



## **THROMBOEMBOLIC DISEASE IN PREGNANCY AND THE PUERPERIUM: ACUTE MANAGEMENT**

This is the second edition of this guideline, which was previously published in April 2001 under the same title. Thromboprophylaxis during pregnancy, labour and after vaginal delivery has been addressed in RCOG Green-top Guideline number 37, published in January 2004.

### **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 (VTE) is suspected during pregnancy or the puerperium.

### **2. Introduction and background**

VTE remains the main direct cause of maternal death in the UK<sup>1</sup> and sequential reports of Confidential Enquiries into Maternal Deaths have highlighted failures in obtaining objective diagnoses and employing adequate treatment. The subjective, clinical assessment of deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) is particularly unreliable in pregnancy and a minority of women with clinically suspected VTE have the diagnosis confirmed when objective testing is employed.<sup>2,3</sup> However, VTE is up to ten times more common in pregnant women than in nonpregnant women of the same age<sup>4</sup> and can occur at any stage of pregnancy but the puerperium is the time of highest risk. 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. The symptoms and signs of VTE include leg pain and swelling (usually unilateral), lower abdominal pain, low-grade pyrexia, dyspnoea, chest pain, haemoptysis and collapse.

### **3. Identification and assessment of evidence**

A search of Medline and PubMed (electronic databases) 1966–2005 was performed to identify all relevant randomised controlled trials, systematic reviews and meta-analyses. The databases were searched using the relevant MeSH terms including all subheadings. The principle 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 women are based on level I evidence,<sup>5,6</sup> however, evidence for the management of VTE during pregnancy is lacking and in general guideline recommendations for management of VTE during pregnancy are extrapolated from studies in nonpregnant women; this is highlighted in this document and annotated as grade C, level IV and 'good practice points'.

## 4. Diagnosis of acute VTE

*How is acute VTE diagnosed in pregnancy?*

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

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



*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. If ultrasound is negative and there is a low level of clinical suspicion, anticoagulant treatment can be discontinued.

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Compression duplex ultrasound is the primary diagnostic test for DVT.<sup>7</sup> If ultrasound confirms the diagnosis of DVT, anticoagulant treatment should be continued. If ultrasound is negative and a high level of clinical suspicion exists, the woman should remain anticoagulated and ultrasound repeated in 1 week or an alternative diagnostic test employed. If repeat testing is negative, anticoagulant treatment should be discontinued.<sup>8</sup>

Evidence level IV

When iliac vein thrombosis is suspected (backpain and swelling of the entire limb), magnetic resonance venography or conventional contrast venography may be considered.<sup>7</sup>

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

Where there is clinical suspicion of acute PTE a chest X-ray should be performed. Compression duplex Doppler should be performed where this is normal. If both tests are negative with persistent clinical suspicion of acute PTE, a ventilation–perfusion (V/Q) lung scan or a computed tomography pulmonary angiogram (CTPA) should be performed.

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Alternative or repeat testing should be carried out where V/Q scan or CTPA and duplex Doppler are normal but the clinical suspicion of PTE is high. Anticoagulant treatment should be continued until PTE is definitively excluded.

C

Women with suspected PTE should be advised that V/Q scanning carries a slightly increased risk of childhood cancer compared with CTPA (1/280,000 versus less than 1/1,000,000) but carries a lower risk of maternal breast cancer (lifetime risk increased by up to 13.6% with CTPA, background risk of 1/200 for study population).

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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.



Chest X-ray may identify other pulmonary disease such as pneumonia, pneumothorax or lobar collapse.<sup>9</sup> Whilst the X-ray is normal in over 50% of pregnant women with objectively proven PTE, abnormal features caused by PTE include atelectasis, effusion, focal opacities, regional oligoemia or pulmonary oedema.<sup>10</sup> The radiation dose to the fetus from a chest X-ray performed at any stage of pregnancy is negligible.<sup>11</sup> If the X-ray is abnormal with a high clinical suspicion of PTE, CTPA should be performed.

Evidence level IV

If the X-ray is normal, bilateral Doppler ultrasound leg studies should be performed. Although the use of lower-limb Doppler ultrasound in the investigation of PTE has not been validated in pregnancy, there have been several studies investigating its role in nonpregnant women with suspected PTE.<sup>12-15</sup> A diagnosis of DVT may indirectly confirm a diagnosis of PTE 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.<sup>7</sup>

The choice of technique for definitive diagnosis (V/Q scan or CTPA) will depend on local availability and should be made after discussion with a radiologist. The ventilation component of the ventilation/perfusion lung scan can often be omitted during pregnancy, thereby minimising the radiation dose for the fetus (which is in any event small and not associated with a substantial increased risk of complications), especially if the X-ray is normal. The British Thoracic Society recommends CTPA as first-line investigation for non-massive PTE in nonpregnant women. This technique has potential advantages over radionuclide (V/Q) imaging including better sensitivity and specificity (at least in nonpregnant women)<sup>16</sup> and a lower radiation dose to the fetus (see section below). In addition, it can identify other pathology, such as aortic dissection. The main disadvantage of CTPA is the high radiation dose to the maternal breasts, which is associated with an increased lifetime risk of developing breast cancer. This is particularly relevant when it is known that only around 5% of such investigations will have a positive result. In addition, CTPA may not identify small peripheral PTE. In contrast to CTPA, V/Q scanning may be delayed because of availability of isotope. 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<sup>7,17</sup> and its substantially lower radiation dose to pregnant breast tissue (see below).

Evidence  
level IV

The average fetal radiation dose with CTPA is less than 10% of that with V/Q scanning during all trimesters of pregnancy.<sup>17-19</sup> Cook and Kyriou<sup>17</sup> estimated that the risk of fatal cancer to the age of 15 years is less than 1/1,000,000 after in utero exposure to CTPA and 1/280,000 following a perfusion scan. While CTPA is associated with a lower risk of radiation for the fetus, this must be offset by the relatively high radiation dose (20 mGy) to the mother's thorax and, in particular, breast tissue. The delivery of 10 mGy of radiation to a woman's breast increases her lifetime risk of developing breast cancer. It has been estimated that the increased risk is 13.6% (background risk 1/200), a figure that has been cited widely.<sup>20</sup> More recently, Allen and Demetriades<sup>21</sup> have suggested that this risk is an overestimate, at least in the nonpregnant woman. Nevertheless, breast tissue is especially sensitive to radiation exposure during pregnancy and it therefore seems sensible 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 woman has had a previous chest CT scan.<sup>17</sup> Pulmonary angiography carries the highest radiation exposure (at least 0.5 mSv to the fetus and 5-30 mSv to the mother).

There have been concerns over the safety of iodinated contrast medium with CTPA, as this can potentially alter fetal or neonatal thyroid function. Current European guidelines indicate that iodinated contrast media may be given to a pregnant woman when radiographic examination is essential and that, following administration of iodinated agents to the mother during pregnancy, thyroid function should be checked in the neonate.<sup>22</sup>

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

##### **D-dimer testing should not be performed to diagnose acute VTE in pregnancy**

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In pregnancy, D-dimer can be elevated because of the physiological changes in the coagulation system and levels become 'abnormal' at term and in the postnatal period in most healthy pregnant women.<sup>23</sup> In one study, all of 23 women tested in the third trimester of pregnancy had elevated D-dimer levels.<sup>24</sup> Furthermore, D-dimer levels are increased if there is a concomitant problem such as pre-eclampsia.<sup>25</sup> Thus a 'positive' D-dimer

test in pregnancy is not necessarily consistent with VTE and objective testing is required. However, a low level of D-dimer in pregnancy is likely, as in the nonpregnant woman, to suggest that there is no VTE. It is important to note, however, that in the nonpregnant woman, even with a high pretest probability and a highly sensitive D-Dimer assay, 4% of DVTs will not be identified by the D-dimer test, increasing to 17% with a moderately sensitive D-dimer assay.

## 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.**



**Performing a thrombophilia screen prior to therapy is not routinely recommended. When undertaken, thrombophilia screens should be interpreted by clinicians (usually haematologists) with specific expertise in the area.**



The use of anticoagulant therapy can be influenced by renal and hepatic function and blood should be taken to confirm that these are normal before starting treatment.

Performing a thrombophilia screen prior to therapy is controversial and it is therefore not routinely recommended. This is because the results of a thrombophilia screen will not influence immediate management of acute VTE but it can provide information that can influence the duration and intensity of anticoagulation, such as when antithrombin deficiency or antiphospholipid syndrome is identified. If a thrombophilia screen is performed, it is important to be aware of the effects of pregnancy and thrombus on the results of a thrombophilia screen. For example, protein S levels fall in normal pregnancy, making it extremely difficult to make a diagnosis of protein S deficiency during pregnancy. Activated protein C (APC) resistance is found with the APC sensitivity ratio test in around 40% of pregnancies, owing to the physiological changes in the coagulation system. Antithrombin may be reduced when extensive thrombus is present. In nephrotic syndrome and pre-eclampsia (conditions associated with an increased risk of thrombosis) antithrombin levels are reduced and in liver disease protein C and S will be reduced. It is important, therefore, that thrombophilia screens are interpreted by clinicians (usually haematologists) with specific expertise in the area.

## 6. Initial anticoagulant treatment of VTE in pregnancy

*6.1 What is the initial treatment of VTE in pregnancy?*

**In clinically suspected DVT or PTE, treatment with LMWH should be given until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated.**



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 women.<sup>26,27</sup> A meta-analysis of randomised controlled trials has shown equivalent efficacy of LMWH to unfractionated heparin in the initial treatment of PTE.<sup>28</sup>

Evidence level Ia (for pregnancy: evidence level Ib, supported by levels II & III)

With regard to safety, there is substantial accumulating evidence with the use of LMWHs, both in pregnant and nonpregnant women, for the prevention and treatment of VTE.<sup>29</sup> Systematic reviews and large series of cases have concluded that LMWH is a safe alternative to unfractionated heparin as an anticoagulant during pregnancy.<sup>30-33</sup> There is also evidence that LMWHs do not cross the placenta.<sup>34,35</sup> Data reporting the experience of several LMWH preparations for treatment of DVT or PTE in pregnancy have now been published<sup>36-42</sup> in a

systematic review of 64 reports with 2777 pregnancies.<sup>33</sup> This review demonstrated a risk of recurrent VTE of 1.15% when treatment doses of LMWH were used to manage VTE in pregnancy. This compares favourably with recurrence rates of 5–8% reported in trials carried out in nonpregnant women treated with LMWH or unfractionated heparin followed by coumarin therapy who are followed-up for 3–6 months<sup>43,44</sup> and confirms that LMWHs are effective in the treatment of acute VTE in pregnancy.<sup>45</sup>

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 postpartum hemorrhage remains the most common cause of severe obstetric morbidity.<sup>46</sup> LMWHs are not associated with an increased risk of severe bleeding peripartum. In one systematic review,<sup>33</sup> the observed rate of major bleeding of 1.98% compares favourably with the rate of massive haemorrhage (0.7%) (defined as blood loss greater than 1500 ml) from one prospective study without the use of LMWH.<sup>46</sup> It is known that the risk of heparin-induced thrombocytopenia 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,<sup>33</sup> no cases of thrombocytopenia associated with thrombosis were reported.

These data on LMWH also substantiate a much-reduced risk of LMWH compared with unfractionated heparin for heparin-induced osteoporosis.<sup>53,47-51</sup> The overall risk of this complication on systematic review was 0.04%.<sup>33</sup> Four cases of osteoporotic fractures in association with LMWH use in pregnancy in one UK centre have been reported (three cases received tinzaparin and dalteparin was administered in the fourth), although in each case there were additional and significant risk factors for osteoporosis.<sup>52</sup> More data are required to evaluate the safety and efficacy of the commonly used LMWHs in pregnancy.

## 6.2 What is the therapeutic dose of LMWH in pregnancy?

**LMWH should be given daily in two subcutaneous divided doses with dosage titrated against the woman's booking or most recent weight. There should be clear local guidelines for the dosage of LMWH to be used.**



In nonpregnant women, the recommended therapeutic doses of LMWH varies according to the manufacturer (enoxaparin 1.5 mg/kg once daily; dalteparin 10,000–18,000 units once daily depending on body weight; tinzaparin 175 units/kg once daily). In view of recognised alterations in the pharmacokinetics of dalteparin and enoxaparin during pregnancy,<sup>53-54</sup> a twice-daily dosage regimen is recommended for these LMWHs in the treatment of VTE in pregnancy (enoxaparin 1 mg/kg twice daily; dalteparin 100 units/kg twice daily). Preliminary biochemical data from a relatively small number of women suggests that once-daily administration of tinzaparin (175 units/kg) may be appropriate in the treatment of VTE in pregnancy<sup>42</sup> but this has not yet been substantiated with published clinical outcome data on safety and efficacy in contrast to twice-daily dosing of enoxaparin and dalteparin (Table 1).<sup>33</sup>

**Table 1. Calculation of initial doses of drugs by early pregnancy weight**

Initial dose	Early pregnancy weight (kg)			
	< 50	50–69	70–89	> 90
Enoxaparin	40 mg bd	60 mg bd	80 mg bd	100 mg bd
Dalteparin	5000 iu bd	6000 iu bd	8000 iu bd	10,000 iu bd
Tinzaparin	175 units/kg once daily (all weights)			

bd = twice daily

### 6.3 *Should blood tests be performed to monitor LMWH 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) putting them at high risk.**



**Routine platelet count monitoring should not be carried out (unless unfractionated heparin has been given).**



If the diagnosis of VTE is confirmed (DVT or PTE), treatment should be continued. Experience indicates that satisfactory anti-Xa levels (peak anti-Xa activity, 3 hours post-injection, of 0.5–1.2 units/ml) are obtained using a weight-based regimen and monitoring of anti-Xa is not routinely required in women with VTE on therapeutic doses of LMWH, particularly as there are concerns over the accuracy of anti-Xa monitoring.<sup>57</sup> There may be a case for monitoring levels at extremes of body weight (less than 50 kg and 90 kg or more) and women with other complicating factors, including renal disease and recurrent VTE.

Guideline documents recommend that routine platelet count monitoring is not required in obstetric women who have received only LMWH<sup>58,59</sup> as there have been no cases of heparin-induced thrombocytopenic thrombosis in pregnancies managed with LMWH. If unfractionated heparin is employed, or if the obstetric patient is receiving LMWH after first receiving unfractionated heparin, or if she has received unfractionated heparin in the past, the platelet count should ideally be monitored every 2–3 days from day 4 to day 14 or until heparin is stopped, whichever occurs first.<sup>58,59</sup>

### 6.4 *How should massive life-threatening PTE in pregnancy be managed?*

**Collapsed, shocked patients need to be assessed by a 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.**



**Intravenous unfractionated heparin is the preferred treatment in massive PTE with cardiovascular compromise.**



**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 PTE is confirmed or, in extreme circumstances prior to confirmation, immediate thrombolysis should be considered.**



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



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



Intravenous unfractionated heparin is the traditional method of heparin administration in acute VTE and remains the preferred treatment in massive PTE because of its rapid effect and extensive experience of its use in this situation<sup>5,60-64</sup> One regimen for the administration of intravenous, unfractionated heparin is:<sup>65</sup>

- loading dose of 80 units/kg, followed by a continuous intravenous infusion of 18 units/kg/hour
- if a woman 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) 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.

- using this weight-adjusted regimen, the infusion rate should be adjusted according to the APTT as shown in Table 2.

There is an increasing realisation that APTT monitoring of unfractionated heparin is technically problematic, particularly in late pregnancy when an apparent heparin resistance occurs because of increased fibrinogen and factor VIII, which influence the APTT.<sup>66,67</sup> This can lead to unnecessarily high doses of heparin being used, with subsequent haemorrhagic problems. Where such problems are considered to exist, senior 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 0.35–0.70 units/ml<sup>68</sup> or 0.5–1.0 units/ml for women with life-threatening PTE).

In massive life-threatening PTE with haemodynamic compromise there is a case for considering thrombolytic therapy, as anticoagulant therapy will not reduce the obstruction of the pulmonary circulation. After thrombolytic therapy has been given, an infusion of unfractionated heparin can be given but the loading dose (outlined above) should be omitted.

Data are limited in pregnancy and there have been concerns about maternal bleeding and adverse fetal effects.

Several randomised controlled trials using thrombolytic agents for PTE have established that thrombolytic therapy is more effective than heparin therapy in reducing clot burden and rapidly improving haemodynamics. 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.<sup>69</sup> Because of this, current recommendations suggest that thrombolytic therapy should be reserved for women with severe pulmonary thromboembolism with haemodynamic compromise. There are now many published case reports on the use of thrombolytic therapy in pregnancy. Over 172 women treated with thrombolytic therapy have been reported: 164 with streptokinase, three with urokinase and five with recombinant tissue plasminogen activator. Problems associated with treatment included five non-fatal maternal bleeding complications (2.9%) and three fetal deaths (1.7%). No maternal deaths associated with thrombolytic therapy have been reported. These data are summarised by Ahearn *et al.*<sup>70</sup> Overall, data suggest that the maternal bleeding complication rate is in the range of 1–6%, which is consistent with that in nonpregnant women receiving thrombolytic therapy. Most bleeding events occur around catheter and puncture sites and, in pregnant women, there have been no reports of intracranial bleeding.

If the woman is not suitable for thrombolysis or is moribund, a discussion with the cardiothoracic surgeons with a view to urgent thoracotomy should be undertaken.

**Table 2. Infusion rates according to activated partial thromboplastin time (APTT)**

APTT ratio	Dose change (units/kg/hour)	Additional action	Next APTT (hours)
< 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

## 7. Additional therapies

*What additional therapies should be employed in the 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.**



**Consideration should be given to the use of a temporary inferior vena caval filter in the perinatal period for women with iliac vein VTE, to reduce the risk of PTE or in women with proven DVT and who have continuing PTE despite adequate anticoagulation.**



Pain and swelling in the affected leg are debilitating symptoms of DVT. Short-term studies in patients with proximal DVT showed that pain and swelling improved faster in mobile patients wearing compression hosiery than in those resting in bed without any compression. This approach can also prevent the development of post-thrombotic syndrome (see section 11). Below-knee compression socks are acceptable for patients without thigh or knee swelling. For patients with persisting leg oedema after DVT, class II compression hosiery is more effective than class I stockings. Accurate fitting and careful instruction in the correct application of the hosiery is essential to avoid discomfort and assist rather than prevent venous return. Class II compression socks and stockings should be taken off at night and do not need to be worn on the unaffected leg. Studies in the nonpregnant have shown that early mobilisation with compression therapy does not increase the likelihood of developing PTE. Thus, there is no requirement for bed rest in a stable patient on anticoagulant treatment with acute DVT.<sup>71-7</sup> Where DVT threatens leg viability through venous gangrene, the leg should be elevated, anticoagulation given and consideration given to surgical embolectomy or thrombolytic therapy.

There is evidence that the use of an inferior vena caval filter prior to labour or delivery reduces the risk of PTE.<sup>77</sup> However, when VTE occurs in the antepartum period, delivery should be delayed, if possible, to allow maximum time for anticoagulation rather than putting in a filter.

## 8. Maintenance treatment of VTE

*8.1 What is the maintenance treatment of DVT or PTE?*

**Treatment with therapeutic doses of subcutaneous LMWH should be employed during the remainder of the pregnancy.**



**Arrangements should be made to allow safe disposal of needles and syringes. Outpatient follow-up should include clinical assessment and advice with assessment of blood platelets and peak anti-Xa levels if appropriate (see sections 5 and 6.3).**



**Women receiving therapeutic-dose unfractionated heparin should have their platelet count monitored at least every other day until day 14 or until the unfractionated heparin is stopped, whichever occurs first.**



**Pregnant women who develop heparin-induced thrombocytopenia or have heparin allergy and require continuing anticoagulant therapy should be managed with the heparinoid, danaparoid sodium or fondaparinux, under specialist advice.**



Women with antenatal VTE can be managed with subcutaneous LMWH for the remainder of the pregnancy<sup>36,37,49,57,78</sup> using LMWH administered 12-hourly. If LMWH therapy requires monitoring, (for example, extremes of body weight or renal impairment, see section 6.3) the aim is to achieve a peak anti-Xa 3 hours post-injection, of 0.5–1.2 units/ml.

Evidence level III

Subcutaneous LMWH appears to have advantages over APTT-monitored unfractionated heparin in the maintenance treatment of VTE in pregnancy. The simplified therapeutic regimen for LMWH is convenient and allows outpatient treatment. Women should be taught to self-inject and can then be managed as outpatients until delivery.

The rationale for this recommendation is based on the continuing risk of recurrent venous thromboembolism during this time period. A high recurrence rate of VTE was reported (47%) 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.<sup>79</sup> There are now compelling safety data for LMWHs<sup>33</sup> and thus we continue to recommend continuation of therapeutic doses based on the patient's weight (for example, enoxaparin 1 mg/kg 12-hourly; dalteparin 100 units/kg twice daily up to a maximum of 20 000 units/24 hours; tinzaparin 175 units/kg) throughout pregnancy. 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 several weeks of therapeutic anticoagulation. However, such regimens have been successfully used in patients with contraindications to warfarin and in patients with underlying malignancy.<sup>80</sup> Although there have been no studies directly comparing these two types of dosing strategies in pregnant women, this type of modified dosing regimen may be useful in pregnant women at increased risk of bleeding or osteoporosis. In pregnancy, the duration of anticoagulation reflects the balance between the risk of recurrence compared with the risk of serious bleeding on oral anticoagulants. In pregnancy, oral anticoagulants are not used and LMWH is not associated with significant bleeding risk.<sup>3</sup> There are significant risk factors for recurrence, including pregnancy-related changes in the coagulation system, reduced venous flow velocity and in at least 50% a thrombophilia will be present. In addition, the location of the thrombus is important with regard to recurrence risk. In contrast to the nonpregnant, where the vast majority of DVTs are popliteofemoral, the majority of DVTs in pregnancy are ileofemoral, with a greater risk of both embolisation and recurrence. Thus, the balance of risks for recurrence versus bleeding on oral anticoagulants in nonpregnant patients is not directly applicable to pregnancy, emphasising the need for a longer duration of treatment and treatment throughout pregnancy.<sup>30</sup>

Prolonged unfractionated heparin use during pregnancy may result in osteoporosis and fractures.<sup>81,82</sup> Allergic skin reactions to heparin can occur and may require the heparin preparation to be changed.<sup>83</sup>

## 8.2 *Can oral anticoagulants be used during pregnancy for the maintenance treatment of VTE?*

**Because of their adverse effects on the fetus, oral anticoagulants should not be used for antenatal VTE treatment.**

**C**

Oral anticoagulants cross the placenta readily and are associated with a characteristic embryopathy in the first trimester, central nervous system abnormalities which occur during any trimester, fetal haemorrhage<sup>84</sup> and neonatal haemorrhage following the trauma of delivery.

## 9. Anticoagulant therapy during labour and delivery

### 9.1 *Should anticoagulant therapy be altered during labour and delivery?*

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

**Where delivery is planned, LMWH maintenance therapy should be discontinued 24 hours before planned delivery.**

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

**A thromboprophylactic dose of LMWH should be given by 3 hours after a caesarean section (more than 4 hours after removal of the epidural catheter, if appropriate).**



**The epidural catheter should not be removed within 12 hours of the most recent injection.**



In order to avoid an unwanted anticoagulant effect during delivery, LMWH should be stopped as soon as a woman is in established labour or thinks she is in labour. For elective delivery, LMWH should be stopped 24 hours before induction of labour or caesarean section. Bleeding complications appear to be very uncommon with LMWH.<sup>29</sup>

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. Subcutaneous unfractionated heparin should be discontinued 12 hours before and intravenous unfractionated heparin stopped 6 hours before induction of labour or regional anaesthesia.

Epidural anaesthesia can be sited only after discussion with a senior anaesthetist, in keeping with local anaesthetic protocols. When a woman presents while on a therapeutic regimen of LMWH (a twice-daily regimen), regional techniques should not be employed for at least 24 hours after the last dose of LMWH.<sup>85</sup> LMWH should not be given for at least 4 hours after the epidural catheter has been removed and the cannula should not be removed within 12 hours of the most recent injection.<sup>86-88</sup>

For delivery by elective caesarean section, the treatment doses of LMWH should be omitted for 24 hours before surgery. A thromboprophylactic dose of LMWH (enoxaparin 40 mg, dalteparin 5000 iu, tinzaparin 75 iu/kg) should be given by 3 hours post-operatively (more than 4 hours after removal of the epidural catheter, if appropriate) and the treatment dose recommenced that evening. There is an increased risk of wound haematoma following caesarean section with both unfractionated heparin and LMWH of around 2%.

### *9.2 Are specific surgical measures required for anticoagulated women undergoing delivery by caesarean section?*

**In women 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 staples or interrupted sutures to allow drainage of any haematoma.**



### *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.**



Risk factors include major antepartum haemorrhage, coagulopathy, progressive wound haematoma, suspected intra-abdominal bleeding and postpartum haemorrhage. Unfractionated heparin has a shorter half-life than LMWH and its activity is more completely reversed with protamine sulphate. If a woman develops a haemorrhagic problem while on LMWH, the treatment should be stopped and expert haematological advice sought.

## **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.**



**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**



**Women should be advised that neither heparin (unfractionated or LMWH) nor warfarin is contra-indicated in breastfeeding.**



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



National guidelines in the UK recommend that, in nonpregnant patients, anticoagulant therapy should be continued for 6 weeks for calf vein thrombosis and 3 months for proximal DVT or pulmonary embolism when VTE has occurred in relation to a temporary risk factor and 6 months for a first episode of idiopathic VTE.<sup>6,89</sup> The presence of continuing risk factors and the safety of LMWH has led authorities to propose that anticoagulant therapy should be continued for the duration of the pregnancy and until at least 6 weeks postpartum,<sup>29,66,90</sup> and to allow a total duration of treatment of **at least** 3 months. Both heparin and warfarin are satisfactory for use postpartum. Before discontinuing treatment, the continuing risk of thrombosis should be assessed, including a review of personal and family history of VTE and any thrombophilia screen results.<sup>8</sup> Arrangements should be made for completion of the thrombophilia tests (if necessary: see section 5) after anticoagulants are stopped; in some units this will be undertaken in haematology clinics.

Neither heparin (unfractionated or LMWH) nor warfarin is contraindicated in breastfeeding. There are few published data on whether LMWHs are secreted in breast milk, although extensive experience of enoxaparin in the puerperium reports no problems during breastfeeding and other heparins are known not to cross the breast.<sup>91</sup> Neither unfractionated heparin nor LMWH is orally active and no effect would therefore be anticipated in the fetus.

If the woman chooses to continue with LMWH postnatally, then either the doses that were employed antenatally can be continued or the manufacturers' recommended doses for the nonpregnant patient can be employed (enoxaparin 1.5mg/kg once daily, dalteparin 10,000–18,000 units once daily depending on body weight, tinzaparin 175 units/kg once daily). If the woman chooses to commence warfarin postpartum, this should be avoided until at least the third 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 with risk of postpartum haemorrhage. The regimen for commencing warfarin should be based on local protocols developed with haematologists (see Appendix 1). The INR should be checked on day 2 of warfarin treatment and subsequent warfarin doses titrated to maintain the INR between 2–3.<sup>79,92–96</sup> Heparin treatment should be continued until the INR is greater than 2 on two successive days.

## **11. Prevention of post-thrombotic leg syndrome**

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

**Graduated elastic compression stockings should be worn on the affected leg for 2 years after the acute event, if swelling persists, to reduce the risk of post-thrombotic syndrome.**



Graduated elastic compression stockings (class II) should be worn on the affected leg for 2 years after the acute event to reduce the risk of post-thrombotic syndrome. A randomised controlled trial in nonpregnant patients has shown that such therapy can reduce the incidence of post thrombotic syndrome from 23% to 11% over this period.<sup>74</sup>

The post-thrombotic syndrome is a common complication following DVT. It is found in over 60% of cases<sup>97</sup> followed up over a median of 4.5 years. It is characterised by chronic persistent leg swelling, pain, a feeling of

heaviness, dependent cyanosis, telangiectasis, chronic pigmentation, eczema, associated varicose veins and in some cases lipodermatosclerosis and chronic ulceration. Symptoms are made worse by standing or walking and improve with rest and recumbancy. The syndrome is more common where there is a recurrent DVT, with obesity and where there has been inadequate anticoagulation<sup>98</sup> Graduated elastic compression stockings will improve the microcirculation by assisting the calf muscle pump, reducing swelling and reflux, and reducing venous hypertension. A randomised trial<sup>74</sup> reported that mild to moderate post-thrombotic syndrome decreased from 47% to 20% and severe post-thrombotic syndrome decreased from 23% to 11% with use of compression stockings over 2 years.

## 12. Postnatal clinic review

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



At the postnatal review, an assessment should be made of post-thrombotic venous damage, thrombophilia tests should be reviewed and arrangements made to repeat them if necessary. Advice should be given on the need for thromboprophylaxis in any future pregnancy and at other times of increased risk. Hormonal contraception should be discussed; for further information, see the *UK Medical Eligibility Criteria for Contraceptive Use 2005/06*.<sup>99</sup>

## 13. Auditable standards

1. Documentation of risks of VTE investigations and management.
2. Correct therapeutic management of suspected and proven VTE.
3. Appropriate interval for administration of postpartum anticoagulant therapy.
4. Documentation of postpartum management plan.
5. Attendance for postnatal review and appropriate thrombophilia testing

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## APPENDIX 1

### Suggested protocol for commencing warfarin treatment in the puerperium (adapted from British Society for Haematology Guidelines, 1998)

Day of treatment	INR	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
Fourth	> 4.0	0.0
	< 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 day's doses then give 1 mg	

INR = international normalised ratio

## APPENDIX 2

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: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at [www.rcog.org.uk/clingov1](http://www.rcog.org.uk/clingov1)). 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	Grades of recommendations
Ia Evidence obtained from meta-analysis of randomised controlled trials.	<b>A</b> Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
Ib Evidence obtained from at least one randomised controlled trial.	<b>B</b> Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
IIa Evidence obtained from at least one well-designed controlled study without randomisation.	<b>C</b> Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)
IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.	<b>Good practice point</b>
III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.	<input checked="" type="checkbox"/> Recommended best practice based on the clinical experience of the guideline development group.
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.	

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

#### DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

Guideline review process will commence in February 2010  
unless otherwise indicated