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Thromboembolic disorders in obstetrics

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Thromboembolic disorders remain a leading cause of maternal mortality in the developed world. The halving of the number of deaths from thromboembolic disorders in the last Confidential Enquiry provides further proof that they are largely preventable. A formal assessment of risk factors (e.g. previous thromboembolic disorders, thrombophilia, obesity) should be made at booking and at the time of delivery, or when intercurrent problems develop or the woman is admitted. Women with risk factors pre-dating pregnancy should be offered pre-pregnancy counselling and planning. Thromboprophylaxis should be instituted as soon as practical, bearing in mind that potentially fatal thromboembolic disorders may occur in the first trimester. All women presenting in pregnancy with new chest symptoms should be thoroughly investigated. Imaging is safe and should not be withheld. Treatment should be started empirically while the investigations are completed. Both prophylaxis and treatment doses should be carefully adjusted to take into account the weight of the woman.

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Introduction

Thromboembolic disease (TED) remains an important cause of preventable maternal mortality. The report on the last triennium (2006–2008) of the Confidential Enquiry into Maternal Deaths[1] shows a sharp and statistically significant fall in deaths for the first time since 1985, when the UK-wide enquiry began. This was attributable mainly to a reduction from antenatal deaths and deaths after vaginal delivery. This fall follows dissemination and implementation of national guidelines on prevention, diagnosis and treatment of TED in pregnancy.[2,3]

Epidemiology

Thromboembolic disease encompasses a variety of clinical entities, most important of which are deep-venous thrombosis (DVT), pulmonary embolism (PE) and cerebral-vein thrombosis (CVT). The epidemiology of TED in pregnancy differs significantly from that of the disease in non-pregnant women, and these differences have important clinical implications.

The incidence of TED has been estimated in retrospective studies to be between five and 12 in 10,000 in pregnancy and three to seven in 10,000 in the puerperium.[4,5] This represents a seven- to 10-fold increase compared with age-matched non-pregnant women.[5,6] The incidence of DVT is about three times that of pulmonary embolism,[5] but pulmonary embolism is significantly more frequent in the puerperium than in pregnancy.[5] The incidence of CVT is 8.9 in 100,000 pregnancies.[7]

Numerically, the incidence of morbidity is relatively evenly distributed[8]; however, the per day risk is four times higher in the puerperium. In the antenatal period, there is a steady increase in the event rate from 22% in the first, 34% in the second to 48% in the third trimester, according to a meta analysis of cases.[8] In the postnatal period, the incidence is highest in the first 3 weeks after delivery, after which it returns to antenatal levels then to pre-pregnant levels after 6 weeks.[9,10] A wide variation exists between reports on the time distribution of fatal pulmonary embolism. Some reports suggest that 44% of deaths occur in the first trimester[11]; the proportion was just under 20% in the recent UK Maternal death enquiry.[1] The important fact to bear in mind is that pulmonary embolism does occur and may be fatal in this period, highlighting the importance of pre-pregnancy counselling and increased vigilance from early pregnancy.

Pathophysiology

The components of the classical Vichow's triad are present in pregnancy and puerperium: hypercoagulability, venous stasis and vascular damage.

Pregnancy is a hypercoagulable state; the balance of natural pro and anticoagulant factors is significantly changed. From early in pregnancy, an increase in thrombin generation is evident as measured by global tests,[12] prothrombin fragment 1 + 2 and thrombin-antithrombin complexes.[13,14] Levels of pro-coagulant factors: VII, VIII, X, fibrinogen, von Willebrand factor increase. Levels of endogenous anticoagulant protein S decrease. Antithrombin and protein C remain the same, and acquired resistance to activated protein C develops.[13,15] Fibrinolysis is diminished as levels of tissue plasminogen activator fall and levels of plasminogen activator inhibitor (PAI) rise.[14]

Venous stasis also develops from early pregnancy owing to the effects of progesterone on the vessel wall. As pregnancy progresses, mechanical factors become more important, and the gravid uterus increasingly obstructs venous return through the pelvic veins. The decrease in flow velocity is most pronounced in the common femoral veins, which are also the most common site of DVT in pregnancy.[16] In pregnancy, the thrombosis is in the left leg in 85% of cases. This is thought to be caused by compression of the left iliac vein by the ipsilateral ovarian and iliac arteries.[17] Venous stasis is more pronounced if a previous thrombosis has occurred, as this can lead to permanent damage to the vessel wall and valvular reflux.[18,19]

Damage to the pelvic veins occurs mainly during childbirth, from the mechanical pressure of the fetal head. Use of forceps and caesarean section may also damage the pelvic veins.

Risk factors

Identification of risk factors informs appropriate assessment on the need for thromboprophylaxis. The list is extensive (Table 1), and the increased risk conferred by various factors varies widely; however, it must be remembered that small effects can be additive or multiplicative,[20] and new ones may occur at any point during the pregnancy and puerperium.[21]

Previous venous thromboembolism and thrombophilia

Women with previous thrombotic events have a higher risk of recurrence in pregnancy and postpartum.[22] Although available studies are heterogeneous in design and enrolled a relatively small number of women, the risk can be stratified: the highest risk of recurrence is intuitively in women with previous recurrent venous thromboembolism (VTE), although the rate is unknown.[23] Recurrence rates for women with a history of a single previous episode of thrombosis are 5.8–6.2% overall during pregnancy, equally distributed along trimesters and 8.3–10% in the postpartum period.[24,25] The risk is higher for previous pregnancy-related or oestrogen-provoked events: 9.5–10%,[24,25] compared with 2.7% if the previous event was not pregnancy- or oestrogen-related.[24] Although the exact recurrence rates vary between studies, recent data support a higher risk attributable to this group.[26] The smallest risk is associated with a previous event, which was provoked by a temporary event, no longer present.

Thrombophilia can be inherited (antithrombin, protein C, protein S deficiency, factor V Leiden and prothrombin gene variant) or acquired (antiphospholipid syndrome, including lupus anticoagulant or anticardiolipin antibodies). Twenty to 50 per cent of women with thrombosis have a thrombophilia.[27] Again, the risk of VTE associated with each of these factors varies widely, and is also dependent on previous thrombotic history. The risk associated with asymptomatic defects is small, with the exception of those with antithrombin deficiency and combinations of defects.

Obesity

Obesity has emerged in recent years as an independent and important risk factor for TED.[9,22,28–31] Although the risk associated with obesity is moderate, it is prevalent in women of childbearing age;

Table 1
Risk factors for venous thromboembolism in pregnancy with adjusted odds ratios compared with women without the risk factor.[21]

Risk factor	Adjusted odds ratio
Pre-existing	
Previous venous thromboembolism	24.8 (22)
Obesity (body mass index over 30)	2.65–5.3 (22, 73)
Age over 35 years	1.3 (9)
Parity	1.5–4.03 (38)
Smoking	2.7 (22)
Sickle cell disease	1.7–6.7 (9)
Heart disease	5.4–7.1 (9)
Systemic lupus erythematosus	8.7 (22)
Varicose veins	2.4
New onset or transient	
Assisted reproductive therapy	4.3 (20)
Hyperemesis gravidarum	2.5 (20)
Pre-eclampsia	2.9–5.8 (11, 29)
Immobility	7.7–10.3 (20)
Multiple pregnancy	1.8–2.6
Postpartum specific	
Caesarean section	3.6 (9, 22)
Massive postpartum haemorrhage	9
Postpartum haemorrhage and major surgery	12 (22)
Postpartum infection	4.1 (22)

18% of those aged 25–34 years and 22% of those aged 35–44 years fell into this category in 2003 in the UK. The risk is most likely stratified, becoming stronger, the higher the body mass index.[28,32] In the recent Confidential Enquiry[1] of the 16 women who died from pulmonary embolism, three women had a BMI greater than 25, nine had a BMI greater than 30, including one with a BMI greater than 40. How obesity causes thrombosis is not entirely clear, and has been the subject of many studies. An association between obesity and increased hypercoagulability certainly exists as is reflected in increased thrombin generation.[33] Evidence is emerging that levels of PAI-1 are significantly raised in obese individuals,[34] with consequent inhibition of fibrinolysis. In addition, oxidative stress has been associated with adipose tissue. This leads to platelet activation, endothelial damage and shredding of activated platelet and endothelial cell derived microparticles, which in turn are thrombogenic.[34–36]

Diagnosis

The diagnosis of TED in pregnancy is not straightforward. Clinical decision rules[37] used in non-pregnant women cannot be easily extrapolated, and signs and symptoms commonly overlap with those of normal pregnancy. D-dimer, widely used in non-pregnant women, is often positive in pregnancy, and a negative test does not exclude the diagnosis; therefore, its use in the diagnosis of VTE in pregnancy is not recommended. Clinical judgement will dictate a high index of suspicion and objective diagnosis by the best imaging test available. The diagnostic yield of the investigations will remain low: only 5–10% of the women investigated will have confirmed TED.[38] Most diagnostic methods have not been specifically validated for pregnancy, and invalid concerns are still raised about their safety to the fetus.[39] The data on which these concerns are based are old and involve radiographic pelvimetry, with direct radiation to the gravid uterus and fetus. These procedures are no longer used and, even for these, the risk was small and not statistically significant.[39] Given the importance of the diagnosis of TED, accurate diagnosis is paramount,[40] and withholding imaging is hazardous and unjustified.[41]

Deep-vein thrombosis

Most DVT will occur in the lower limb and the pelvis. Significant differences exist in the location of the DVT in pregnant women compared with non-pregnant women. Eighty-two per cent of thrombi are left sided[42] and, importantly, 71% of clots are in the proximal veins, with 64% in the iliac or femoral veins without involvement of the calf veins.[43] The risk of embolisation posed by these thrombi is significant.

Clinical manifestations include swelling, feeling of heaviness, warmth and tenderness if the DVT is in the calf. These symptoms and signs, especially the swelling, can be present in normal pregnancy, and may be absent in isolated proximal DVT. Lower abdominal and groin pain, mild pyrexia, mild leukocytosis and swelling of the whole lower limb should raise the clinical suspicion of proximal thrombosis. It has been shown that experienced clinicians' subjective prediction of DVT is good, and that three variables contribute significantly to this prediction (the LEFt rule): symptoms in the left leg (L), calf circumference difference greater or equal to 2 cm (E), and first trimester presentation (Ft).[44]

The investigation of choice is compression ultrasound (CUS), preferably with Doppler (duplex ultrasound). The method is non-invasive, readily available, does not involve radiation and has good diagnostic performance. The sensitivity is 97%, and the specificity is 94%.[45] The method is relatively insensitive for calf-vein thrombosis, but these rarely embolise. In cases of high clinical suspicion, where the CUS is negative, treatment should be instituted on clinical grounds, and either the CUS repeated in 1 week, or an alternative imaging method used.

The alternative method of choice is magnetic resonance venography (MRV). MRV can be carried out without intravenous contrast, and is highly superior in the assessment of thrombosis in the vena cava, pelvic veins and lower extremities.[46] The sensitivity is 100% in the pelvis and thigh and 87% in the calf, with a specificity of 95–100%.[46] To date, no harmful effect has been shown at any stage in pregnancy.[47] Nevertheless, the current UK guidelines recommend that magnetic resonance imaging is not advisable in the first trimester, but it is preferable to ionising radiation. The major limitation of this imaging modality will be its local availability.

Pulmonary embolism

The most common clinical manifestations of pulmonary embolism are in decreasing frequency order (from 70% to 10%) dyspnoea, tachypnoea, chest pain, apprehension, tachycardia, cough with haemoptysis.[48] Hypoxaemia and haemodynamic collapse are less common.[49] Difficulties arise from the overlap of these symptoms with those of normal pregnancy, and the differentiation is often problematic. There are no hard and fast rules, but the occurrence of new chest symptoms, particularly if of sudden onset in a pregnant woman with risk factors, should always prompt investigations.[1] Clinicians should use their clinical judgement and pursue diagnostic imaging for suspected pulmonary embolism.[6]

The definitive imaging methods are associated with radiation exposure. The radiation to the mother and fetus (Table 2) should not be a deterrent, but the basis of careful risk-benefit considerations. The choice of imaging test will also be dependent on the clinical suspicion and local availability, and should be made by discussion with the radiologist. Generally, the risk from missing such an important diagnosis far outweighs the risk to the mother and fetus from the investigations. A proposed algorithm is included below (Fig. 1).

In individuals who are haemodynamically compromised with suspected pulmonary embolism, emergent bedside echocardiography is a useful adjunct. A massive pulmonary embolism will cause right ventricular enlargement and systolic dysfunction. Conversely, the absence of these makes pulmonary embolism as the cause of haemodynamic compromise unlikely.[50]

The first investigation in a stable individual is a chest X ray. The role of the chest X ray is not diagnostic and will be normal in over 50% of cases. Its role is to detect alternative pathology, which may explain the symptoms and make an alternative diagnosis to help inform the definitive diagnostic imaging test. The fetal radiation dose, especially with abdominal shielding from a chest X ray, is negligible.

Many authorities have proposed CUS as the next step,[2] and this should certainly be undertaken if there are signs of lower limb DVT. A diagnosis of DVT indicates full anticoagulation and obviates the need for further imaging and radiation. A proximal thrombus is found in 23–52% of pregnant women with confirmed pulmonary embolism,[51] most of whom will have symptoms. In the absence of symptoms, at least outside pregnancy, CUS is not recommended, as it is often negative: 30% of women with negative CUS will have a pulmonary embolism.

If the chest X ray is normal, the lung perfusion element of a ventilation–perfusion (V–Q) scan should be preformed next. Seventy per cent of pregnant women had negative scans in a retrospective study,[52] and the rate of recurrent events in this group was reassuringly low[52,53]; therefore, they were true negatives. If the perfusion scan is normal, the ventilation component can be omitted, thereby significantly reducing the risk from radiation. There are two main problems with V–Q scanning. The first concerns the high proportion of indeterminate results, up to 21% in older studies,[52] which would imply that many women would have to undergo a further test with added radiation risk. More recent studies have shown that this is not the case if the chest X ray is normal, in which case the proportion of non-diagnostic V–Q scans is about 1.3–6%.[54] The second concern relates to the increased risk of radiation to the fetus (Table 2). It was estimated that the added risk of childhood cancer after V–Q (both perfusion and ventilation component) scan is 1 out of 280,000, compared with 1 out of 1,000,000 for computed tomography pulmonary angiography (CTPA).[55] Interpretation of these estimates should also take into account the background risk of childhood cancer, which is 140 out of 1,000,000 per year in the UK (from Cancer research UK for childhood cancer: http://info.cancerresearchuk.org/cancerstats/childhoodcancer/incidence).

Table 2
Radiation doses associated with diagnostic tests for pulmonary embolism.[6,62]

	Radiation to the fetus (mGy)	Radiation to the maternal breast (mGy)
Chest X ray	0.001	0.01
Ventilation and perfusion scan	0.28–0.58 (adapted from Ref. 59)	0.014 (adapted from Ref. 58)
Perfusion scan only	0.12–0.25 (adapted from Ref. 59)	
Computer tomography pulmonary angiography	0.003–0.131 (adapted from Refs. 58,59)	20–60 (adapted from Refs. 60–62,76)
Total permitted dose	50–100 (adapted from Refs. 6,62,77)	

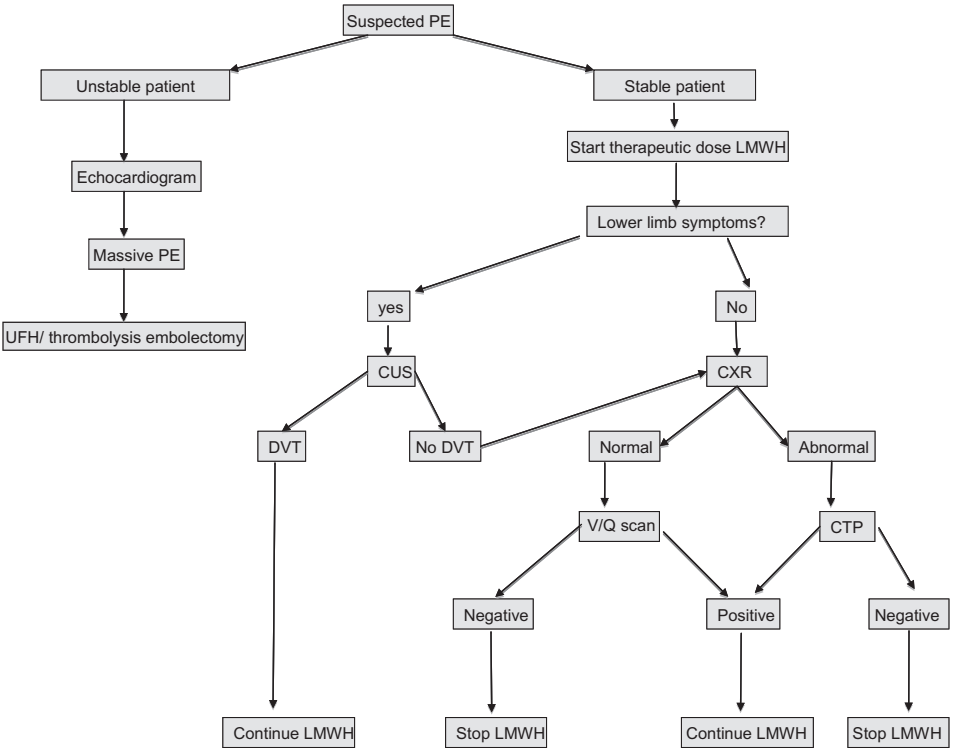

Fig. 1. Proposed algorithm for the diagnosis and treatment of PE in pregnancy.

If the chest X ray is abnormal, or there is unavailability or contraindication to the V–Q scan, and in those cases when the V–Q scan is non-diagnostic, CTPA should be carried out. This is the first-line investigation outside pregnancy owing to its higher sensitivity and specificity and smaller proportion of equivocal results.[56] In addition, it can offer an alternative diagnosis, including serious and potentially fatal aortic dissection. In pregnancy, it seems that the diagnostic performance is not necessarily superior.[57] The radiation to the fetus is lower than with the V–Q scan[58,59]; however, the radiation dose delivered to the mother's breasts is significantly higher.[60] This results in an estimated increase in the life-time risk of breast cancer, which is dependent on the age at the time of the computed tomography scan, one in 143 at age 20 years and one in 284 at the age of 40 years.[61] These estimates are for non-pregnant women undergoing computed tomography scanning; they may be higher for the pregnant, lactating breast, or both.[62] In view of these concerns, most authorities conclude that it should remain the second-line imaging in pregnancy and puerperium. Again, when weighing up these risks, it must be born in mind that the one in 8 women will develop breast cancer in their life-time (Cancer Research UK).

Cerebral vein thrombosis

Clinical features include, in reducing order of frequency, the following: a severe headache in 72%; seizures that can be partial, complex or generalised in 45%; confusion and altered consciousness in 43%; and signs of increased intracranial pressure (e.g. papilloedema, vomiting, photophobia) in 30% of women. One-third to two-thirds of women may have hemiparesis or hemineglect, but focal signs may be absent.[63,64] Again, it must be remembered that CVT can occur from early pregnancy. The diagnosis is confirmed by imaging, and MRV is the investigation of choice.[65] If this is not available, computed tomography is acceptable, but it must be contrast-enhanced (computed tomography venogram).

Treatment

The treatment of VTE in pregnancy in haemodynamically stable women is with low-molecular-weight heparin (LMWH). LMWH is a mixture of heparins with molecular weights around 5000 kDa. They have been derived from the older, unfractionated heparin (UFH), and have rapidly been set as standard in clinical situations previously indicating UFH. Its several advantages include the following: higher anti-Xa and anti IIa activity translating into less bleeding for the same antithrombotic effect; reduced platelet binding, leading to virtually no heparin-induced thrombocytopaenia; higher bioavailability (92–100%); and longer half-life resulting in the need for less frequent dosing.[66] Heparins do not cross the placenta and pose no danger to the fetus.

The efficacy and safety of LMWH in pregnancy is now well established,[67] and there is a large body of experience accumulated worldwide with this agent in pregnancy. The risk of heparin-induced thrombocytopaenia is low, and a platelet count is only necessary if there is a history of exposure to UFH. The risk of osteoporotic fractures is also low (0.04%). Allergic skin reactions occur with a frequency of 1.8%; in these cases, an alternative preparation can be tried, although there is a 30% chance of cross-reaction. If this occurs, a preparation such as danaparoid or fondaparinux is indicated. The risk of significant bleeding is 1.9% (this is mainly related to wound haematomas after caesarean section) owing to increased renal clearance of LMWH in pregnancy. Most LMWH are given twice daily for treatment (Table 3). As the anticoagulant effect is predictable and reliable, and the risk of bleeding is small, and no laboratory monitoring is considered necessary.[2]

Circumstances in which standard LMWH treatment is inadequate include women who are haemodynamically unstable with massive pulmonary embolism, and women who are in labour or have a high risk of bleeding, heparin allergy and severe renal impairment. These women should be managed with the help of the obstetric clinician, haematologist and anaesthetist.

Massive pulmonary embolism

The approach to managing women with massive pulmonary embolism and haemodynamic compromise should be individualised. Cardio-pulmonary bypass and surgical embolectomy followed by caesarean section would be the choice in most severe cases; however, these procedures are limited to large centres with expertise. Thrombolysis is not contraindicated and has been used successfully in over 172 reported cases. Reported rates of maternal bleeding complications are between 1 and 6%, with no maternal deaths. Reported rates of fetal loss are between 2 and 5.8%.[68,69] Unfractionated heparin remains the most used treatment for massive acute pulmonary embolism, as it reduces clot burden faster than LMWH. A weight-adjusted loading dose (80 IU/kg) followed by continuous infusion (18 IU/kg/h) and monitoring of the activated partial thromboplastin time (APTT) should be followed.[2]

Table 3
Suggested regimens for low-molecular-weight heparin.[21] [a]

Weight	Enoxaparin	Dalteparin	Tinzaparin (75 u/kg/day)
Less than 50 kg	20 mg daily	2500 units daily	3500 units daily
50–90 kg	40 mg daily	5000 units daily	4500 units daily
91–130 kg	60 mg daily[b]	7500 units daily[b]	7000 units daily[b]
131–170 kg	80 mg daily[b]	10,000 units daily[b]	9000 units daily[b]
Over 170 kg	0.6 mg/kg/day[b]	75 u/kg/day[b]	75 u/kg/day[b]
High prophylactic (intermediate) dose for women weighing 50–90 kg	40 mg 12 hourly	5000 units 12 hourly	4500 units 12 hourly
Treatment dose	1 mg/kg/12 hourly antenatal 1.5 mg/kg/daily postnatal	100 u/kg/12 hourly or 200 u/kg/daily postnatal	175 u/kg/daily (antenatal and post natal)

[a] Reproduced with permission.
[b] May be given in two divided doses.

Peri-delivery management and peri-delivery venous thromboembolism

In women who experience a VTE at least 2 weeks before term, the clot is 'stable', and delivery can be timed by induction of labour to avoid complications related to full anticoagulation. Alternatively, pregnancy can be allowed to progress until the onset of spontaneous labour, accepting that this may preclude the use of regional anaesthetic or analgesic techniques. Regional anaesthesia is contraindicated for 24 h after the last therapeutic dose of LMWH. Caesarean section should be for obstetric indication only. Low molecular weight heparin can be re-started as soon as delivery has occurred and the bleeding has stopped. When the risk of postpartum haemorrhage is minimal (5 days after birth), the woman can receive anticoagulation treatment with warfarin. If the VTE occurred early in pregnancy, it may be more appropriate to continue LMWH for 6 weeks postpartum without the need for formal warfarin. The total duration of the treatment (including that given in pregnancy) should be at least 3–6 months or 6 weeks postnatally, whichever is the longer.

The 'fresh' clot, within 2 weeks from the acute event, is fragile, with a high embolisation potential; therefore, induction of labour and delivery should be avoided for as long as possible in women who experience VTE at or near term. If a woman needs delivery or labours during this period, consideration should be given to switching to intravenous UFH at the onset of labour, and APTT should be carefully monitored. In active labour, the UFH infusion can be stopped and, provided 4 h have passed and APTT is confirmed normal, regional anaesthesia is possible. Should caesarean section become necessary, this should not proceed while the woman is fully anticoagulated, as it can lead to uncontrolled bleeding.[70] The effect of UFH should be reversed with protamine sulphate and fresh frozen plasma.

If there is a high level of concern regarding the potential for a large iliofemoral DVT or one reaching to the IVC embolizing and/or there are contraindications to anticoagulation, consideration should be given to placement of a vena cava filter. A retrievable filter is highly recommended and should be removed as soon as practical, as placement and retrieval can be associated with complications.[71] In practice, filters are rarely indicated.

Prevention

No large randomised-controlled trials have proved that antenatal thromboprophylaxis is effective[72]; however, successive reports from the Confidential Enquiry into maternal deaths[1,73] have suggested that fatal outcomes from TED in pregnancy are preventable. A recent study from Sweden reports a reduction of 88% in the relative risk of thrombosis in pregnancy when thromboprophylaxis is used.[74]

A comprehensive guideline has been published and recently updated by the Royal College of Obstetrics and Gynaecology.[21] This contains an extensive list of risk factors and management guidelines, based on assessment and stratification of risk. Tools for clinical practice are provided, including a simple and user-friendly scoring sheet to assist the clinician in risk assessment.

Once-daily use of LMWH is the pharmacological agent of choice in pregnancy. The dose should be dictated by the weight of the individual[21] (Table 3). Deviations from this standard are sometimes needed and will be described below.

Ideally, women with risk factors for thrombosis should be identified before pregnancy or at least in early pregnancy. It is particularly important to identify, investigate and counsel those with a previous thrombotic event. If such has occurred, the circumstances (details of the presentation, any precipitating factors, means of diagnosis drug treatment and duration) should be clarified. Investigations for both inherited and acquired thrombophilia should be completed ideally before pregnancy, as this is much more difficult in pregnancy, when the interpretation of protein S deficiency and lupus anticoagulant are not reliable. Other risk factors, including family history, should be considered (Table 1).

At the time of risk assessment, a detailed management plan should be written after discussion with the woman, and communicated with the general practitioner, whose help is essential. A prescription for LMWH can be given for women planning pregnancy, and women should be taught how to self-administer thromboprophylaxis. As soon as a woman is pregnant, LMWH should be started. Those who are on long-term oral anticoagulation with warfarin should also switch to LMWH as soon as pregnancy occurs, to avoid warfarin embryopathy (see below).

It must be remembered that circumstances may change the VTE risk of a particular woman at any time during pregnancy. Hyperemesis, pre-eclampsia, immobility due to hospital admission, and systemic infection, all increase the risk. Therefore, the assessment should be repeated if circumstances change.

Counselling should include the risk of bleeding, which is small with prophylaxis, but the woman should be advised not to inject and to present to hospital if this happens. Issues related to regional anaesthesia should also be discussed, and referral for antenatal anaesthetic review should be considered. Regional anaesthesia is contraindicated for 12 h after the last prophylactic dose of LMWH. The woman should be advised not to inject if there are signs of labour.

The risk assessment should be repeated at childbirth. In the highest risk cases, a clear plan would have been made during pregnancy. In women who do not score highly on the risk assessment, and are not on antenatal thromboprophylaxis, delivery by caesarean section, mid-cavity, forceps may change this. It is also important to remember that re-admission in the puerperium, especially for reasons of systemic infection or even minor surgery, is an indication to commence or recommence thromboprophylaxis.

Deviations from standard thromboprophylaxis

Deviations from standard thromboprophylaxis include high prophylactic doses, warfarin and alternative agents. Women requiring management by a haematologist with expertise in pregnancy include those with antiphospholipid syndrome (APS) and previous VTE; women with antithrombin deficiency, requiring high prophylactic doses of LMWH (Table 3); women requiring long-term anticoagulant treatment with warfarin outside pregnancy and may require therapeutic doses of LMWH. Monitoring of anti-Xa activity is not usually required for VTE treatment or prophylaxis except in some of these highest risk cases.

Warfarin is of limited use in pregnancy. When used in the first trimester between weeks 6–12, it causes a characteristic embryopathy (nasal hypoplasia, epiphyseal stippling) in 5% of exposed fetuses. Other risks are miscarriage, stillbirth, neurological damage (due to cerebral haemorrhage) and maternal bleeding complications.[75] On the basis of carefully considered risk–benefit, however, its judicious use may be appropriate for women with recurrent thrombotic events on therapeutic doses of heparin and some women with mechanical heart valves.

Danaparoid, fondaparinux and lepirudin are agents with heparin-like activity, mostly anti-Xa and direct thrombin inhibition. Their use is limited to women who are intolerant of heparin because of HIT or allergic reactions. The experience in pregnancy is limited, danaparoid seems safe, and does not cross the placenta. Small amounts of fondaparinux do cross the placenta, but no adverse effects have been described. Lepirudin is teratogenic in high doses in rabbits, and its use should be reserved to cases where there is no alternative.[21]

Conclusion

Venous thromboembolism in pregnancy is a potentially fatal, yet preventable event. In the same age group, VTE is at least four times more common in pregnancy. This is due to an increase in natural procoagulant activity, venous stasis and direct trauma to the pelvic veins.

Deep-vein thrombosis occurring in pregnancy is more commonly (85%) in the left leg and in the iliac and femoral veins. The best diagnostic method is CUS, and the alternative imaging modality is magnetic resonance imaging of the pelvic veins.

New, sudden-onset chest symptoms in a pregnant woman should always be investigated. Chest X ray will confirm alternative diagnoses and help choose the most appropriate imaging modality. The options are V–Q scan and CTPA, both involving ionising radiation to mother and fetus. With careful consideration, this can be minimised and there is no justification for withholding imaging. The diagnosis requires exclusion or confirmation.

Treatment is with LMWH and should be started immediately while the investigations are ongoing.

Great importance should be placed on formal risk assessment for every pregnant woman. This should take place at booking, at delivery or whenever the woman is admitted or suffers intercurrent illness in pregnancy. Thromboprophylaxis is with LMWH. Both prophylactic and therapeutic doses of LMWH are determined by the woman's weight. Clear guidelines have been published by the

Royal College of Obstetrics and Gynaecology, for acute management and prevention of VTE in pregnancy.

Practice points

- All pregnant women should undergo a formal, written risk assessment of factors for TED at booking and at delivery.
- New chest symptoms presenting in pregnancy should be investigated.
- Treatment and prophylactic doses of LMWH should be adjusted on the basis of an individual's weight.

Research agenda

- Is widespread use of LMWH for thromboprophylaxis in pregnancy cost-effective?
- Are newer (oral) direct thrombin inhibitors safe in pregnancy?
- Can an alternative diagnostic tree be developed to exclude pulmonary embolism without recourse to ionising radiation?

Conflict of interest

None declared.

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