaesthesia or analgesia is usually permitted 12 hours after a prophylactic dose of LMWH, but most obstetric anaesthetists recommend a 24-hour interval between a treatment dose of LMWH and neuroaxial blockade. Therefore some women receiving treatment doses of LMWH may be denied regional anaesthesia, necessitating general anaesthesia if a caesarean section is required. However, with careful multidisciplinary planning of delivery this can usually be avoided by reducing the dose of LMWH on the day prior to planned induction of labour or delivery by caesarean section.

Following delivery, treatment should continue for at least 6 to 12 weeks, and at three months the woman should be assessed for continuing risk factors for VTE. Warfarin and LMWHs are safe to use in breast-feeding mothers.

THROMBOPROPHYLAXIS DURING PREGNANCY, LABOUR, AND POSTPARTUM

Caesarean section is associated with the highest risk of VTE in the puerperal woman. Guidelines exist (from 1995) detailing thromboprophylaxis in gynaecology and obstetrics and highlight the particular risks in those women who have undergone caesarean section. However, deaths from VTE following vaginal delivery also occur, and more recent Guidelines (from 2004) from the RCOG address this group. Ideally, women with a previous VTE should have pre-pregnancy (or at least early pregnancy) screening for both inherited and acquired thrombophilia. Regardless of their risk of VTE, immobilisation of women during pregnancy, labour, and puerperium should be minimised, and dehydration should be avoided.

Women with previous VTE and no thrombophilia should be offered prophylaxis with LMWH for six weeks after delivery. Whether they also require antenatal thromboprophylaxis with LMWH is controversial and it is reasonable to avoid it in women with a previous single VTE with a temporary risk factor that has now resolved.

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TABLE 2 Prevalence and Risk of VTE with different thrombophilias. (Adapted from Kujovich JL. Thrombophilia and pregnancy complications. *Am J Obstet Gynecol* 2004; **191:**412–424.)

Thrombophilic disorder	% of general population	Relative risk of VTE
Antithrombin deficiency	0·07	10–20
Protein C deficiency	0·3	6–8
Protein S deficiency	0·2	2–6
Factor V Leiden (heterozygous)	5–8	4–8
Factor V Leiden (homozygous)	0·06	80
Prothrombin gene mutation	3	2–4
Antiphospholipid antibodies	2	9
Acquired APC resistance without Factor V Leiden	8–11	2–4

TABLE 3 Summary of the recommendations for thromboprophylaxis for pregnant women with previous VTE or those with identified thrombophilias. (Adapted from Royal College of Obstetricians and Gynaecologists. *Thromboprophylaxis During Pregnancy, Labour and After Vaginal Delivery. Guideline no. 37.* London: RCOG Press; 2004.)

Very high risk	Previous VTE (± thrombophilia) on long term warfarin	Antenatal high dose or therapeutic LMWH and at least six weeks postnatal warfarin. These women require specialist management by experts in haemostasis and pregnancy
	Antithrombin deficiency	
High risk	Previous recurrent VTE	Antenatal and six weeks postnatal prophylactic LMWH
	Previous VTE + thrombophilia	
	Previous VTE + family history of VTE	
	Asymptomatic thrombophilia (combined defects, homozygous Factor V Leiden L)	
Moderate risk	Single previous provoked VTE without thrombophilia, family history or other risk factors	Six weeks postnatal prophylactic LMWH ± antenatal low dose aspirin
	Asymptomatic thrombophilia (except antithrombin deficiency, combined defects, homozygous Factor V Leiden)	

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In contrast, women with previous recurrent VTE and those with a single previous VTE and a family history of VTE in a first-degree relative should be offered thromboprophylaxis throughout pregnancy and for six weeks postpartum.

Thrombophilias offer different risks of VTE depending upon the specific abnormality. The risk of VTE with different thrombophilias is summarised in Table 2. Current evidence supports, and existing guidelines recommend, that women with previous VTE and an identifiable thrombophilia should also receive LMWH antenatally and for six weeks postpartum.

Women with inherited thrombophilia without previous VTE should be stratified according to the level of risk associated with their individual thrombophilia. Since the risk of VTE is lower in those women without a prior history, antenatal prophylaxis is not always necessary, except in those with combined defects, those who are homozygous for Factor V Leiden or prothrombin gene mutation, or those with antithrombin deficiency. A summary of the recommendations for thromboprohpylaxis for women with previous VTE or those with identified thrombophilias is given in Table 3. Low molecular weight heparin should also be used in women without a previous VTE or thrombophilia if they have three or more persisting risk factors (Table 4). This probably can be discontinued 3–5 days postnatally. The appropriate dose for thromboprophylaxis is 40 mg od enoxaparin or 5,000 units of dalteparin.

HIGHLIGHTS

- Any women with signs and symptoms suggestive of VTE disease should have objective testing performed expeditiously to avoid the risks, inconvenience, and costs of inappropriate anticoagulation.
- In clinically suspected DVT or PTE, treatment with LMWH should be given at the ACS dose until the diagnosis is excluded by objective testing.
- Low molecular weight heparin is a safe alternative to UH, is easier to administer, and is associated with less osteoporosis and HIT. The dose required for treatment is higher than in the non-pregnant woman and is the same as the ACS dose. Maintenance treatment should continue for 6–12 weeks postpartum. In the postpartum period the dose is the same as in the non-pregnant woman.
- Warfarin is usually avoided in pregnancy, except in some cases of mechanical valves. There is a risk of embryopathy if it is used during weeks 6–12 of pregnancy. Warfarin may be used in the postpartum patient and is not contraindicated during breastfeeding.
- Patients with prior history of VTE should be screened for acquired and inherited thrombophilia and treated depending upon their risk. Pregnancy itself can alter the thrombophilia screen, and the results should thus be interpreted by someone with expertise in the area.

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TABLE 4 Risk factors for venous thromboembolism in pregnancy and the puerperium. (Adapted from Royal College of Obstetricians and Gynaecologists. *Thromboprophylaxis During Pregnancy, Labour and After Vaginal Delivery. Guideline no. 37*. London: RCOG Press; 2004.)

Pre existing	**New onset or transient**
Previous VTE	Surgical procedure in pregnancy or puerperium, e.g. ERPC
Thrombophilia	Hyperemesis
Congenital	Dehydration
Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden Prothrombin gene variant	Ovarian hyperstimulation syndrome
	Severe infection, e.g. pyelonephritis
	Immobility (> four days' bed rest)
Acquired (antiphospholipid syndrome)	Pre-eclampsia
Lupus anticoagulant Anticardiolipin antibodies	Excessive blood loss
	Long haul travel
	Prolonged labour
	Midcavity instrumental delivery
Age > 35 years	Immobility after delivery
Obesity (BMI > 30 kg/m^2)	
Parity > 4	
Gross varicose veins	
Paraplegia	
Sickle cell disease	
Inflammatory disorders e.g. UC/Crohn's	
Some medical disorders, e.g. nephrotic syndrome	
Myeloproliferative disorders, e.g. ET, PRV	

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FURTHER READING

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