Royal College of Obstetricians & Gynaecologists

Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management

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Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management

This is the third edition of this guideline. The first edition was published in April 2001 under the same title (numbered Green-top Guideline No. 28) and the second edition was published in February 2007 and reviewed in 2010. Thromboprophylaxis during pregnancy and the puerperium is addressed in Green-top Guideline No. 37a.

Executive summary of recommendations

Diagnosis of acute venous thromboembolism (VTE)

How is acute VTE diagnosed in pregnancy?

Any woman with symptoms and/or signs suggestive of VTE should have objective testing performed expeditiously and treatment with low-molecular-weight heparin (LMWH) given (see section 6) until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated. C

Individual hospitals should have an agreed protocol for the objective diagnosis of suspected VTE during pregnancy. This may recommend the involvement of obstetricians, radiologists, physicians and haematologists. ✓

What investigations are needed for the diagnosis of an acute DVT?

Compression duplex ultrasound should be undertaken where there is clinical suspicion of DVT. B

If ultrasound is negative and there is a low level of clinical suspicion, anticoagulant treatment can be discontinued. If ultrasound is negative and a high level of clinical suspicion exists, anticoagulant treatment should be discontinued but the ultrasound should be repeated on days 3 and 7. [*New 2015*] C

What investigations are needed for the diagnosis of an acute pulmonary embolism (PE)?

Women presenting with symptoms and signs of an acute PE should have an electrocardiogram (ECG) and a chest X-ray (CXR) performed. [*New 2015*] C

In women with suspected PE who also have symptoms and signs of DVT, compression duplex ultrasound should be performed. If compression ultrasonography confirms the presence of DVT, no further investigation is necessary and treatment for VTE should continue. [*New 2015*] C

In women with suspected PE without symptoms and signs of DVT, a ventilation/perfusion (V/Q) lung scan or a computerised tomography pulmonary angiogram (CTPA) should be performed. [*New 2015*] C

When the chest X-ray is abnormal and there is a clinical suspicion of PE, CTPA should be performed in preference to a V/Q scan. [*New 2015*] D

Alternative or repeat testing should be carried out where V/Q scan or CTPA is normal but the clinical suspicion of PE remains. Anticoagulant treatment should be continued until PE is definitively excluded. C

Women with suspected PE should be advised that, compared with CTPA, V/Q scanning may carry a slightly increased risk of childhood cancer but is associated with a lower risk of maternal breast cancer; in both situations, the absolute risk is very small. [*New 2015*] D

Where feasible, women should be involved in the decision to undergo CTPA or V/Q scanning. Ideally, informed consent should be obtained before these tests are undertaken. ✓

Should D-dimer testing be performed prior to objective diagnosis?

D-dimer testing should not be performed in the investigation of acute VTE in pregnancy. D

What is the role of pretest probability assessment?

Clinicians should be aware that, at present, there is no evidence to support the use of pretest probability assessment in the management of acute VTE in pregnancy. [*New 2015*] C

Baseline blood investigations

What baseline blood investigations should be performed before initiating anticoagulant therapy?

Before anticoagulant therapy is commenced, blood should be taken for a full blood count, coagulation screen, urea and electrolytes, and liver function tests. D

Performing a thrombophilia screen prior to therapy is not recommended. B

Initial anticoagulant treatment of VTE in pregnancy

What is the initial treatment of VTE in pregnancy?

In clinically suspected DVT or PE, treatment with low-molecular-weight heparin (LMWH) should be commenced immediately until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated. B

What is the therapeutic dose of LMWH in pregnancy?

LMWH should be given in doses titrated against the woman's booking or early pregnancy weight. There is insufficient evidence to recommend whether the dose of LMWH should be given once daily or in two divided doses. [*New 2015*] C

There should be clear local guidelines for the dosage of LMWH to be used. ✓

Should blood tests be performed to monitor heparin therapy in pregnancy?

Routine measurement of peak anti-Xa activity for patients on LMWH for treatment of acute VTE in pregnancy or postpartum is not recommended except in women at extremes of body weight (less than 50 kg and 90 kg or more) or with other complicating factors (for example, with renal impairment or recurrent VTE). C

Routine platelet count monitoring should not be carried out. D

Obstetric patients who are postoperative and receiving unfractionated heparin should have platelet count monitoring performed every 2–3 days from days 4 to 14 or until heparin is stopped. [*New 2015*] D

How should massive life-threatening PE in pregnancy and the puerperium be managed?

Collapsed, shocked women who are pregnant or in the puerperium should be assessed by a team of experienced clinicians including the on-call consultant obstetrician. ✓

Women should be managed on an individual basis regarding: intravenous unfractionated heparin, thrombolytic therapy or thoracotomy and surgical embolectomy. ✓

Management should involve a multidisciplinary team including senior physicians, obstetricians and radiologists. ✓

Intravenous unfractionated heparin is the preferred, initial treatment in massive PE with cardiovascular compromise. B

Maternity units should develop guidelines for the administration of intravenous unfractionated heparin. ✓

The on-call medical team should be contacted immediately. An urgent portable echocardiogram or CTPA within 1 hour of presentation should be arranged. If massive PE is confirmed, or in extreme circumstances prior to confirmation, immediate thrombolysis should be considered. ✓

Additional therapies

Should graduated elastic compression stockings be employed in the acute management of VTE in pregnancy?

In the initial management of DVT, the leg should be elevated and a graduated elastic compression stocking applied to reduce oedema. Mobilisation with graduated elastic compression stockings should be encouraged. B

What is the role of inferior vena cava filters in the management of VTE in pregnancy?

Consideration should be given to the use of a temporary inferior vena cava filter in the peripartum period for patients with iliac vein VTE to reduce the risk of PE or in patients with proven DVT and who have recurrent PE despite adequate anticoagulation. D

Maintenance treatment of VTE

What is the maintenance treatment of DVT or PE?

Treatment with therapeutic doses of subcutaneous LMWH should be employed during the remainder of the pregnancy and for at least 6 weeks postnatally and until at least 3 months of treatment has been given in total. B

Women should be taught to self-inject LMWH and arrangements made to allow safe disposal of needles and syringes. Outpatient follow-up should include clinical assessment and advice with monitoring of blood platelets and peak anti-Xa levels if appropriate (see sections 5 and 6.3). C

Pregnant women who develop heparin-induced thrombocytopenia or have heparin allergy and require continuing anticoagulant therapy should be managed with an alternative anticoagulant under specialist advice. C

Can vitamin K antagonists be used during pregnancy for the maintenance treatment of VTE?

Because of their adverse effects on the fetus, vitamin K antagonists, such as warfarin, should not be used for antenatal VTE treatment. C

Is there a role for the new anticoagulants in the treatment of VTE in pregnancy?

Consideration should be given to the use of newer anticoagulants (fondaparinux, argatroban or r-hirudin) in pregnant women who are unable to tolerate heparin (LMWH or unfractionated heparin) or danaparoid and who require continuing anticoagulant therapy. [*New 2015*] D

Anticoagulant therapy during labour and delivery

Should anticoagulant therapy be altered during labour and delivery?

When VTE occurs at term, consideration should be given to the use of intravenous unfractionated heparin which is more easily manipulated. [*New 2015*] D

The woman on LMWH for maintenance therapy should be advised that once she is in established labour or thinks that she is in labour, she should not inject any further heparin. ✓

Where delivery is planned, either by elective caesarean section or induction of labour, LMWH maintenance therapy should be discontinued 24 hours prior to planned delivery. D

Regional anaesthetic or analgesic techniques should not be undertaken until at least 24 hours after the last dose of therapeutic LMWH. D

LMWH should not be given for 4 hours after the use of spinal anaesthesia or after the epidural catheter has been removed, and the epidural catheter should not be removed within 12 hours of the most recent injection. [*New 2015*] D

Are specific surgical measures required for anticoagulated patients undergoing delivery by caesarean section?

In patients receiving therapeutic doses of LMWH, wound drains (abdominal and rectus sheath) should be considered at caesarean section and the skin incision should be closed with interrupted sutures to allow drainage of any haematoma. ✓

What anticoagulant therapy should be employed in women at high risk of haemorrhage?

Any woman who is considered to be at high risk of haemorrhage, and in whom continued heparin treatment is considered essential, should be managed with intravenous unfractionated heparin until the risk factors for haemorrhage have resolved. D

Postnatal anticoagulation

How should anticoagulation be managed postnatally?

Therapeutic anticoagulant therapy should be continued for the duration of the pregnancy and for at least 6 weeks postnatally and until at least 3 months of treatment has been given in total. Before discontinuing treatment the continuing risk of thrombosis should be assessed. C

Women should be offered a choice of LMWH or oral anticoagulant for postnatal therapy after discussion about the need for regular blood tests for monitoring of warfarin, particularly during the first 10 days of treatment. ✓

Postpartum warfarin should be avoided until at least the fifth day and for longer in women at increased risk of postpartum haemorrhage. [*New 2015*] ✓

Women should be advised that neither heparin (unfractionated or LMWH) nor warfarin is contraindicated in breastfeeding. D

Prevention of post-thrombotic syndrome

What measures can be employed to prevent the development of post-thrombotic syndrome?

Women should be advised that prolonged use of LMWH (more than 12 weeks) is associated with a significantly lower chance of developing post-thrombotic syndrome. [*New 2015*] B

Following a DVT, graduated elastic compression stockings should be worn on the affected leg to reduce pain and swelling. Clinicians should be aware that the role of compression stockings in the prevention of post-thrombotic syndrome is unclear. [*New 2015*] B

Postnatal clinic review

Postnatal review for patients who develop VTE during pregnancy or the puerperium should, whenever possible, be at an obstetric medicine clinic or a joint obstetric haematology clinic. ✓

Thrombophilia testing should be performed once anticoagulant therapy has been discontinued only if it is considered that the results would influence the woman's future management. [*New 2015*] D

1. Purpose and scope

The aim of this guideline is to provide information, based on clinical evidence where available, regarding the immediate investigation and management of women in whom venous thromboembolism is suspected during pregnancy or the puerperium.

2. Introduction and background epidemiology

Venous thromboembolism (VTE) remains one of the main direct causes of maternal death in the UK[1] and sequential reports on Confidential Enquiries into Maternal Deaths have highlighted failures in obtaining objective diagnoses and employing adequate treatment.[2] In recent years, there has been a significant decline in maternal deaths from VTE in the UK (18 deaths between 2006 and 2008 compared to 41 in 2003–2005), in part owing to better recognition of women at risk and more widespread use of thromboprophylaxis.[1]

The subjective clinical assessment of deep venous thrombosis (DVT) and pulmonary embolism (PE) is particularly unreliable in pregnancy and only a minority of women with clinically suspected VTE have the diagnosis confirmed when objective testing is employed; the prevalence of ultimately diagnosed PE in pregnant women with suspected PE is 2–6%.[3–5] The risk of antenatal VTE is four- to five-fold higher in pregnant women than in nonpregnant women of the same age,[6,7] although the absolute risk remains low at around 1 in 1000 pregnancies.[8] Venous thromboembolism can occur at any stage of pregnancy but the puerperium is the time of highest risk, with estimates of relative risk of approximately 20-fold.[9] Acute VTE should be suspected during pregnancy in women with symptoms and signs consistent with possible VTE, particularly if there are other risk factors for VTE (see Green-top Guideline No. 37a). The majority of women with VTE in pregnancy have clinical symptoms.[10] The symptoms and signs of DVT include leg pain and swelling (usually unilateral) and lower abdominal pain (reflecting extension of thrombus into the pelvic vessels and/or development of a collateral circulation) and the symptoms of PE include dyspnoea, chest pain, haemoptysis and collapse. It is noteworthy that a low-grade pyrexia and leucocytosis can occur with VTE.

3. Identification and assessment of evidence

A search of MEDLINE and PubMed (electronic databases) from 2006–2013 was performed to identify all relevant randomised controlled trials, systematic reviews and meta-analyses. Conference abstracts published during this period that have since been superseded by full papers have been cited as the latter, even when these were published outside the search dates. The databases were searched using the relevant Medical Subject Headings (MeSH) terms including all subheadings. The principal terms used were: 'venous thromboembolism', 'deep venous thrombosis', 'pulmonary thromboembolism' and 'pregnancy'.

Where possible in this document, recommendations are based on and linked to the evidence that supports them. Many of the guidelines for the management of VTE in nonpregnant patients are based on level 1 evidence;[11,12] however, level 1 evidence for the management of VTE during pregnancy is lacking[13] and, in general, guideline recommendations for management of VTE during pregnancy are extrapolated from studies in nonpregnant patients.

4. Diagnosis of acute VTE

How is acute VTE diagnosed in pregnancy?

Any woman with symptoms and/or signs suggestive of VTE should have objective testing performed expeditiously and treatment with low-molecular-weight heparin (LMWH) given (see section 6) until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated. C

Individual hospitals should have an agreed protocol for the objective diagnosis of suspected VTE during pregnancy. This may recommend the involvement of obstetricians, radiologists, physicians and haematologists. ✓

Women presenting with symptoms and/or signs suggestive of VTE should have objective testing performed expeditiously. If DVT remains untreated, 15–24% of these patients will develop PE. PE during pregnancy may be fatal in almost 15% of patients, and in 66% of these, death will occur within 30 minutes of the embolic event.[14,15] Evidence level 2+

All hospitals should have a protocol for the diagnosis of suspected VTE in pregnancy which may require multidisciplinary team involvement.

4.1 What investigations are needed for the diagnosis of an acute DVT?

Compression duplex ultrasound should be undertaken where there is clinical suspicion of DVT. B

If ultrasound is negative and there is a low level of clinical suspicion, anticoagulant treatment can be discontinued. If ultrasound is negative and a high level of clinical suspicion exists, anticoagulant treatment should be discontinued but the ultrasound should be repeated on days 3 and 7. C

Compression duplex ultrasound is the primary diagnostic test for DVT.[16,17] If ultrasound confirms the diagnosis of DVT, anticoagulant treatment should be continued. Evidence level 2++

If ultrasound is negative and a high level of clinical suspicion exists, anticoagulant treatment should be discontinued but the ultrasound repeated on days 3 and 7.[18] If repeat testing is negative, no further treatment is required; if repeat testing confirms the presence of DVT, anticoagulant treatment should be recommenced and continued. This strategy has been evaluated in a prospective cohort study of 221 pregnant women who presented with suspected DVT. The sensitivity of serial compression ultrasonography with Doppler imaging was 94.1% (95% CI 69.2–99.7%), the negative predictive value was 99.5% (95% CI 96.9–100%) and the negative likelihood ratio was 0.068 (95% CI 0.01–0.39).[18] Evidence level 2+

When iliac vein thrombosis is suspected (back and buttock pain and swelling of the entire limb), Doppler ultrasound of the iliac vein, magnetic resonance venography or conventional contrast venography may be considered,[16] although in practice, because of the extensive nature of these thrombi, ultrasound venography will often suffice. Evidence level 3

4.2 What investigations are needed for the diagnosis of an acute PE?

Women presenting with symptoms and signs of an acute PE should have an electrocardiogram (ECG) and a chest X-ray (CXR) performed. C

In women with suspected PE who also have symptoms and signs of DVT, compression duplex ultrasound should be performed. If compression ultrasonography confirms the presence of DVT, no further investigation is necessary and treatment for VTE should continue. C

In women with suspected PE without symptoms and signs of DVT, a ventilation/perfusion (V/Q) lung scan or a computerised tomography pulmonary angiogram (CTPA) should be performed. C

When the chest X-ray is abnormal and there is a clinical suspicion of PE, CTPA should be performed in preference to a V/Q scan. D

Alternative or repeat testing should be carried out where V/Q scan or CTPA is normal but the clinical suspicion of PE remains. Anticoagulant treatment should be continued until PE is definitively excluded. C

Women with suspected PE should be advised that, compared with CTPA, V/Q scanning may carry a slightly increased risk of childhood cancer but is associated with a lower risk of maternal breast cancer; in both situations, the absolute risk is very small. D

Where feasible, women should be involved in the decision to undergo CTPA or V/Q scanning. Ideally, informed consent should be obtained before these tests are undertaken. ✓

In the diagnosis of PE in the nonpregnant individual, both the electrocardiogram (ECG) and arterial blood gas (ABG) measurement are of limited diagnostic value.[19,20] However, in pregnancy and the puerperium, one study found that the ECG was abnormal in 41% of women with acute PE; the most common abnormalities were T wave inversion (21%), $S_1Q_3T_3$ pattern (15%) and right bundle branch block (18% during pregnancy and 4.2% in the puerperium).[21] Given the increasing incidence of ischaemic heart disease in pregnancy, the ECG may also be helpful in identifying alternative diagnoses. In the same cohort of women, ABG analysis showed that only 10% had arterial PO_2 levels less than 60 mmHg and 2.9% had oxygen saturation levels less than 90%.[21] These findings indicate a diagnostic role for ECG in women with suspected acute PE, and that ABG analysis is of limited diagnostic value. Evidence level 2+

Chest X-ray (CXR) may identify other pulmonary disease such as pneumonia, pneumothorax or lobar collapse.[22] While the CXR is normal in over half of pregnant patients with objectively proven PE,[21] abnormal features caused by PE include atelectasis, effusion, focal opacities, regional oligaemia or pulmonary oedema.[23] The radiation dose to the fetus from a CXR performed at any stage of pregnancy is negligible (less than 0.01 mSv).[24,25] A CXR should be performed before deciding upon further diagnostic tests; a normal CXR prior to V/Q scanning improves the likelihood of a definitive V/Q result.[26] If the CXR is abnormal with a clinical suspicion of PE, CTPA should be performed. Evidence level 3

Pregnant women with suspected PE who have symptoms and signs of DVT should have bilateral compression duplex ultrasound leg studies performed. A diagnosis of DVT may indirectly confirm a diagnosis of PE and since anticoagulant therapy is the same for both conditions, further investigation may not be necessary. This would limit the radiation doses given to the mother and her fetus.[27] While several studies have investigated the use of lower limb ultrasonography in the investigation of nonpregnant patients with suspected PE,[28–31] the role of ultrasound leg studies in pregnant women with suspected PE and without symptoms and signs of DVT is unclear. In one case series, Chan et al. found no cases of DVT in 67 women presenting with suspected PE.[4] Given the higher incidence of isolated iliac vein DVT in pregnancy,[32] it would be anticipated that there would be an increased likelihood of false-negative results with this strategy. Therefore, while a positive result is of value, a negative investigation does not help to exclude a PE. Evidence level 2+

The choice of technique for definitive diagnosis (V/Q scan or CTPA) will depend on local availability, and individual hospitals should have an agreed protocol for the objective diagnosis of suspected PE during pregnancy. A matched case–control study in the UK investigated the management of 143 women with antenatal PE; ninety-one women (65%) had a V/Q scan, 42 (30%) had CTPA performed, 22 (16%) had echocardiography and 16 (11%) were diagnosed by angiography.[33] Forty women (28%) were diagnosed using a combination of techniques. With regard to V/Q lung scanning, during pregnancy the ventilation component can often be omitted thereby minimising the radiation dose for the fetus. Studies have compared V/Q or low-dose perfusion (Q) scans with CTPA for the detection of PE in pregnancy and have found comparable negative predictive values (99% and 100% for CTPA and Q scans respectively) and no significant difference between the number of positive, nondiagnostic and normal scans.[5,34,35] One study reported a higher rate of nondiagnostic scans with CTPA (37.5%) compared with V/Q scanning (4%) in pregnancy,[36] although this may be related to the imaging protocol employed.

Evidence level 2+

CTPA has potential advantages over V/Q imaging including: CTPA is more readily available,[37,38] delivers a low radiation dose to the fetus (see section below) and can identify other pathology including pneumonia (5–7%), pulmonary oedema (2–6%) and rarely aortic dissection.[5,35] Despite these potential advantages of CTPA, many authorities continue to recommend V/Q scanning as first-line investigation in pregnancy because of its high negative predictive value in this situation and its substantially lower radiation dose to pregnant breast tissue (see section below).[39,40]

Clinicians arranging imaging scans for suspected PE in pregnancy should be aware of the potential risks surrounding fetal and maternal radiation exposure.[41] CTPA exposes the fetus to similar or lower amounts of radiation as V/Q scanning, although studies have been confounded by the type and model of scanners used, the imaging protocols employed and the methods used to estimate radiation exposure.[42] With both techniques, the doses employed are well below accepted thresholds for teratogenicity, fetal death and fetal growth restriction, and the main concern for the fetus is a very small increased risk of childhood cancer.[43] The International Commission on Radiological Protection has estimated an increased risk of fatal childhood cancer to the age of 15 following in utero radiation exposure of 0.006% per mGy, which equates to a risk of 1 in 17 000 per mGy.[44] The fetal radiation exposure associated with CTPA and V/Q is approximately 0.1 mGy and 0.5 mGy respectively, although quoted figures vary considerably.[25,43,45]

Evidence level 4

While CTPA is associated with a low risk of radiation for the fetus, this must be offset by the relatively high radiation dose (up to 20 mGy) to the mother's breast tissue, which is associated with an increased risk of breast cancer. The dose estimate for CTPA is 20 to 100 times greater than for V/Q scanning. The radiation dose depends on breast size, the technique used and the age of the woman – the risk of cancer being greater in younger women.[46] Estimates of the increased risk of breast cancer associated with CTPA in pregnancy vary considerably and are based on modelling or extrapolated data. The delivery of 10 mGy of radiation to a woman's breast has been estimated to increase her lifetime risk of developing breast cancer by 13.6% above her background risk[47] and this figure has been cited widely. For a 25-year-old whose background risk of developing breast cancer in the following 10 years is 0.1%, the extra risk from 10mGy of radiation increases the risk by 13.6% of 0.1%, which is 0.0136% extra. Furthermore, Allen and Demetriades[48] have suggested that even this small risk is an overestimate. Nevertheless, breast tissue is especially sensitive to radiation exposure during pregnancy because of hormonally induced increased glandular activity.[49] The breast doses associated with CTPA can be reduced by 20–40% by the use of bismuth shields placed over the breasts.[50] It would be prudent to recommend that lung perfusion scans should be considered the investigation of first choice for young women, especially if there is a family history of breast cancer or the patient has had a previous chest CT scan.[45]

Evidence level 3

An algorithm for the investigation of suspected PE in pregnancy and the puerperium is given in Appendix I.

There is a theoretical risk of hypothyroidism for neonates who have been exposed in utero to iodinated contrast medium (such as that employed during CTPA), although this has not been borne out in a study of over 300 neonates.[51]

Evidence level 3

Newer imaging techniques for the diagnosis of PE have been developed but have not been fully evaluated in pregnancy; these include: magnetic resonance pulmonary angiogram, digital subtraction angiography and ventilation and perfusion single-photon emission computed tomography (V/Q_{SPECT}).[52]

4.3 Should D-dimer testing be performed prior to objective diagnosis?

D-dimer testing should not be performed in the investigation of acute VTE in pregnancy.

D

In the nonpregnant individual, D-dimer testing is used successfully in the investigation of acute VTE, having a high sensitivity, moderate specificity and high negative predictive value.[53] In pregnancy, there is a progressive rise in D-dimer levels with advancing gestation and levels become 'abnormal' at term and in the postnatal period in most healthy pregnant women.[54,55] D-dimer levels are increased further in multiple pregnancies,[56] following caesarean section and in major postpartum haemorrhage[57] and if there is concomitant pre-eclampsia.[58] Thus a 'positive' D-dimer test in pregnancy is not necessarily consistent with VTE. The role of D-dimer testing in the investigation of acute VTE in pregnancy remains controversial.[59] Guidelines from the European Society of Cardiology recommend testing D-dimer levels, proposing that normal D-dimer levels can exclude PE in pregnancy just as for other patients, even though normal levels are less likely to be found in pregnancy.[60] In contrast, guidelines from the American Thoracic Society/Society of Thoracic Radiology recommend that D-dimer should not be used to exclude PE in pregnancy.[39]

Evidence level 4

Evidence regarding the safety and clinical use of D-dimer concentrations in the diagnosis of suspected PE in pregnancy is lacking. A retrospective study of pregnant women with suspected PE who had both V/Q scans and D-dimer testing found a negative likelihood ratio of 1.8, suggesting that a negative D-dimer is inadequate to exclude PE in pregnancy.[61] Furthermore, case reports have described negative D-dimer levels in pregnant women with acute VTE.[62–64] In current practice, measurements of D-dimer levels in the nonpregnant should be combined with validated tests to assign a pretest probability before PE can be excluded without imaging, and these tests do not currently exist in pregnancy. Several studies have described the use of gestation-specific, higher 'cut-off' values in the diagnosis of suspected VTE in pregnancy; all, however, conclude that further prospective studies are required before D-dimer testing in pregnancy can be recommended.[65–68]

Evidence level 3

4.4 What is the role of pretest probability assessment?

Clinicians should be aware that, at present, there is no evidence to support the use of pretest probability assessment in the management of acute VTE in pregnancy.

C

In the UK, national guidelines recommend that nonpregnant patients presenting with suspected VTE should have a two-level Wells score (a pretest probability assessment) performed.[12] Various modifications of the Wells score have been described and combine presenting symptoms and signs to stratify risk and determine the need for further investigations. Studies have reported on the performance of pretest probability assessment in pregnancy.[69–71] Chan et al.[69] found that subjective assessment of pretest probability by VTE 'experts' could exclude DVT when the pretest probability is low. Furthermore they reported on three variables that may improve the diagnostic accuracy of DVT in pregnancy (left leg [L], calf circumference difference of at least

Evidence level 2+

2 cm [E for edema] and first trimester presentation [Ft] – the 'LEFt rule'). Righini et al.,[71] in a post hoc analysis of 157 pregnant women with suspected DVT, applied the LEFt rule and found that a negative score accurately identifies pregnant women in whom the proportion of confirmed DVT is very low. O'Connor et al.[70] examined the use of the modified Wells score (MWS) in pregnancy as a risk stratification tool in the diagnosis of PE. They found that a MWS of 6 or higher was 100% sensitive and 90% specific with a positive predictive value of 36% for PE on CTPA. No woman with a MWS of less than 6 had a PE, giving a negative predictive value of 100%. In each of these studies, the authors conclude that prospective trials are required to validate their findings.

Evidence level 2+

5. Baseline blood investigations

What baseline blood investigations should be performed before initiating anticoagulant therapy?

Before anticoagulant therapy is commenced, blood should be taken for a full blood count, coagulation screen, urea and electrolytes, and liver function tests. D

Performing a thrombophilia screen prior to therapy is not recommended. B

The use of anticoagulant therapy can be influenced by renal and hepatic function, and can influence the platelet count, and blood should be taken to confirm that these are normal before commencing treatment.[11]

Evidence level 4

Almost half of all women who have an episode of VTE in pregnancy will have an underlying heritable or acquired thrombophilia.[72,73] In the nonpregnant individual, the presence of thrombophilia does not alter the acute management of VTE with regards to the choice of anticoagulant agent, intensity of treatment or duration of therapy,[74] and therefore testing for thrombophilia is not recommended.[11] Furthermore, the physiological changes of pregnancy and pathophysiology of acute thrombus can influence the results of a thrombophilia screen. Levels of antithrombin and protein C may fall, particularly if the thrombus is extensive. In addition, protein S levels fall in normal pregnancy and an acquired activated protein C resistance is found in around 40% of pregnancies.[75,76] It is recommended therefore that a thrombophilia screen should not be performed in pregnant women on presentation with suspected VTE.

Evidence level 1++

6. Initial anticoagulant treatment of VTE in pregnancy

6.1 What is the initial treatment of VTE in pregnancy?

In clinically suspected DVT or PE, treatment with low-molecular-weight heparin (LMWH) should be commenced immediately until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated. B

Meta-analyses of randomised controlled trials indicate that LMWHs are more effective, are associated with a lower risk of haemorrhagic complications and are associated with lower mortality than unfractionated heparin in the initial treatment of DVT in nonpregnant patients.[77,78] A meta-analysis of randomised controlled trials has shown equivalent efficacy of LMWH to unfractionated heparin in the initial treatment of PE.[79] A Cochrane review of 22 studies had over 8000 patients of whom 75% had DVT and 25% PE without evidence of DVT; compared with unfractionated heparin, LMWH treatment was associated with lower rates of VTE recurrence or extension (3.6% versus 5.4%; OR 0.68, 95% CI 0.55–0.84), lower mortality (4.5% versus 6.0%; OR 0.76, 95% CI 0.63–0.92) and less major bleeding during the initial treatment period (1.2% versus 2.0%; OR 0.57, 95% CI 0.39–0.83).[80]

Evidence level 1++

With regard to safety, there is substantial accumulating evidence with the use of LMWHs, both in pregnant and nonpregnant patients, for the prevention and treatment of VTE.[81] There

Evidence level 2++

is evidence that LMWHs do not cross the placenta.[82] While a Cochrane review concluded that there is no evidence from randomised controlled trials on the effectiveness of anticoagulation for DVT in pregnancy,[13] systematic reviews and large series of cases have concluded that LMWH is a safe and effective alternative to unfractionated heparin as an anticoagulant during pregnancy.[83–87] These have demonstrated a low risk of recurrent VTE when therapeutic doses of LMWH were used to manage VTE in pregnancy; for example, Greer and Nelson-Piercy identified a risk of recurrent VTE of 1.15% in women managed with LMWH.[84] This compares favourably with recurrence rates of 5–8% reported in trials carried out in nonpregnant patients treated with LMWH or unfractionated heparin followed by coumarin therapy who are followed up for 3–6 months.[88,89]

Evidence level 2++

One of the advantages of LMWH over unfractionated heparin is the potential reduced risk of bleeding. This is of particular relevance in obstetric practice where obstetric haemorrhage remains the most common cause of severe obstetric morbidity.[90] LMWHs are not associated with an increased risk of severe postpartum haemorrhage (defined as a blood loss of 1000 ml or more) in vaginal delivery.[91] In one retrospective study[85] the observed rate of massive postpartum haemorrhage (more than 1500 ml) was 1.1%, which compares favourably with the rate of massive haemorrhage (0.7%) from one prospective study without the use of LMWH.[92] It is known that the risk of heparin-induced thrombocytopenia (HIT) is substantially lower with LMWH use compared with unfractionated heparin and in the 2777 pregnancies treated with LMWH and reviewed by Greer and Nelson-Piercy, no cases of HIT associated with thrombosis were reported.[84]

Data on LMWH also substantiate a lower risk of LMWH compared with unfractionated heparin for heparin-induced osteoporosis; the overall risk of this complication on systematic review was 0.04% (compared with 2% for unfractionated heparin).[84,93] A randomised controlled trial investigating bone mineral density in pregnant women receiving long-term dalteparin in pregnancy found no significant difference in bone density between LMWH-treated patients and controls.[94]

Evidence level 1+

In clinically suspected VTE, LMWH should be postponed until objective testing has confirmed the diagnosis in women at risk of bleeding after careful consideration of the balance of risks of haemorrhage and clotting. The risk factors for bleeding are summarised in Green-top Guideline No. 37a. Women who are known to be allergic to LMWH should be offered an alternative anticoagulant preparation (see section 8.3).

Evidence level 4

6.2 What is the therapeutic dose of LMWH in pregnancy?

LMWH should be given in doses titrated against the woman's booking or early pregnancy weight. There is insufficient evidence to recommend whether the dose of LMWH should be given once daily or in two divided doses.

C

There should be clear local guidelines for the dosage of LMWH to be used.

✓

In nonpregnant patients, the recommended therapeutic doses of LMWH vary according to the manufacturer (enoxaparin 1.5 mg/kg once daily; dalteparin 10000–18000 units once daily depending on body weight; tinzaparin 175 units/kg once daily). During pregnancy, changes in volume of distribution and renal glomerular filtration rate result in alterations in the pharmacokinetics of LMWHs.[95–99] Previous editions of this guideline (2001 and 2007) recommended a twice-daily dosage regimen for enoxaparin and dalteparin in the treatment of VTE in pregnancy (enoxaparin 1 mg/kg twice daily; dalteparin 100 units/kg twice daily). This recommendation was based on anti-Xa activity and a paucity of reports on safety and efficacy of once-daily dosing.[100] Since then, a prospective multicentre observational study has found

Evidence level 3

that 60% of practitioners use once-daily dosing of enoxaparin and dalteparin for treatment of VTE in pregnancy.[101]

Evidence level 3

A national case–control study on the management of antenatal PE using the UK Obstetric Surveillance System found that 49% of women were managed with a once-daily dosage schedule.[33]

Evidence level 2+

Further, a large, international retrospective study on the use of tinzaparin in pregnancy (with 254 pregnancies receiving treatment doses and 94.1% of these in a once-daily regimen) has provided reassuring data on safety and efficacy of once-daily dosing.[85]

Evidence level 3

Recommendations on the treatment of pregnancy-associated VTE from clinicians in New Zealand and Australia concluded that there is insufficient evidence to favour one dose regimen over the other, and that treatment of acute VTE in pregnancy can be with LMWH administered either once daily or twice daily.[40]

Evidence level 4

A recent pharmacokinetic study involving 123 pregnant women found that the half-life of enoxaparin is prolonged with the progression of pregnancy; the authors conclude that their study provides further support for the use of once-daily enoxaparin for treatment of VTE in pregnancy.[102]

Evidence level 2+

The doses of different LMWHs are given in Tables 1a–c below.

Table 1a. Initial dose of enoxaparin is determined as follows:

Booking or early pregnancy weight	Initial dose of enoxaparin
< 50 kg	40 mg twice daily or 60 mg once daily
50–69 kg	60 mg twice daily or 90 mg once daily
70–89 kg	80 mg twice daily or 120 mg once daily
90–109 kg	100 mg twice daily or 150 mg once daily
110–125 kg	120 mg twice daily or 180 mg once daily
> 125 kg	Discuss with haematologist

Table 1b. Initial dose of dalteparin is determined as follows:

Booking or early pregnancy weight	Initial dose of dalteparin
< 50 kg	5000 iu twice daily or 10 000 iu once daily
50–69 kg	6000 iu twice daily or 12 000 iu once daily
70–89 kg	8000 iu twice daily or 16 000 iu once daily
90–109 kg	10 000 iu twice daily or 20 000 iu once daily
110–125 kg	12 000 iu twice daily or 24 000 iu daily
> 125 kg	Discuss with haematologist

Table 1c. Initial dose of tinzaparin is determined as follows:

Initial dose of tinzaparin *(based on booking or early pregnancy weight)*
175 units/kg once daily

Lower doses of LMWH should be employed if the creatinine clearance is less than 30 ml/minute (enoxaparin and dalteparin) or less than 20 ml/minute with tinzaparin.[103,104]

6.3 Should blood tests be performed to monitor heparin therapy in pregnancy?

Routine measurement of peak anti-Xa activity for patients on LMWH for treatment of acute VTE in pregnancy or postpartum is not recommended except in women at extremes of body weight (less than 50 kg and 90 kg or more) or with other complicating factors (for example, with renal impairment or recurrent VTE). C

Routine platelet count monitoring should not be carried out. D

Obstetric patients who are postoperative and receiving unfractionated heparin should have platelet count monitoring performed every 2–3 days from days 4 to 14 or until heparin is stopped. D

Initial experience with enoxaparin for the treatment of VTE in pregnancy indicated that satisfactory anti-Xa levels (peak anti-Xa activity, 3 hours post-injection, of 0.5–1.2 u/ml) were obtained using a weight-based regimen.[105] A recent case series of 13 pregnant women treated with therapeutic doses of tinzaparin found that 11 required dose adjustments to maintain the anti-Xa activity, assessed 4 hours post-injection, in the therapeutic range.[99] However, a retrospective case–control study from Denmark assessed 166 women managed with prophylactic and therapeutic doses of LMWH in pregnancy without anti-Xa monitoring and reported excellent clinical outcomes.[106] Monitoring of anti-Xa is therefore not routinely required in patients with VTE on therapeutic doses of LMWH, particularly as there are concerns over the accuracy of anti-Xa monitoring.[107,108] There may be a case for monitoring levels at extremes of body weight (less than 50 kg and 90 kg or more) and in women with other complicating factors including renal disease and recurrent VTE.[109]

Evidence level 2+

Guideline documents recommend that routine platelet count monitoring is not required in obstetric patients who receive heparin,[110,111] as the risk of HIT is low; one case report of HIT with thrombosis was identified in a pregnancy managed with enoxaparin.[112] The platelet count should be checked after 24 hours of initiating treatment if the patient has previously received heparin (unfractionated or LMWH) in the last 100 days.[111] The frequency of HIT is greater in surgical than medical patients, and is more likely with unfractionated heparin. It is therefore recommended that obstetric patients who are postoperative and receiving unfractionated heparin should have platelet count monitoring performed every 2–3 days from days 4 to 14 or until heparin is stopped.[110]

Evidence level 4

6.4 How should massive life-threatening PE in pregnancy and the puerperium be managed?

Collapsed, shocked women who are pregnant or in the puerperium should be assessed by a team of experienced clinicians including the on-call consultant obstetrician. ✓

Women should be managed on an individual basis regarding: intravenous unfractionated heparin, thrombolytic therapy or thoracotomy and surgical embolectomy. ✓

Management should involve a multidisciplinary team including senior physicians, obstetricians and radiologists. ✓

Intravenous unfractionated heparin is the preferred, initial treatment in massive PE with cardiovascular compromise. B

Maternity units should develop guidelines for the administration of intravenous unfractionated heparin. ✓

The on-call medical team should be contacted immediately. An urgent portable echocardiogram or CTPA within 1 hour of presentation should be arranged. If massive PE is confirmed, or in extreme circumstances prior to confirmation, immediate thrombolysis should be considered. ✓

Massive PE may present with shock, refractory hypoxaemia and/or right ventricular dysfunction on echocardiogram and is a medical emergency. Collapsed, shocked women who are pregnant or in the puerperium should be assessed by a multidisciplinary resuscitation team of experienced clinicians including the on-call consultant obstetrician, who should decide on an individual basis whether a woman receives intravenous unfractionated heparin, thrombolytic therapy or thoracotomy and surgical embolectomy.

Maternal resuscitation should commence following the principles of ABC and if cardiac arrest occurs, cardiopulmonary resuscitation should be performed with the woman in a left lateral tilt. A perimortem caesarean section should be performed by 5 minutes if resuscitation is unsuccessful and the pregnancy is more than 20 weeks.[113]

Evidence level 4

Intravenous unfractionated heparin is the preferred, initial treatment in massive PE because of its rapid effect, extensive experience of its use in this situation and since it can be adjusted more readily if thrombolytic therapy is administered.[11]

Evidence level 1+

One regimen for the administration of intravenous unfractionated heparin is:[114]

- loading dose of 80 units/kg, followed by a continuous intravenous infusion of 18 units/kg/hour
- if a patient has received thrombolysis (see below), the loading dose of heparin should be omitted and an infusion started at 18 units/kg/hour
- it is mandatory to measure activated partial thromboplastin time (APTT) level 4–6 hours after the loading dose, 6 hours after any dose change and then at least daily when in the therapeutic range. The therapeutic target APTT ratio is usually 1.5–2.5 times the average laboratory control value. (This will depend on the APTT reagent used in the laboratory and, when unfractionated heparin is employed, the advice of a haematologist should be sought)
- using this weight-adjusted regimen, the infusion rate should be adjusted according to the APTT as described in Table 2.

Table 2. Adjustments in the infusion rate of unfractionated heparin according to the APTT

APTT ratio	Dose change (units/kg/hour)	Additional action	Next APTT (hour)
< 1.2	+ 4	Re-bolus 80 units/kg	6
1.2–1.5	+ 2	Re-bolus 40 units/kg	6
1.5–2.5	no change		24
2.5–3.0	– 2		6
> 3.0	– 3	Stop infusion 1 hour	6

It is recognised that APTT monitoring of unfractionated heparin is technically problematic, particularly in late pregnancy when an apparent heparin resistance occurs due to increased fibrinogen and factor VIII which influence the APTT.[115,116] This can lead to unnecessarily high doses of heparin being used with subsequent haemorrhagic problems. Where such problems are considered to exist, haematologists should be involved in the patient's management. It may be useful to determine the anti-Xa level as a measure of heparin dose. With unfractionated heparin, a lower level of anti-Xa is considered therapeutic (target range 0.35–0.7 u/ml or 0.5–1.0 u/ml for patients with life-threatening PE).[117]

Evidence level 2+

In massive life-threatening PE with haemodynamic compromise (or with limb- or life-threatening ischaemic complications from extensive iliofemoral vein thrombosis), thrombolytic therapy should be considered as anticoagulant therapy alone will not reduce the obstruction in the circulation. After thrombolytic therapy has been given, an infusion of unfractionated heparin can be given, but the loading dose (outlined above) should be omitted.

A meta-analysis of randomised controlled trials using thrombolytic agents for PE has established that thrombolytic therapy is more effective than heparin therapy in reducing clot burden and improving haemodynamics.[118] These studies, however, have not shown any impact on long-term survival over and above that of conventional therapy with heparin or LMWH, and no thrombolytic agent has been shown to be superior to any of the others.[118] However, when Wan et al. restricted their analysis to those trials with massive PE, they identified a significant reduction in recurrent PE or death from 19.0% with heparin alone to 9.4% with thrombolysis (OR 0.45, 95% CI 0.22–0.90).[118] Current recommendations suggest that thrombolytic therapy should be reserved for patients with severe pulmonary thromboembolism with haemodynamic compromise.[119]

Evidence level 1++

There are now a large number of published case reports and case series on the use of thrombolytic therapy in pregnancy,[120–123] including cases treated with: streptokinase,[123–125] urokinase,[126] recombinant tissue plasminogen activator (rtPA; alteplase)[121,127,128] and tenecteplase.[129] A major concern regarding the use of thrombolytic therapy in pregnancy is fetal and maternal bleeding. In one literature review, Ahearn et al.[121] reported on 172 women treated with thrombolytic therapy (167 of whom had DVT or PE); problems associated with treatment included five nonfatal maternal bleeding complications (2.9%) and three fetal deaths (1.7%). No maternal deaths associated with thrombolytic therapy have been reported. More recently, te Raa et al.[123] reported on 13 cases of massive PE during pregnancy – four had haemorrhagic complications and there were two fetal deaths. Most bleeding events occur around catheter and puncture sites and, in pregnant women, there have been no reports of intracranial bleeding.

Evidence level 3

If the patient is not suitable for thrombolysis or is moribund, a discussion with the cardiothoracic surgeons with a view to urgent thoracotomy should be had.[112]

7. Additional therapies

7.1 Should graduated elastic compression stockings be employed in the acute management of VTE in pregnancy?

In the initial management of DVT, the leg should be elevated and a graduated elastic compression stocking applied to reduce oedema. Mobilisation with graduated elastic compression stockings should be encouraged.

B

Patients with acute DVT have traditionally been recommended bed rest and immobilisation for fear of dislodging an unstable thrombus and causing PE, and by the belief that rest relieves pain and swelling. However, randomised controlled trials have shown that early ambulation, with leg compression, does not increase the risk of PE, does not increase thrombus propagation, and that pain and swelling improved faster compared to those patients who had their mobility restricted.[130–138] This approach may also prevent the development of post-thrombotic syndrome (see section 11). A randomised controlled trial comparing knee-length with thigh-length hosiery concluded that thigh-length compression elastic stockings do not offer better protection against post-thrombotic syndrome than below-knee hosiery and are less well tolerated.[139] National guidance in the UK recommends that patients with proximal DVT should be offered below-knee compression stockings with an ankle pressure greater than 23 mmHg and that hosiery does not need to be worn on the unaffected leg.[12] Accurate fitting and careful instruction in the correct application of the hosiery is essential to avoid discomfort and assist rather than prevent venous return. A pilot audit of compliance with graduated compression stockings in pregnancy showed poor levels of compliance related to discomfort and side effects.[140]

Evidence level 1+

7.2 What is the role of inferior vena cava filters in the management of VTE in pregnancy?

Consideration should be given to the use of a temporary inferior vena cava filter in the peripartum period for patients with iliac vein VTE to reduce the risk of PE or in patients with proven DVT and who have recurrent PE despite adequate anticoagulation. D

Placement of a temporary inferior vena cava (IVC) filter in obstetric practice is indicated when recurrent thromboembolism occurs despite adequate anticoagulation, or when anticoagulation is contraindicated (such as the peripartum period). Case reports and case series have reported favourable outcomes with regard to safety and effectiveness on the use of IVC filters in pregnancy.[141-145] The long-term safety of IVC filters is uncertain and the main complications associated with vena cava filters are migration, an increased risk of lower limb DVT and caval thrombosis and, rarely, infection.[12]

Evidence level 3

8. Maintenance treatment of VTE

8.1 What is the maintenance treatment of DVT or PE?

Treatment with therapeutic doses of subcutaneous LMWH should be employed during the remainder of the pregnancy and for at least 6 weeks postnatally and until at least 3 months of treatment has been given in total. B

Women should be taught to self-inject LMWH and arrangements made to allow safe disposal of needles and syringes. Outpatient follow-up should include clinical assessment and advice with monitoring of blood platelets and peak anti-Xa levels if appropriate (see sections 5 and 6.3). C

Pregnant women who develop heparin-induced thrombocytopenia or have heparin allergy and require continuing anticoagulant therapy should be managed with an alternative anticoagulant under specialist advice. C

Women with antenatal VTE can be managed with subcutaneous therapeutic doses of LMWH for the remainder of the pregnancy[77-79,81,83-87] (see section 6.2). If LMWH therapy requires monitoring (e.g. extremes of body weight or renal impairment, see section 6.3), the aim is to achieve a peak anti-Xa activity, 3 hours post-injection, of 0.5–1.2 u/ml.

Evidence level 3

The rationale for recommending therapeutic doses of LMWH (rather than reduced, prophylactic doses) throughout the remainder of the pregnancy is based on the continuing risk of recurrent VTE during this time arising from: pregnancy-related changes in the coagulation system, reduced venous flow velocity, a higher incidence of isolated iliac vein DVT in pregnancy and in at least 50% of patients a thrombophilia will be present. A high recurrence rate of VTE (9 of 35 patients) was reported in a prospective randomised controlled trial in nonpregnant patients, when thromboprophylactic doses of unfractionated heparin (5000 iu every 12 hours) were employed after initial management with intravenous unfractionated heparin.[146]

Evidence level 1+

In their observational study on the management of antenatal VTE in Britain and Ireland, Voke et al.[101] found that doses of LMWH were reduced in 22% of women after initial treatment; the reasons given included clinical improvement several weeks after diagnosis and transfer from twice- to once-daily injections.

Evidence level 3

It is not yet established whether the dose of LMWH or unfractionated heparin can be reduced to an intermediate dose after an initial period of therapeutic anticoagulation. In view of the compelling safety data for LMWHs,[83-87] we continue to recommend continuation of therapeutic doses based on the patient's weight throughout pregnancy. Reducing to an intermediate dose may be useful in pregnant women at increased risk of bleeding or osteoporosis.

Evidence level 2++

Women should be taught to self-inject and can then be managed as outpatients until delivery; arrangements should be made to allow safe disposal of needles and syringes. A clinical audit and a prospective cohort study have shown good levels of compliance with LMWH self-injection therapy during the antenatal period.[147,148]

Evidence level 2+

Prolonged unfractionated heparin use during pregnancy may result in osteoporosis and fractures.[93,149] As discussed previously (section 6.1), the risk of osteoporosis with LMWH is much less than with unfractionated heparin, with one systematic review reporting a risk of 0.04%.[84]

Evidence level 2++

Allergic skin reactions to heparin can occur and may require the heparin preparation to be changed.[150] A prospective observational study of 111 pregnant women receiving heparin treatment (94 had LMWH and 17 had unfractionated heparin) found heparin-induced skin reactions in 22 (19.8%).[151] All lesions were caused by allergic delayed-type hypersensitivity reactions and the median time of onset was 50.5 days (range 5–184 days).

Evidence level 2–

In women who are unable to tolerate heparin, usually because of allergic skin reactions without evidence of HIT, an alternative LMWH can be prescribed, although the cross-reactivity rate to different heparin preparations is 33.3%.[151] Where the problem persists or in women with HIT, the use of danaparoid, a low-molecular-weight heparinoid, can be considered. A review of 91 pregnancies in 83 women concluded that danaparoid is an effective and safe antithrombotic in pregnancy for women who are intolerant of heparin.[152]

Evidence level 3

8.2 Can vitamin K antagonists be used during pregnancy for the maintenance treatment of VTE?

Because of their adverse effects on the fetus, vitamin K antagonists, such as warfarin, should not be used for antenatal VTE treatment.

C

Vitamin K antagonists cross the placenta readily and are associated with adverse pregnancy outcomes including miscarriage, prematurity, low birthweight, neurodevelopmental problems and fetal and neonatal bleeding. They are also associated with a characteristic embryopathy following fetal exposure in the first trimester.[153,154]

Evidence level 2+

8.3 Is there a role for the new anticoagulants in the treatment of VTE in pregnancy?

Consideration should be given to the use of newer anticoagulants (fondaparinux, argatroban or r-hirudin) in pregnant women who are unable to tolerate heparin (LMWH or unfractionated heparin) or danaparoid and who require continuing anticoagulant therapy.

D

Case reports and case series have described the use of newer anticoagulants in pregnancy following the development of HIT or skin allergy to heparins; these preparations are administered parenterally and include fondaparinux (a selective factor-Xa inhibitor),[112,155,156] argatroban (a direct thrombin inhibitor)[157–160] and r-hirudin (a direct thrombin inhibitor).[161–165] While these drugs are not licensed for use in pregnancy, preliminary data regarding their safety and efficacy in pregnancy are reassuring; fondaparinux has been recommended by a group of experts (the Pregnancy and Thrombosis Working Group) as an alternative to LMWH when HIT occurs in pregnancy.[166]

Evidence level 3

There are no reports on the use of the non-vitamin K antagonist oral anticoagulants (NOACs, previously called new or novel oral anticoagulants, e.g. rivaroxaban, apixaban, betrixaban and dabigatran) in pregnancy or the puerperium and as they are likely to cross the placenta and have potential direct fetal effects, they should therefore be avoided in the antenatal period.[154]

Evidence level 4

9. Anticoagulant therapy during labour and delivery

9.1 Should anticoagulant therapy be altered during labour and delivery?

When VTE occurs at term, consideration should be given to the use of intravenous unfractionated heparin which is more easily manipulated. D

The woman on LMWH for maintenance therapy should be advised that once she is in established labour or thinks that she is in labour, she should not inject any further heparin. ✓

Where delivery is planned, either by elective caesarean section or induction of labour, LMWH maintenance therapy should be discontinued 24 hours prior to planned delivery. D

Regional anaesthetic or analgesic techniques should not be undertaken until at least 24 hours after the last dose of therapeutic LMWH. D

LMWH should not be given for 4 hours after the use of spinal anaesthesia or after the epidural catheter has been removed, and the epidural catheter should not be removed within 12 hours of the most recent injection. D

Where possible, anticoagulant therapy should be altered to avoid an unwanted anticoagulant effect during delivery. Women should be advised not to inject any further heparin if they are in established labour or think they are in labour.

For elective delivery, LMWH should be stopped 24 hours before induction of labour or caesarean section. Subcutaneous unfractionated heparin should be discontinued 12 hours before and intravenous unfractionated heparin stopped 6 hours before induction of labour or regional anaesthesia.[167] Women who present in labour shortly after injecting LMWH can be reassured that bleeding complications are very uncommon with LMWH (see section 6.1). If spontaneous labour occurs in women receiving therapeutic doses of subcutaneous unfractionated heparin, careful monitoring of the APTT is required (see above for use of APTT in pregnancy). If it is markedly prolonged near delivery, protamine sulfate may be required to reduce the risk of bleeding.

When VTE occurs at term, the risk of recurrent thrombosis may be increased if anticoagulant therapy is discontinued to allow a planned induction of labour or caesarean section; one study suggested that the risk of recurrent VTE is higher within 2 weeks of the initial thrombosis.[168] Consideration can be given to the use of intravenous unfractionated heparin which is more easily manipulated and, because of its shorter half-life, minimises the duration without anticoagulant therapy. However, as noted previously, there are issues in monitoring unfractionated heparin in pregnancy using the APTT. One approach to the use of anticoagulant therapy in this situation has been described by McLintock et al.[40] Evidence level 4

The incidence of spinal haematoma after regional anaesthesia (with or without antithrombotic therapy) in the obstetric population is unknown. It is considered that obstetric patients have a lower incidence of spinal haematoma than elderly patients.[169,170] Epidural anaesthesia can be sited in obstetric patients undergoing treatment for VTE only after discussion with a senior anaesthetist, in keeping with local anaesthetic protocols. When a woman presents while on a therapeutic regimen of LMWH, regional techniques should not be employed for at least 24 hours after the last dose of LMWH. LMWH should not be given for at least 4 hours after the epidural catheter has been removed and the catheter should not be removed within 12 hours of the most recent injection.[167]

For delivery by elective caesarean section, the treatment doses of LMWH should be omitted for 24 hours prior to surgery. A thromboprophylactic dose of LMWH (enoxaparin 40 mg;

dalteparin 5000 iu; tinzaparin 75 iu/kg) should be given 4 hours postoperatively (at least 4 hours after removal of the epidural catheter, if appropriate) and the treatment dose recommenced 8 to 12 hours later.

Evidence level 4

9.2 Are specific surgical measures required for anticoagulated patients undergoing delivery by caesarean section?

In patients receiving therapeutic doses of LMWH, wound drains (abdominal and rectus sheath) should be considered at caesarean section and the skin incision should be closed with interrupted sutures to allow drainage of any haematoma. ✓

Measures should be taken to allow drainage of any haematoma, including the use of drains and interrupted skin sutures. A case–control study has reported an increased incidence of wound complications in women receiving peripartum anticoagulation.[171] The incidence of wound haematoma was 9.1% in women receiving anticoagulation and 1.3% in controls.

Evidence level 2+

9.3 What anticoagulant therapy should be employed in women at high risk of haemorrhage?

Any woman who is considered to be at high risk of haemorrhage, and in whom continued heparin treatment is considered essential, should be managed with intravenous unfractionated heparin until the risk factors for haemorrhage have resolved. D

Unfractionated heparin has a shorter half-life than LMWH and its activity is more completely reversed with protamine sulfate. It should therefore be used in situations when anticoagulation is required but concerns exist regarding bleeding; these situations include: antepartum haemorrhage, coagulopathy, progressive wound haematoma, suspected intra-abdominal bleeding, and postpartum haemorrhage. One regimen for the administration of unfractionated heparin is given in section 6.4. If a woman develops a haemorrhagic problem while on LMWH, the treatment should be stopped and advice sought from a haematologist. Protamine sulfate reverses the anti-IIa fraction of LMWH, but does not fully reverse the anti-Xa effect; case series have shown that it is useful in the management of bleeding associated with LMWH in some, but not all, patients.[172]

Evidence level 3

10. Postnatal anticoagulation

How should anticoagulation be managed postnatally?

Therapeutic anticoagulant therapy should be continued for the duration of the pregnancy and for at least 6 weeks postnatally and until at least 3 months of treatment has been given in total. Before discontinuing treatment the continuing risk of thrombosis should be assessed. C

Women should be offered a choice of LMWH or oral anticoagulant for postnatal therapy after discussion about the need for regular blood tests for monitoring of warfarin, particularly during the first 10 days of treatment. ✓

Postpartum warfarin should be avoided until at least the fifth day and for longer in women at increased risk of postpartum haemorrhage. ✓

Women should be advised that neither heparin (unfractionated or LMWH) nor warfarin is contraindicated in breastfeeding. D

National guidelines in the UK recommend that in nonpregnant patients anticoagulant therapy should be continued for at least 3 months for proximal DVT or PE and longer if the risk of recurrent VTE is considered to be high.[12] The presence of continuing prothrombotic factors that are a feature of pregnancy (see section 8.1) and the safety of LMWH have led authorities

Evidence level 4

to propose that, in the management of VTE in pregnancy, anticoagulant therapy should be continued for the duration of the pregnancy and until at least 6 weeks postpartum and to allow a total duration of treatment of *at least* 3 months.[81] Both heparin and warfarin are satisfactory for use postpartum. NOACs (see section 8.3) could be considered in women who are not breastfeeding, although no reports were identified of their use in the puerperium. Before discontinuing treatment the continuing risk of thrombosis should be assessed.

Evidence level 4

Women should be offered a choice of LMWH or oral anticoagulant for postnatal therapy after discussion about the need for regular blood tests for monitoring of warfarin. If the woman chooses to continue with LMWH postnatally, then the doses and dosage schedule that were employed antenatally should be continued.

A prospective cohort study has shown that women's adherence to LMWH therapy decreases postnatally (mean percentage adherence to LMWH antenatally was 97.92% and 93.37% postnatally). The authors conclude that healthcare workers should reinforce the necessity of adherence to LMWH treatment during the postpartum period.[148]

Evidence level 2+

If the woman chooses to commence warfarin postpartum, this should be avoided until at least the fifth postnatal day. Daily testing of the international normalised ratio (INR) is recommended during the transfer from LMWH to warfarin to avoid over-anticoagulation. Warfarin administration should be delayed in women considered to be at risk of postpartum haemorrhage.

A systematic review on dosage regimens for initiating warfarin found no evidence to suggest a 10 mg loading dose is superior to 5 mg, although no studies in that review involved obstetric patients.[173]

Evidence level 2++

A case–control study investigated the number of days and total warfarin dose required to achieve therapeutic INR in a group of postpartum women compared to a group of matched nonpregnant women.[174] The postpartum women required larger doses of warfarin and took significantly longer to reach therapeutic INR; the authors propose that the coagulation changes that occur in pregnancy and persist into the puerperium antagonise warfarin and may justify higher loading doses.

Evidence level 2+

The regimen for commencing warfarin should be based on nomograms developed with haematologists[175] (for an example, see Appendix II). The INR should be checked on day two of warfarin treatment and subsequent warfarin doses titrated to maintain the INR between 2.0 and 3.0; heparin treatment should be continued until the INR is greater than 2.0 for at least 24 hours.[176]

Evidence level 4

Neither heparin (unfractionated or LMWH) nor warfarin is contraindicated in breastfeeding. There is little published data on whether LMWHs are secreted in breast milk; in a case series of 15 women receiving LMWH after caesarean section, small amounts of heparin were detected in the breast milk of 11 patients.[177] Since neither unfractionated heparin nor LMWH is orally active, no clinical effect would be anticipated in the infant.[178] Warfarin does not pass into breast milk to any measurable degree; it is 99% bound to serum proteins which results in minimal transfer to breast milk.[179,180]

Evidence level 3

11. Prevention of post-thrombotic syndrome

What measures can be employed to prevent the development of post-thrombotic syndrome?

Women should be advised that prolonged use of LMWH (more than 12 weeks) is associated with a significantly lower chance of developing post-thrombotic syndrome. **B**

Following a DVT, graduated elastic compression stockings should be worn on the affected leg to reduce pain and swelling. Clinicians should be aware that the role of compression stockings in the prevention of post-thrombotic syndrome is unclear. B

The post-thrombotic syndrome (PTS) is characterised by chronic persistent leg swelling, pain, a feeling of heaviness, dependant cyanosis, telangiectasis, chronic pigmentation, eczema, associated varicose veins and in the most severe cases, venous ulceration. A case–control study from Norway found a prevalence of PTS of 42% following DVT in pregnancy; proximal postnatal thrombosis, smoking and age greater than 33 years were independent predictors of the development of PTS.[181] Other recognised risk factors include: recurrent ipsilateral DVT and obesity.[182] A randomised controlled trial of long-term use of LMWH (tinzaparin for more than 12 weeks) versus tinzaparin for 5 days then warfarin for 12 weeks in patients with proximal DVT reported a significantly lower rate of PTS in patients allocated to prolonged LMWH.[183] A subanalysis has shown that the benefits of prolonged LMWH are even greater for iliac vein DVT (OR 0.53, 95% CI 0.33–0.83) than with non-iliac DVT (OR 0.79, 95% CI 0.67–0.93).[184] While this study was conducted in nonpregnant subjects, the results may be relevant to the pregnant population where iliac vein DVT is more common and prolonged use of LMWH is standard treatment. Evidence level 1+

Graduated elastic compression stockings have been shown in meta-analyses of randomised controlled trials to offer substantial protection against the development of PTS in the nonpregnant (relative risk 0.54)[185] and national guidelines recommend that compression hosiery (more than 23 mmHg) should be worn on the affected leg for at least 2 years.[12] More recently, the benefits of compression stockings in preventing PTS have been questioned. A high-quality randomised controlled trial of over 800 patients with proximal DVT has reported the effectiveness of 30–40 mmHg (class II) compression stockings compared to a placebo stocking worn daily for 2 years on the incidence of PTS; compression stockings did not prevent the occurrence of PTS after a first proximal DVT and did not influence the severity of PTS or rate of recurrent VTE.[186] Evidence level 1++

12. Postnatal clinic review

Postnatal review for patients who develop VTE during pregnancy or the puerperium should, whenever possible, be at an obstetric medicine clinic or a joint obstetric haematology clinic. ✓

Thrombophilia testing should be performed once anticoagulant therapy has been discontinued only if it is considered that the results would influence the woman's future management. D

At the postnatal review, an assessment should be made of post-thrombotic venous damage and advice should be given on the need for thromboprophylaxis in any future pregnancy and at other times of increased risk (see Green-top Guideline No. 37a). Thrombophilia testing should be performed once anticoagulant therapy has been discontinued and only if it is considered that the results would influence the woman's future management; testing will not alter the duration and intensity of acute treatment but may alter prophylaxis in subsequent pregnancy (Green-top Guideline No. 37a). Hormonal contraception should be discussed with reference to guidance from the Faculty of Sexual and Reproductive Healthcare.[187] Evidence level 4

13. Recommendations for future research

- The role of D-dimer testing and pretest probability scoring in the diagnosis of VTE in pregnancy require further investigation.
- The maternal and fetal radiation risks of tests used in the diagnosis of PE in pregnancy need to be clarified.

- The role of newer diagnostic modalities (e.g. V/Q_{SPECT}) in the diagnosis of PE in pregnancy needs further evaluation.
- The optimum dosage regimen of LMWH for treatment of VTE in pregnancy (once daily versus two divided doses) merits further investigation.
- Doses of LMWH required in obese pregnant and puerperal women.
- The value and role of anti-Xa monitoring, including measurement of trough anti-Xa activity, of LMWH treatment in pregnancy needs further study.
- Studies are required to establish the safety and efficacy of newer anticoagulant agents in pregnancy.
- Studies are required to determine whether thrombophilia status alters the risk of recurrence of VTE and whether thrombophilia status requires an alteration in the duration of treatment.
- Strategies to prevent and treat post-thrombotic syndrome following DVT in pregnancy are required.

14. Auditable topics

- Documentation of risks of VTE investigations and management (100%).
- Correct therapeutic management of suspected and proven VTE (100%).
- Appropriate interval for administration of postpartum anticoagulant therapy (100%).
- Documentation of postpartum management plan (100%).
- Attendance for postnatal review and appropriate thrombophilia testing (100%).

15. Useful links and support groups

- Royal College of Obstetricians and Gynaecologists. *Information for you: Treatment of venous thrombosis in pregnancy and after birth*. London: RCOG; 2011 [https://www.rcog.org.uk/en/patients/patient-leaflets/treatment-of-venous-thrombosis-in-pregnancy-and-after-birth/].
- Lifeblood: The Thrombosis Charity. *Thrombosis and pregnancy*. Llanwrda: Lifeblood: The Thrombosis Charity; 2013 [http://www.thrombosis-charity.org.uk/perch/resources/thrombosis-pregnancy-crystal-mark-feb-2013.pdf].

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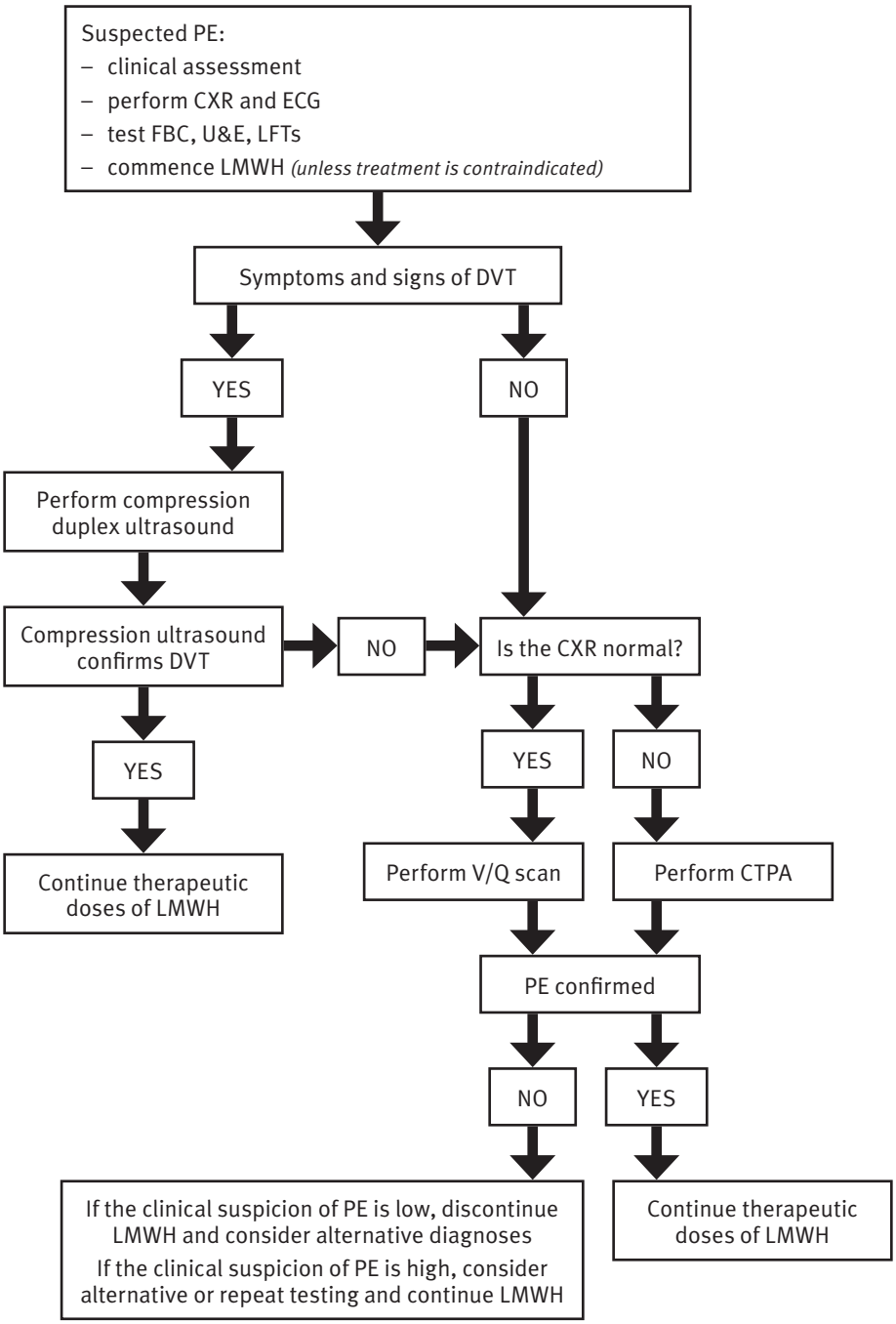
Appendix I: Algorithm for the investigation and initial management of suspected PE in pregnancy and the puerperium



Abbreviations

CTPA computerised tomography pulmonary angiogram; **CXR** chest X-ray; **DVT** deep venous thrombosis; **ECG** electrocardiogram; **FBC** full blood count; **LFTs** liver function tests; **LMWH** low-molecular-weight heparin; **PE** pulmonary embolism; **U&Es** urea and electrolytes; **V/Q scan** ventilation/perfusion scan.

Appendix II: Suggested nomogram for commencing warfarin treatment in the puerperium

Day of warfarin treatment	International normalised ratio (INR)	Warfarin dose (mg)
First		7.0
Second		7.0
Third	< 2.0	7.0
	2.0–2.1	5.0
	2.2–2.3	4.5
	2.4–2.5	4.0
	2.6–2.7	3.5
	2.8–2.9	3.0
	3.0–3.1	2.5
	3.2–3.3	2.0
	3.4	1.5
	3.5	1.0
	3.6–4.0	0.5
	> 4.0	0.0
Fourth	< 1.4	> 8.0
	1.4	8.0
	1.5	7.5
	1.6–1.7	7.0
	1.8	6.5
	1.9	6.0
	2.0–2.1	5.5
	2.2–2.3	5.0
	2.4–2.6	4.5
	2.7–3.0	4.0
	3.1–3.5	3.5
	3.6–4.0	3.0
	4.1–4.5	omit next day's dose then give 2 mg
	> 4.5	omit two days' doses then give 1 mg

Appendix III: Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

This guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by:
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The final version is the responsibility of the Guidelines Committee of the RCOG.

The review process will commence in 2018, unless otherwise indicated.

