



## REDUCING THE RISK OF THROMBOSIS AND EMBOLISM DURING PREGNANCY AND THE PUERPERIUM

This is the second edition of this guideline, which was published in 2004 under the title *Thromboprophylaxis During Pregnancy, Labour and after Vaginal Delivery*.

### Executive summary of recommendations

#### *Recommendations for thromboprophylaxis during pregnancy*

All women should undergo a documented assessment of risk factors for venous thromboembolism (VTE) (listed in Table 1, Figure 1 and Appendix III) in early pregnancy or before pregnancy. This assessment should be repeated if the woman is admitted to hospital for any reason or develops other intercurrent problems.

C

Women at high risk of VTE in pregnancy, such as those with previous VTE, should be offered prepregnancy counselling and a prospective management plan for thromboprophylaxis in pregnancy. Those who become pregnant before receiving such counselling should be referred to a consultant obstetrician or trust-nominated expert in thrombosis in pregnancy early in pregnancy.

✓

Women with a previous non-estrogen-related VTE provoked by a minor risk factor should undergo testing for thrombophilia, as this will influence management and decisions regarding thromboprophylaxis antenatally.

C

Antenatal thromboprophylaxis should begin as early in pregnancy as practical.

B

Low molecular weight heparins (LMWH) are the agents of choice for antenatal thromboprophylaxis. These are at least as effective as and safer than unfractionated heparin.

A

Any woman with three or more current or persisting risk factors listed in Table 1 should be considered for prophylactic LMWH antenatally.

C

Women with a previous single provoked (excluding estrogen-related) VTE and no other risk factors require close surveillance; antenatal LMWH is not routinely recommended.

C

Women with previous recurrent VTE or a previous unprovoked or estrogen or pregnancy-related VTE or a previous VTE and a history of VTE in a first-degree relative (or a documented thrombophilia) or other risk factors should be offered antenatal thromboprophylaxis with LMWH.

C

Women with asymptomatic inherited or acquired thrombophilia may be managed with close surveillance antenatally. Exceptions are women with antithrombin deficiency, those with more than one thrombophilic defect (including homozygosity for factor V Leiden) or those with additional risk factors, where advice of a local expert should be sought and antenatal prophylaxis considered. C

Women receiving antenatal LMWH should be advised that, if they have any vaginal bleeding or once labour begins, they should not inject any further LMWH. They should be reassessed on admission to hospital and further doses should be prescribed by medical staff. ✓

*Recommendations for thromboprophylaxis following delivery*

All women should be assessed after delivery for the risk factors listed in Figure 1, Table 1 and Appendix III. C

All women should be encouraged to mobilise both during labour and postpartum. Dehydration should be avoided. ✓

Women with two or more persisting risk factors listed in Table 1 should be considered for LMWH for 7 days after delivery. C

Women with three or more persisting risk factors listed in Table 1 should be given graduated compression stockings in addition to LMWH. C

All women with class-three obesity: body mass index (BMI) > 40kg/m<sup>2</sup>, should be considered for thromboprophylaxis with LMWH for 7 days after delivery. ✓

All women who have had an emergency caesarean section (category 1, 2 or 3) should be considered for thromboprophylaxis with LMWH for 7 days after delivery. C

All women who have had an elective caesarean section (category 4) who have one or more additional risk factors (such as age over 35 years, BMI greater than 30) should be considered for thromboprophylaxis with LMWH for 7 days after delivery. C

All women with asymptomatic heritable or acquired thrombophilia should be considered for LMWH for at least 7 days following delivery, even if they were not receiving antenatal thromboprophylaxis. This could be extended to 6 weeks if there is a family history or other risk factors present. C

Women with VTE before the current pregnancy should be offered LMWH for 6 weeks following delivery. C

Women receiving LMWH antenatally should usually continue prophylactic doses of LMWH until 6 weeks postpartum but a postnatal risk assessment should be made. If they are receiving long-term anti-coagulation with warfarin, this can be started when the risk of haemorrhage is low. C

Both warfarin and LMWH are safe when breastfeeding. B

Women should be repeatedly assessed for risk factors for VTE if they develop intercurrent problems or require surgery or readmission in the puerperium. C

In women who have additional persistent (lasting more than 7 days postpartum) risk factors, such as prolonged admission or wound infection, thromboprophylaxis should be extended for up to 6 weeks or until the additional risk factors are no longer present. ✓

## 1. Purpose and scope

The aim of this guideline is to provide advice, based on clinical evidence where available, regarding the prevention of VTE during pregnancy, birth and following delivery. Of note, the National Institute for Health and Clinical Excellence (NICE) guideline on venous thromboembolism (due November 2009) includes pregnancy and the puerperium as risk factors and the present guideline aims to be consistent with the clinical practice recommendations included in the NICE guideline.<sup>1</sup>

This guideline reviews the risk factors for VTE in pregnancy and the puerperium and provides guidance as to which women require thromboprophylaxis in and after pregnancy. It reviews the safety and efficacy of different forms of thromboprophylaxis. For the diagnosis and management of acute VTE in pregnancy please refer to Green-top guideline No. 28.<sup>2</sup> This guideline covers thromboprophylaxis after caesarean section and thus it replaces the previously published *Report of the RCOG Working Party on Prophylaxis Against Thromboembolism in Gynaecology and Obstetrics* from 1995.<sup>3</sup> This guideline excludes the management of pregnancy loss and other pregnancy complications, even in women with documented thrombophilia. For anticoagulation for mechanical heart valves in pregnancy, the reader is directed to the chapter covering this problem within the proceedings of the RCOG study group on *Heart Disease and Pregnancy*.<sup>4</sup> A summary of the guideline for antenatal and postnatal thromboprophylaxis is given in Figure 1 and the 23 recommendations are listed in the executive summary at the start of this document. **As is apparent from the low grading of the evidence for many of the recommendations, they have been developed to provide a broad practical guide for obstetricians in clinical practice. However, it is recognised that, in individual women, alternative approaches may be reasonable, particularly following discussion with the woman concerned and, where available, input from a local expert in the field of thrombosis in pregnancy.**

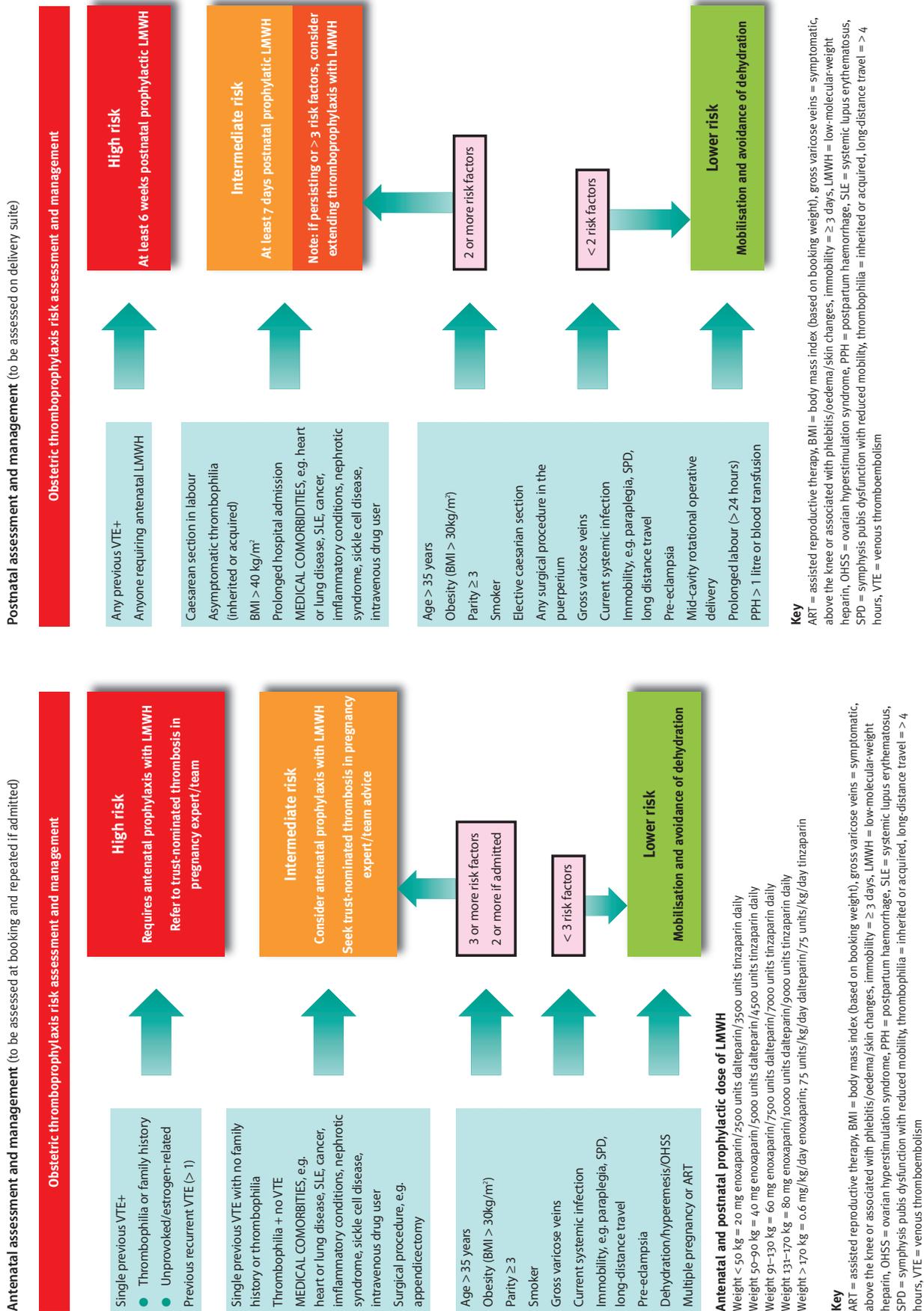
## 2. Introduction and background epidemiology

Pulmonary embolism remains the leading direct cause of maternal death in the UK (1.56/100 000 maternities)<sup>5</sup> and is the second most common cause of maternal death overall (11% of maternal deaths). Many pulmonary embolisms are preventable with appropriate thromboprophylaxis. NICE estimates that LMWH reduces VTE risk in medical and surgical patients by 60% and 70%, respectively.<sup>1</sup> It is reasonable, therefore, to assume that it may reduce the risk of VTE in obstetric patients by up to two-thirds. Seventy-nine percent of the women who died from pulmonary embolism in the UK between 2003 and 2005 had identifiable risk factors<sup>5</sup> and a similar proportion (70%) from the UK Obstetric Surveillance System cohort ( $n = 143$ ) of fatal and nonfatal antenatal pulmonary embolisms also had identifiable risk factors.<sup>6</sup> The UK incidence of antenatal pulmonary embolism is 1.3/10 000 maternities.<sup>6</sup> The case fatality rate of pulmonary embolism was 3.5%.

Many antenatal VTE events occur in the first trimester and therefore prophylaxis, if given, should begin early in pregnancy.<sup>7-9</sup> The highest risk period for VTE, and pulmonary embolism in particular, is during the postpartum period.<sup>10,11</sup> Caesarean section is a significant risk factor<sup>12,13</sup> but women having vaginal deliveries are also at risk and 55% (25/45) of the postpartum maternal deaths from VTE in the UK between 1997 and 2005 occurred in women who had delivered vaginally.<sup>5</sup> Although the relative risk of VTE in pregnancy is increased four- to six-fold<sup>11</sup> and this is increased further postpartum,<sup>10</sup> the absolute risk is low, with an overall incidence of VTE in pregnancy and the puerperium of 1–2/1000.<sup>11,13-15</sup> A cohort study from Rochester, Minnesota, showed that the annualised incidence of VTE was five times higher postpartum compared with pregnancy.<sup>11</sup> A large population-based case-control study from the Netherlands found a 60-fold increase in the risk of VTE in the first 3 months after delivery compared with non-pregnant controls.<sup>10</sup> Thus, with approximately 700 000 births/year in the UK, the above incidence of VTE would translate into 700–1400 pregnancy-related VTE episodes/year nationally in addition to those related to miscarriage and termination. With about ten fatalities per year from pulmonary embolism, this translates into an overall case fatality for VTE in pregnancy of approximately 1%.

Updated internationally developed evidence-based guidelines for antithrombotic therapy in pregnancy have

**Figure 1. Obstetric thromboprophylaxis risk assessment and management**



recently been published.<sup>16</sup> As the absolute risk of VTE in pregnancy is low, some form of risk stratification is required to decide which women warrant pharmacological thromboprophylaxis.<sup>17</sup> The threshold for recommending postpartum thromboprophylaxis is lower because the risk/day is higher and the duration of risk is shorter.<sup>16</sup>

### 3. Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing RCOG Green-top guidelines. The Cochrane Library (including the Database of Systematic Reviews and the Control Register of Controlled Trials), the Database of Abstracts of Reviews and Effects (DARE), Embase, the ACP Journal Club and Medline (including in-process and other non-indexed citations) were searched from 2002 to 2008 to identify all relevant randomised controlled trials (RCTs), systematic reviews and meta-analyses published since the previous edition of the guideline. The databases were searched using the relevant MeSH terms including all sub-headings. The principal search terms used were: 'venous thromboembolism', 'thrombosis', 'pregnancy', 'postpartum', 'puerperium', 'antenatal', 'prenatal'. The search was limited to humans and English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews.

Current guidelines for the prevention of VTE in pregnancy and the puerperium were reviewed.<sup>16,18,19</sup> A recent Cochrane systematic review of randomised trials comparing one method of thromboprophylaxis with placebo or no treatment and randomised trials comparing two (or more) methods of thromboprophylaxis concluded that there was insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period. Large-scale randomised trials of currently-used interventions should be conducted.<sup>20</sup>

### 4. Prepregnancy and antenatal risk assessment

*What are the risk factors for VTE in pregnancy and the puerperium? What is the magnitude of risk for these factors?*

The risk factors for VTE are listed in Table 1, Appendix 1 and Appendix IV. For most risk factors the level of evidence is 2+ but it varies from 2- to 2++ depending on the risk factor.

Some women can be identified as being at increased risk because of the presence of one or more well-documented risk factors.<sup>13,15,17,21-26</sup> Appendix 1 summarises the odds ratios (OR) for VTE associated with each risk factor derived from various studies.

#### Previous VTE and inherited thrombophilia

Two well-recognised significant risk factors for VTE in pregnancy are thrombophilia and previous VTE. Inherited thrombophilia is found in 20-50% of pregnancy-related VTE.<sup>27,28</sup> A large retrospective study calculated an OR of 24.8 (95% CI 17.1-36) for previous VTE.<sup>23</sup> Both these risk factors are identifiable before women become pregnant. They are discussed in more detail in sections 4.1 and 4.2.

#### Age and obesity

Table 1 and Appendix 1 highlight the importance of other risk factors. Women with multiple risk factors for VTE, even those who are not known to have a thrombophilia or a previous VTE, may be at greatly increased risk of VTE in pregnancy. Indeed, age over 35 years, obesity and caesarean section contribute most substantially to the rates of VTE because of their high (and increasing) prevalence.<sup>29</sup> Obesity warrants particular consideration as a risk factor,<sup>6,13,22-24</sup> as highlighted by *Saving Mothers' Lives*.<sup>5</sup> Twelve of the 33 women (36%) who died from pulmonary embolism in the UK between 2003 and 2005 were obese (BMI greater than 30). This is likely an underestimate as, if only the 21 women for whom a BMI was recorded are considered, 57% were obese. This compares with the prevalence of obesity in the female population of childbearing age of 18% in women aged 25-34 years and 22% in women aged 35-44 years in the Health

**Table 1:** Risk factors for venous thromboembolism in pregnancy

Timeframe	Factors
Pre-existing	Previous venous thromboembolism Thrombophilia: <i>Heritable:</i> Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden Prothrombin gene G20210A <i>Acquired (antiphospholipid syndrome):</i> Persistent lupus anticoagulant Persistent moderate/high-titre anticardiolipin antibodies or $\beta_2$ glycoprotein 1 antibodies Medical comorbidities (e.g. heart or lung disease, SLE, cancer, inflammatory conditions (inflammatory bowel disease or inflammatory polyarthropathy), nephrotic syndrome (proteinuria > 3 g/day), sickle cell disease, <sup>36</sup> intravenous drug user Age > 35 years Obesity (BMI > 30 kg/m <sup>2</sup> ) either prepregnancy or in early pregnancy Parity $\geq$ 3 Smoking Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes) Paraplegia
Obstetric	Multiple pregnancy, assisted reproductive therapy Pre-eclampsia Caesarean section PPH (> 1 litre) requiring transfusion } Prolonged labour, mid-cavity rotational operative delivery
New-onset/transient Potentially reversible <sup>a</sup>	Surgical procedure in pregnancy or puerperium (e.g. ERPC, appendicectomy, postpartum sterilisation) Hyperemesis, dehydration Ovarian hyperstimulation syndrome Admission or immobility ( $\geq$ 3 days' bed rest) e.g. symphysis pubis dysfunction restricting mobility Systemic infection (requiring antibiotics or admission to hospital) e.g. pneumonia, pyelonephritis, postpartum wound infection Long-distance travel (> 4 hours)

BMI = body mass index; ERPC = evacuated PPH = postpartum haemorrhage; evacuation of retained products of conception; SLE = systemic lupus erythematosus

<sup>a</sup> May develop at later stages in gestation than the initial risk assessment or may resolve and therefore continuing individual risk assessment is important

Survey for England 2003.<sup>30</sup> Thus, obesity is a moderate risk factor for VTE but is particularly important because of its high prevalence within the population. Furthermore, in one study, obesity was associated with a higher risk of pulmonary embolism (adjusted OR 14.9, 95% CI: 3.0–74.8) than of deep venous thrombosis (adjusted OR 4.4, 95% CI 1.6–11.9).<sup>24</sup> Although the data in pregnancy are limited, the risk of VTE appears to increase further with increasing obesity.<sup>31</sup> Being overweight (BMI 25–30) is also a weak risk factor for pregnancy-related VTE and is extremely common, with a prevalence within the childbearing population of almost 50%.<sup>30</sup>

### Immobility and long distance travel

Some workers have demonstrated interaction between the effects of the risk factors listed in Table 1 and Appendix 1. For example, in a Norwegian case-control study,<sup>13</sup> BMI greater than 25 and antepartum immobilisation (defined as strict bed rest 1 week or more before delivery) had a multiplicative effect on the risk for antepartum (adjusted OR 62.3, 95% CI: 11.5, 337.7) and postpartum VTE (adjusted OR 40.1, 95% CI: 8.0, 201.5). In the same study, assisted reproduction and multiple pregnancy had additive effects. For some risk factors, such as immobility, cardiac disease and long-distance travel, data for pregnancy-related risk are limited and extrapolation from studies in nonpregnant patients is appropriate.<sup>25</sup>

The NICE guideline on antenatal care<sup>32</sup> and the RCOG Scientific Advisory Committee Opinion Paper on air travel in pregnancy<sup>33</sup> state that long-haul air travel increases the risk of VTE but the present guideline considers all long distance (more than 4 hours) travel (not exclusively by air) to be a risk factor for VTE in pregnancy.

### Admission to hospital

In nonpregnant medical and surgical patients, there is increasing recognition of the role of hospitalisation as a major risk factor for VTE. It is believed that at least 25 000 deaths/year in England resulting from pulmonary embolism complicating hospital admission may be preventable. An independent expert working group on the prevention of venous thromboembolism in hospitalised patients, set up by the Chief Medical Officer, has recommended that it become mandatory for all patients to be risk assessed for VTE on admission to hospital; this report has been accepted by the Department of Health.<sup>34</sup> In terms of converting risk assessment into thromboprophylaxis practice, a NICE guideline on prevention of VTE in patients admitted for surgery was published in 2007<sup>35</sup> and a further guideline on prevention of VTE in all hospitalised patients, which will include a review of the surgical guideline, is due to be published in November 2009.<sup>1</sup> Pregnant women are included in this guideline which states 'Consider offering VTE prophylaxis with LMWH to women who are pregnant or six or fewer weeks postpartum who are admitted to hospital and expected to be immobile for three or more days and assessed to be at increased risk of VTE'. Increased risk in this context is identified by the presence of one or more risk factors including obesity (BMI greater than 30) and significant medical comorbidities.

An individual assessment of thrombotic risk should therefore be undertaken **before** pregnancy or in early pregnancy and **at each hospital admission**. Appendix III provides a suggested checklist for documentation of this risk assessment. Women at high risk of VTE (either because of previous confirmed VTE and/or thrombophilia or those with multiple risk factors) should be offered prepregnancy counselling with a prospective management plan. This has implications for general practitioners, physicians and gynaecologists. This is particularly important in view of:

- the increased thrombotic risks associated with complications in the first trimester. For example, in one study, the odds ratio for VTE in women with hyperemesis gravidarum was 2.5 (95% CI 2.0–3.2)<sup>23</sup>
- the fact that many antenatal VTE events (including fatal events) occur in the first trimester<sup>5,7-9</sup>
- the fact that 'booking' often does not occur until the end of the first trimester, after the stage at which thromboprophylaxis should have ideally begun.

**All women should undergo a documented assessment of risk factors for VTE in early pregnancy or before pregnancy. This assessment should be repeated if the woman is admitted to hospital for any reason or develops other intercurrent problems. The assessment should be repeated again intrapartum or immediately postpartum.**



Available evidence does not allow an accurate risk of VTE to be determined from combinations of the different risk factors listed in Table 1 and Appendix 1. However, multiple risk factors increase the risk of VTE.<sup>13</sup> Therefore, as a pragmatic approach to women with risk factors except previous VTE (see text below and Figure 1 and Appendix 2), it is suggested that thromboprophylaxis with LMWH be considered antenatally if there are three or more risk factors and postnatally if there are two or more factors. This approach to thromboprophylaxis was taken in a prospective German study of 810 women.<sup>17</sup> The authors administered dalteparin 50–100 iu/kg/day antenatally to women at 'low risk' of VTE with three or more risk factors (including obesity, age over 35 years, family history of VTE, varicose veins, smoking, immobilisation, surgery, hyperemesis/dehydration, thrombophlebitis) and postnatally for 2 weeks to those with two or more risk factors. This approach resulted in a low rate of VTE (0.6%, 95% CI 0.2–1.5%) and a low incidence of both bleeding related to thromboprophylaxis (1.1%, 95% CI 0.5–2.2%) and osteoporosis (0.1%, 95% CI 0.01–0.8%) and no heparin-induced thrombocytopenia.<sup>17</sup> There was no VTE in 225 women at 'low risk', although, in practice, 85% of women in this group received antenatal prophylaxis (median from 24 weeks and 74% at first presentation) because of additional risk factors.

Any woman with three or more current or persisting risk factors shown in Figure 1 and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH antenatally and will usually require prophylactic LMWH for 6 weeks postnatally; a postnatal risk reassessment should be made.



Any woman with two or more current or persisting risk factors shown in Figure 1 and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH for at least 7 days postpartum.



The risk of VTE should be discussed with women at risk and the reasons for individual recommendations explained.



#### 4.1 Previous VTE

##### *How should women with previous VTE be managed in pregnancy?*

Women with previous VTE have an increased risk of recurrence in pregnancy and postpartum,<sup>23</sup> with reported recurrence rates of 1.4–11.1%.<sup>37–41</sup> A retrospective comparison of the recurrence rate of VTE during pregnancy and the nonpregnant period revealed recurrence rates of 10.9% during and 3.7% outside pregnancy, giving a relative risk during pregnancy of 3.5 (95% CI 1.6–7.8).<sup>37</sup> The risk of recurrence appears to be constant over the whole period of pregnancy.<sup>39,41</sup>

All women with prior VTE should receive postpartum prophylaxis,<sup>16</sup> as this is the period of greatest risk. There are no randomised trials on which to base measures to prevent antenatal VTE in women with prior VTE and decisions are therefore based on estimates from observational studies in which antenatal thromboprophylaxis was withheld and assumptions on the likely benefit of intervention based on data from nonpregnant medical and surgical patients.<sup>1</sup> Available studies come from Canada,<sup>38</sup> Europe<sup>37,39</sup> and the USA.<sup>42</sup> Numbers of women included were inevitably small and, as well as varying in design, the studies differed, for example, on whether or not a previous estrogen-provoked VTE was regarded as a temporary risk factor in the subsequent pregnancy. The Canadian study has the advantage of being prospective but the median gestational age at enrolment was 15 weeks, potentially missing women with first trimester recurrences, and women with known thrombophilia were excluded so the risks of recurrence may have been underestimated.<sup>38</sup>

For the purposes of antenatal risk assessment, women with previous VTE can be stratified into those with recurrent or single previous VTE. The latter group may be further subdivided into those with

- unprovoked VTE
- estrogen-provoked (estrogen-containing contraception or pregnancy) VTE
- thrombophilia (heritable or acquired) or family history-associated VTE
- temporary risk factor (e.g. major trauma or surgery) associated VTE.

#### Recurrent VTE

Individuals with recurrent VTE are at increased risk of further recurrence<sup>43</sup> and many will be on long-term warfarin. Although data are lacking, it would be expected that they would have a high risk of recurrence in pregnancy. Advice should be sought from a clinician with expertise in haemostasis and pregnancy. For some women in this category, higher doses of LMWH may be appropriate. Women should be counselled about the risks of warfarin to the fetus (see section 8.7) and advised to stop warfarin and change to LMWH as soon as pregnancy is confirmed, ideally within two weeks of the missed period and before the sixth week of pregnancy. Women not on warfarin should be advised to start LMWH as soon as they have a positive pregnancy test.

#### Single previous VTE

**Unprovoked:** Outside pregnancy, unprovoked VTE is associated with an increased risk of recurrence compared with those provoked by a temporary risk factor that is no longer present.<sup>43</sup> During pregnancy, post hoc subgroup analysis in a prospective study by Brill-Edwards *et al.*<sup>38</sup> of 125 pregnant women with a single prior episode of VTE reported a recurrence rate of 5.9% (95% CI 1.2–16%) in women with a previous VTE

episode that was either unprovoked or associated with thrombophilia compared with no recurrences in 44 women (95% CI 0–8.0%) with previous VTE associated with a temporary risk factor and who did not have a thrombophilic abnormality. In support of this, in a retrospective study of 155 pregnancies in 88 women with a previous VTE, De Stefano *et al.*<sup>41</sup> reported a recurrence rate during pregnancy of 4.2% (95% CI 1.1–14.2%) in women with a previously unprovoked VTE who were not given thromboprophylaxis compared with none in 36 pregnancies where the prior VTE was associated with a transient risk factor. In contrast, Pabinger *et al.*<sup>37</sup> found that presence or absence of a temporary risk factor did not influence risk of recurrence in subsequent pregnancy although, as with the Brill-Edwards study,<sup>38</sup> estrogen-provoked VTE was included as a temporary risk factor.

**Estrogen-provoked:** Although prior estrogen-provoked VTE was not seen to be a risk factor for VTE in subsequent pregnancy in the study by Brill-Edwards,<sup>38</sup> retrospective studies from Pabinger<sup>37,39</sup> and De Stefano<sup>41</sup> suggest the contrary. For example, where the previous VTE was associated with use of the estrogen-containing contraception the recurrence rate of VTE in subsequent pregnancies where thromboprophylaxis was withheld was 9.5% (95%CI 2.6–28.9%).<sup>41</sup> The risk was very similar (9.8%, 95% CI 4.2–20.9%) if the prior VTE had occurred during previous pregnancy. In the study by Pabinger *et al.*,<sup>39</sup> the recurrence rate of VTE in pregnancy, when the prior episode was provoked by the estrogen-containing contraceptive, was 10% compared with 2.7% whose first episode was not associated with pill intake. These data are supported by a recent retrospective study using Californian hospital discharge data. This study demonstrated that, although women with an initial pregnancy-related VTE had a lower risk of recurrent VTE (5.8% versus 10.4%) 6–60 months later, their risk of recurrent VTE in subsequent pregnancies (4.5%) was higher than women with previous unprovoked VTE (2.7%, relative risk 1.7, 95% CI 1–2.8)<sup>42</sup> Overall, 35.3% of recurrent VTE in the women with previous pregnancy-related VTE were in pregnancy compared with only 8.7% in the group with unprovoked VTE. Furthermore, most of the recurrences (71%) were antenatal in the former group compared with 54% in the latter. This adds further support to stratification of women with previous estrogen-related VTE as at high risk of VTE in pregnancy and the puerperium.

#### *Thrombophilia-associated VTE*

**Heritable:** Heritable thrombophilia is found in 20–50% of women with pregnancy-related VTE.<sup>44</sup> Outside pregnancy, the most common heritable thrombophilias do not substantially increase the risk of recurrence. For example, a recent systematic review of prospective studies<sup>45</sup> suggests that factor V Leiden slightly increases the risk with an OR of 1.39 (95% CI 1.15–1.67). Data regarding the effect of heritable thrombophilia on the risk of recurrent VTE in pregnancy are extremely sparse.<sup>37–39,41</sup> In the prospective study of Brill-Edwards *et al.*,<sup>38</sup> in which antenatal thromboprophylaxis was withheld, there were two recurrences in 25 women with a thrombophilic tendency compared with one in 70 women without thrombophilia but these numbers are too small to draw firm conclusions. In the retrospective studies, heritable thrombophilia was found to be at most a weak risk factor for recurrent VTE during pregnancy; for example, relative risk 1.9, 95% CI 0.5–6.6.<sup>41</sup> In practice, most women will have sustained their prior VTE either as an unprovoked episode or related to previous pregnancy or estrogen-containing contraception and, as discussed above, will thereby be candidates for antenatal and postpartum prophylaxis. Testing for thrombophilia will therefore not usually influence thromboprophylaxis in the current pregnancy unless detected in a woman with a prior VTE related to a temporary risk factor who would not otherwise receive thromboprophylaxis. How far to investigate for a thrombophilic tendency in the latter group remains controversial but might be considered where the provoking stimulus was minor (such as long-distance travel) but not where it was major (such as surgery or major trauma with prolonged immobility or cancer).

Women with antithrombin deficiency (particularly type-1 with reductions in both activity and antigen) have a very high risk of recurrence and may require higher doses of LMWH in pregnancy. They are likely to be on long-term anticoagulation with warfarin. An intermediate or treatment dose of LMWH is required throughout pregnancy and should be continued postpartum for a minimum of 6 weeks or until converted back to long-term warfarin. Such conditions should be managed in collaboration with a haematologist with expertise in thrombosis in pregnancy.

**Acquired:** see section 4.3.

#### *Temporary risk factor-associated VTE*

Outside pregnancy, the risk of recurrence of VTE resulting from a transient major risk factor is considered to be low.<sup>43</sup> As outlined above, evidence from a prospective<sup>38</sup> and a retrospective<sup>41</sup> study suggests that the risk of antenatal recurrence is very low if the prior VTE was provoked by a transient major risk factor that is no longer present. This might include, for example, a DVT in an intravenous drug user who is no longer injecting or a DVT in association with surgery or major trauma.

### **Management**

In terms of antenatal management of women with prior VTE, there are limited data. Pabinger *et al.*<sup>39</sup> reported that thromboprophylaxis appeared to prevent VTE during pregnancy – there were no recurrences in 87 pregnancies where thromboprophylaxis was administered compared with eight recurrences in 197 pregnancies without thromboprophylaxis. Administration of antenatal LMWH depending on categorisation of women with prior VTE into higher and lower risk groups, depending on the presence or absence of a temporary risk factor and/or thrombophilia, was associated with a low risk of recurrence in the prospective German study.<sup>17</sup>

These data and recent international guidelines<sup>16</sup> support a recommendation to stratify women with previous VTE into the following categories, which are described in Figure 1 and Appendix II:

- **Very high risk**  
Women with recurrent VTE associated with either antithrombin deficiency or the antiphospholipid syndrome (who will often be on long-term oral anticoagulation). These women require thromboprophylaxis with higher-dose LMWH (either high prophylactic (12-hourly) or weight-adjusted (75% of treatment dose)<sup>16,46</sup> (see Table 3) antenatally and for 6 weeks postpartum or until converted back to warfarin after delivery. These women require specialist management by experts in haemostasis and pregnancy.
- **High risk**  
Women in whom the original VTE was unprovoked, idiopathic or related to estrogen (estrogen-containing contraception or pregnancy) or who have other risk factors, a family history of VTE in a first-degree relative (suggestive of thrombophilia) or a documented thrombophilia. These women require thromboprophylaxis with LMWH antenatally and for 6 weeks postpartum.
- **Intermediate risk**  
Women in whom the original VTE was provoked by a transient major risk factor that is no longer present and who have no other risk factors. In these women, thromboprophylaxis with LMWH can be withheld antenatally, provided that no additional risk factors are present (in which case they should be offered LMWH). They require close surveillance for the development of other risk factors. They should be offered thromboprophylaxis with LMWH for 6 weeks postpartum.

Any woman with objective documentation of previous VTE should have a careful history documented and, if appropriate, should undergo testing for both heritable and acquired thrombophilia, preferably before pregnancy. Where objective documentation is not available, the previous diagnosis of VTE can be assumed in cases where the woman gives a good history and received prolonged (more than 6 weeks) therapeutic anticoagulation.

#### *Testing for thrombophilia in women with prior VTE*

*Which women with prior VTE require thrombophilia testing?*

**Women with a previous non-estrogen-related VTE provoked by a minor risk factor should undergo testing for thrombophilia, as this will influence management and decisions regarding thromboprophylaxis antenatally.**



The relevant heritable and acquired thrombophilias are listed in Appendix 1. It is important to be aware of the effects of pregnancy on the results of thrombophilia tests. These effects are described in another RCOG guideline.<sup>2</sup> In particular, protein S levels are reduced by pregnancy and protein S deficiency cannot be

diagnosed in pregnancy. It is also important that thrombophilia testing is not requested inappropriately and is only used if the finding of a thrombophilia would alter the proposed management. Before testing, women should be counselled about the implications of a positive result for themselves and their family members. The results should be interpreted by clinicians with specific expertise in the area.<sup>2</sup> Women with a prior unprovoked or estrogen-provoked VTE should be considered for thromboprophylaxis and hence testing for heritable thrombophilia is not required.

There are two reasons for testing women with previous VTE for thrombophilia before or in early pregnancy:

- if detected in a woman with a prior VTE related to a minor temporary risk factor, such as long distance travel, it may influence the decision whether to offer antenatal thromboprophylaxis
- if antiphospholipid syndrome or antithrombin deficiency are detected, this will influence the dose of thromboprophylaxis offered in pregnancy.

## RECOMMENDATIONS FOR WOMEN WITH A PREVIOUS VTE

**Women at high risk of VTE in pregnancy, such as those with previous VTE, should be offered prepregnancy counselling and a prospective management plan for thromboprophylaxis in pregnancy. Those who become pregnant before receiving such counselling should be referred to a consultant obstetrician or trust-nominated expert in thrombosis in pregnancy early in pregnancy.**



**Women with a previous single provoked (excluding estrogen-related) VTE (and no other risk factors) require close surveillance antenatally and thromboprophylaxis with LMWH for 6 weeks postpartum.**



**Women with previous recurrent VTE or a previous unprovoked or estrogen/pregnancy-related VTE or a previous VTE and a history of VTE in a first-degree relative (or a documented thrombophilia) or other risk factors should be offered thromboprophylaxis with LMWH antenatally and for 6 weeks postpartum.**



### 4.2 Asymptomatic heritable thrombophilia

*How should women with asymptomatic thrombophilia be treated?*

**Women with asymptomatic inherited thrombophilia without other risk factors may be managed with close surveillance antenatally but should be considered for LMWH for at least 7 days postpartum. Exceptions are in women with antithrombin deficiency or more than one thrombophilic defect (including homozygous factor V Leiden, homozygous prothrombin G20210A and compound heterozygotes) or those with additional risk factors where advice of a local expert should be sought and antenatal prophylaxis considered.**



Increasingly, women who are asymptomatic present in pregnancy with a known thrombophilia, typically detected because of screening following identification of heritable thrombophilia in a family member. Indeed family history alone may be a predictor of risk of VTE.<sup>56</sup> Management of such situations is not straightforward because there are limited reliable data on the absolute risk of VTE in women who are asymptomatic without prior VTE and on the benefits of thromboprophylaxis in this setting. It is desirable to discuss the options as fully as possible with the woman, ideally in conjunction with a clinician with expertise in this area. It is also important that laboratory thrombophilia results are not viewed in isolation but considered in combination with the family history and other clinical risk factors, such as increasing age, obesity or immobility, in coming to a judgement on the risk of VTE in the individual and therefore the benefit of thromboprophylaxis. The risk of VTE associated with thrombophilic defects varies considerably,<sup>27,44,47,57</sup> both between defects and between studies (Tables 2a and 2b), probably reflecting differences in study methodology and uncertainties owing to small numbers of affected individuals.

### Factor V Leiden and prothrombin G20210A

The most common heritable thrombophilic tendencies in the UK are factor V Leiden and prothrombin G20210A (present in about 3–5% and 1% of the population, respectively). Case-control studies show that

**Table 2a:** Adjusted odds ratios (OR) for risk of VTE in pregnancy and/or postpartum with different thrombophilias (data from Lim<sup>44</sup> and Robertson<sup>47</sup>)

Thrombophilia	Risk of VTE		
	OR		95% CI
	Lim <sup>44</sup>	Robertson <sup>47</sup>	
Antithrombin deficiency	10–unknown	4.7	(1.3–17.0)
Protein C deficiency	2–unknown	4.8	(2.2–10.6)
Protein S deficiency	–	3.2	(1.5–6.9)
Factor V Leiden (heterozygous)	5–7	8.3	(5.4–12.7)
Prothrombin G20210A (heterozygous)	3–10	6.8	(2.5–18.8)
Factor V Leiden (homozygous)	10–41	34.4	(9.9–120.1)
Prothrombin G20210A (homozygous)		26.4	(1.2–559.2)
Compound heterozygote (factor V Leiden and prothrombin G20210A)	9–107	–	–

Evidence level 2++

individuals heterozygous for these genes are at roughly five-fold increased risk of VTE in both the general population<sup>58</sup> and in pregnancy.<sup>10,59</sup> With a background incidence of VTE in pregnancy of one in 1000 this would translate into an absolute risk of less than 1%. Cohort studies undertaken in the general population are consistent with this: in two such studies<sup>60,61</sup> referred to in a recent meta-analysis<sup>62</sup> and a further study by Heit,<sup>11</sup> three episodes of VTE occurred in women heterozygous for factor V Leiden in 752 pregnancies and the benefit of thromboprophylaxis at this level of risk would be limited.

The absolute risk may be higher in women with a family history of VTE and a thrombophilic genotype. In the meta-analysis of cohort studies of factor V Leiden and pregnancy-related thrombosis referred to above,<sup>62</sup> 19 of 903 carriers (2%) had a pregnancy-related VTE. In the cohort studies where the cases were selected because of family screening (two or more first-degree relatives with VTE but excluding the proband from analysis), 16/499 of V Leiden carriers (3%) had a pregnancy-related VTE compared with 2/330 family members who were not carriers. This absolute risk is similar in magnitude to that seen in retrospective analyses in women

**Table 2b:** Estimated absolute risk of pregnancy-associated VTE with different thrombophilic defects in women with one or more symptomatic first-degree relatives

Thrombophilic defect	Pregnancy		Antenatal		Postpartum	
	%/pregnancy	95% CI	%/pregnancy	95% CI	%/pregnancy	95% CI
Antithrombin, protein C or protein S deficiency <sup>48</sup>	4.1	1.7–8.3	1.2	0.3–4.2	3.0	1.3–6.7
Antithrombin deficiency type 1 (range) <sup>49–53*</sup>	15–50 (range)	–	0–40	–	11–28	–
V Leiden heterozygous <sup>48</sup>	2.1	0.7–4.9	0.4	0.1–2.4	1.7	0.7–4.3
Prothrombin G20210A heterozygous <sup>48</sup>	2.3	0.8–5.3	0.5	0.1–2.6	1.9	0.7–4.7
V Leiden homozygous or compound heterozygosity V Leiden and prothrombin G20210A (range) <sup>54,55</sup>	1.8–15.8 (range)	–	0–5	–	1–10	–

\* From population-based not family study

with pregnancy-related thrombosis and with the prothrombin gene variant, selected because of a family history of VTE<sup>63,64</sup> and to those observed in a recent retrospective family study in carriers of factor V Leiden and the prothrombin variant.<sup>54</sup> In a recent review,<sup>48</sup> the incidence of a first episode of VTE occurring in association with pregnancy in heterozygous V Leiden carriers with at least one symptomatic first-degree relative was estimated at 2.1% (95% CI 0.7–4.9%). However, the risk during pregnancy was only 0.4% (0.1–2.4%) compared with 1.7% (95% CI 0.7–4.3%) in the postpartum period. Very similar incidences were estimated for the prothrombin variant: 0.5% (95% CI 0.1–2.6%) during pregnancy and 1.9% (95% CI 0.7–4.7%) during the postpartum period.<sup>48</sup>

The risk of pregnancy-related VTE in women who were previously asymptomatic is thought to be higher in compound heterozygotes for factor V Leiden and the prothrombin variant,<sup>26</sup> with an absolute risk of about 4%,<sup>55</sup> although a 2008 retrospective family cohort study has called this relative difference into question.<sup>54</sup> A systematic review in 2005 suggested that women who are homozygous for factor V Leiden or the prothrombin variant are also at much higher risk of pregnancy-related VTE<sup>47</sup> and absolute risks of pregnancy-related VTE of 9–16% have been reported for homozygous V Leiden.<sup>15</sup>

### **Antithrombin, protein C and protein S deficiency**

Outside pregnancy, the risk of first VTE appears to be higher in individuals with deficiencies of antithrombin, protein C or protein S compared with factor V Leiden and the prothrombin variant.<sup>65</sup> Women with protein C or protein S deficiencies who are asymptomatic probably have a moderately increased risk of VTE associated with pregnancy with most events occurring postpartum.<sup>52</sup> The risk associated with antithrombin deficiency appears to vary according to the subtype but may be associated with a very high risk (15–50%)<sup>52,66</sup> and higher than for other thrombophilias.<sup>52</sup> Thus, in a retrospective study of 72 000 pregnancies in which women with VTE were investigated for a thrombophilic tendency and the background prevalence of these defects was known, the risk of VTE in pregnancy was estimated to be 1/2.8 in type-1 antithrombin deficiency (with reduced activity and antigen), 1/42 for type-2 antithrombin deficiency (with reduced activity and normal antigen level), 1/113 for protein C deficiency and 1/437 for factor V Leiden.<sup>53</sup> In a more recent retrospective cohort study of women from families with hereditary antithrombin, protein C or protein S deficiency, 12 pregnancy-related VTE episodes had been objectively diagnosed in 162 pregnancies (7%), two-thirds of these in the postpartum period.<sup>67</sup> A similar incidence was reported in a prospective cohort study in families with antithrombin, protein C or protein S deficiency or factor V Leiden.<sup>68</sup> Two episodes occurred in 28 pregnancies (7%) in women who did not receive thromboprophylaxis, whereas there were no episodes in 43 women who did receive thromboprophylaxis. In a 2008 review,<sup>48</sup> in women with a deficiency of antithrombin, protein C or protein S and at least one symptomatic first-degree relative, the incidence of a first episode of VTE occurring in association with pregnancy was estimated at 4.1% (95% CI 1.7–8.3%). Again, the incidence appeared to be higher during the postpartum period (3.0%, 95% CI 1.3–6.7%) than during pregnancy (1.2%, 95% CI 0.3–4.2%).

### **Methylene tetrahydrofolate reductase**

Homozygosity for a thermolabile variant of the gene for methylene tetrahydrofolate reductase (MTHFR) is sometimes included in thrombophilia testing but there is no evidence of an association with a clinically relevant increase in the risk of VTE in pregnancy.<sup>47</sup>

### *Management*

The above evidence suggests that patients should be stratified according to both the level of risk associated with their thrombophilia and the presence or absence of a family history or other risk factors.<sup>69</sup> In the family history, details considered should include the number of affected relatives, the age at which thrombosis developed and the presence or absence of additional risk factors in the affected relatives.<sup>46</sup> Since the risk of VTE is lower in women who are asymptomatic, antenatal thromboprophylaxis is not usually necessary, except in those with antithrombin deficiency or with combined or homozygous defects.<sup>28,46,70</sup> However, since asymptomatic thrombophilia is a risk factor, if combined with other risk factors such as increasing age, obesity

or immobility, there may be a justification for the use of antenatal thromboprophylaxis in individual circumstances. Similarly, for women with thrombophilia who are asymptomatic without either a personal or a family history of a VTE (who may have been inappropriately screened following recurrent miscarriage or in association with assisted reproductive therapy); 6 weeks of postpartum thromboprophylaxis may be unnecessary. Decisions about whether to recommend thromboprophylaxis should be based, as for other women, on a global risk assessment. For example, if the woman has other risk factors, such as obesity or caesarean section, thromboprophylaxis with LMWH may be appropriate.

The validity of this approach was reported in the 2007 prospective study by Bauersachs *et al.*<sup>17</sup> Women categorised into a low-risk group, which included those with heritable thrombophilia (excluding antithrombin deficiency) without prior VTE, were managed antenatally by clinical surveillance alone (unless there were additional risk factors). Of the 225 women in this low-risk group, 70% had either a heritable laboratory-detected thrombophilia or a positive family history in a first-degree relative and none developed a pregnancy-related episode of VTE. However, in practice, 85% of the women in this group received antenatal thromboprophylaxis because of additional risk factors and median treatment initiation was at 24 weeks (range 4–41 weeks). The duration of postpartum thromboprophylaxis the women received was intended to be 2 weeks but evidence from other studies<sup>71</sup> suggests that the risk of VTE remains elevated for up to 6 weeks postpartum.<sup>11</sup> If thromboprophylaxis is given antenatally for a persisting risk factor it should therefore be continued postpartum for 6 weeks.

## RECOMMENDATIONS ON THROMBOPHILIA

**Women should be stratified according to level of risk associated with their thrombophilia and the presence or absence of a family history or other risk factors.**

C

**If thromboprophylaxis is given antenatally for a persisting risk factor, it should be continued postpartum for 6 weeks.**

C

### *Antithrombin deficiency*

In women with antithrombin deficiency who are asymptomatic, an intermediate dose of heparin may be required.<sup>46</sup> Heparins may not be as effective in antithrombin deficiency, as their mode of action is antithrombin-dependent and it is reasonable to monitor anti-Xa levels in this setting aiming for a level 4 hours following injection of 0.35–0.5 u/ml.<sup>46</sup> Different subtypes of antithrombin deficiency are associated with different levels of VTE risk and therefore advice should be sought from a local expert in this area. Treatment should start in early pregnancy and continue for 6 weeks postpartum.

### *4.3 Acquired thrombophilia (Antiphospholipid syndrome)*

*How should women with antiphospholipid syndrome be treated?*

**Women with previous thromboses and antiphospholipid syndrome should be offered both antenatal and 6 weeks of postpartum thromboprophylaxis. Women with persistent antiphospholipid antibodies with no previous VTE and no other risk factors or fetal indications for LMWH may be managed with close surveillance antenatally but should be considered for LMWH for 7 days postpartum.**

C

Antiphospholipid syndrome is defined as the presence of a lupus anticoagulant and/or anticardiolipin and/or  $\beta_2$ -glycoprotein 1 antibodies of medium to high titre on two occasions 12 weeks apart (persistently positive), in association with a history of thrombosis (which may be arterial or venous) or adverse pregnancy outcome (defined as three or more unexplained miscarriages before 10 weeks of gestation, a fetal death after 10 weeks of gestation or a premature birth [before 35 weeks] due to severe pre-eclamptic toxemia or intrauterine growth restriction).<sup>72</sup> Management in this guideline is limited to the prevention of VTE and not to that of other adverse pregnancy outcomes. Pregnant women with antiphospholipid syndrome should have their condition managed in collaboration with a haematologist and/or rheumatologist with expertise in this area.

Antiphospholipid antibodies, and lupus anticoagulants in particular, are associated with an increased risk of recurrent thrombosis.<sup>73</sup> It is common for such women to be on long-term warfarin after a first thrombotic event. Recent randomised trials in the non-pregnancy setting suggest that standard intensity warfarin (target international normalised ratio, INR, 2.0–3.0) is at least as safe and efficacious as higher intensity therapy in the prevention of recurrent thrombosis, at least for those with previous VTE and without a recurrence while on warfarin.<sup>74,75</sup> This is in contrast to previous retrospective data and suggests that many cases of VTE due to antiphospholipid syndrome could be managed in a standard manner rather than with high intensity therapy. Optimal management for the prevention of recurrent thrombosis in pregnancy is problematic because of the lack of randomised trials and the paucity of prospective studies in women with antiphospholipid syndrome and prior thrombosis. In the Bauersachs *et al.* study,<sup>17</sup> 98 of 565 tested women had positive antiphospholipid antibodies and were classified as low risk if asymptomatic ( $n = 12$ ), high risk in women with a history of three or more pregnancy losses ( $n = 58$ ) and very high risk if prior venous or arterial thrombosis ( $n = 28$ ). Women with antiphospholipid antibodies in the high and very high risk groups received a prophylactic and intermediate/treatment dose LMWH antenatally and for 6 weeks postpartum or until switched back to oral anticoagulants. They also received 100 mg aspirin daily from week 12 to week 36 of pregnancy. Women at low risk received LMWH for only 2 weeks postpartum unless there were additional risk factors. No episodes of VTE occurred in women in the low and high risk groups but two episodes occurred postpartum in the 28 women in the very high risk group, despite higher intensity LMWH, suggesting a significant thrombotic risk in this setting. In a series from the St Thomas' group of 33 women with primary antiphospholipid syndrome, there were no thromboses in women with the syndrome but without previous VTE given 3–5 days of thromboprophylaxis postpartum.<sup>76</sup>

On the basis of the above evidence and the perceived high risk of recurrent thrombosis, it is recommended that pregnant women with antiphospholipid syndrome and previous VTE should receive antenatal thromboprophylaxis with LMWH.<sup>16,77</sup> Women on warfarin should convert to LMWH before the sixth week of pregnancy. Those not on warfarin should commence LMWH in the first trimester as soon as possible after diagnosis of the pregnancy. For women with a single previous VTE event, a high prophylactic (12-hourly) dose of LMWH is often used.<sup>76</sup> For women with a history of recurrent VTE, particularly where this has entailed an increase in the usual target INR from 2.0–3.0 to 3.0–4.0, an intermediate (75% of treatment dose) or full treatment dose should be used. Low-dose aspirin is recommended for all women with antiphospholipid syndrome.<sup>77</sup> However, the presence of antiphospholipid antibodies alone, even if persistent, with no previous antiphospholipid syndrome-classifiable pregnancy loss or thrombosis, does not equate to antiphospholipid syndrome<sup>78</sup> and such women do not require antenatal LMWH.

After delivery, women with antiphospholipid syndrome and prior VTE should continue the appropriate dose (high prophylactic or intermediate/treatment) of LMWH until re-established on long-term oral anticoagulation or for a minimum of 6 weeks if not on long-term therapy. The risk of postpartum VTE in women with antiphospholipid syndrome characterised by recurrent miscarriage or fetal loss without prior thrombosis is unclear but data from randomised trials in this area suggest that the risk is likely to be low. Antenatal antithrombotic therapy administered to improve pregnancy outcome in these trials was typically stopped between 35 weeks and delivery and no maternal VTE events were reported.<sup>79–81</sup> The risks of VTE in women with a persistent lupus anticoagulant or high-titre antiphospholipid antibodies without prior thrombosis or recurrent miscarriage or fetal loss (that is, without antiphospholipid syndrome) are small but it is reasonable, in the absence of additional risk factors, to administer LMWH at prophylactic dose for 7 days. For those with antiphospholipid syndrome without VTE (that is, those with obstetric antiphospholipid syndrome) many clinicians advocate postpartum thromboprophylaxis for 6 weeks in a similar way to those with asymptomatic inherited thrombophilia.<sup>16</sup>

## 5. Timing of initiation of thromboprophylaxis

*When should thromboprophylaxis be started?*

**Antenatal thromboprophylaxis should begin as early in pregnancy as practical.**

**B**

Meta-analysis has shown that most VTE occurs antenatally, with an equal distribution throughout gestation.<sup>82</sup> However, the Confidential Enquiries into Maternal Deaths in the United Kingdom have shown that two-thirds of antenatal fatal pulmonary VTE in 2003–2005 occurred in the first trimester.<sup>5</sup> A study by Gherman *et al.* showed almost 50% of antenatal VTE occurred before 15 weeks of gestation.<sup>7</sup> A study from the USA found that 44% of DVTs in pregnancy occurred in the first trimester.<sup>8</sup> A more recent Spanish study similarly found that 40% of antenatal VTE occurred in the first trimester.<sup>9</sup> These data emphasise the need for risk assessment before pregnancy and institution of prophylaxis, if appropriate, in early pregnancy.

Certain additional risk factors may complicate the first trimester (Table 1 and Appendix 1), such as hyperemesis, surgery for miscarriage, termination of pregnancy, ectopic pregnancy or ovarian hyperstimulation following in vitro fertilisation.<sup>13,83</sup> A 2008 case-control study from Norway<sup>13</sup> found that the adjusted odds ratio for VTE with pregnancy following assisted reproductive techniques was 4.3 (95% CI 2.0–9.4). Women with ovarian hyperstimulation syndrome are particularly prone to VTE in the upper body<sup>83,84</sup> and require thromboprophylaxis for at least the period of inpatient stay. A review of the risks of VTE during assisted reproductive techniques including a management guideline for women undergoing controlled ovarian stimulation has recently been published.<sup>84</sup> A retrospective study found the odds ratio for VTE with hyperemesis gravidarum was 2.5 (95% CI, 2-3.2).<sup>23</sup>

In view of this evidence, if a decision is made to initiate thromboprophylaxis antenatally, this should begin as early in pregnancy as practical.<sup>7-9</sup>

## 6. Thromboprophylaxis during labour and delivery, including the use of regional anaesthesia and analgesia

*When should thromboprophylaxis be interrupted for delivery?*

**Women receiving antenatal LMWH should be advised that if they have any vaginal bleeding or once labour begins, they should not inject any further LMWH. They should be reassessed on admission to hospital and further doses should be prescribed by medical staff.**



The pregnancy-associated prothrombotic changes in the coagulation system are maximal immediately following delivery. It is therefore desirable to continue LMWH during labour or delivery in women receiving antenatal thromboprophylaxis with LMWH. However, to allow for the use of regional analgesia or anaesthesia if requested or required, women are advised to discontinue LMWH at the onset of labour or prior to planned delivery.

For women receiving high prophylactic or therapeutic doses of LMWH, the dose of heparin should be reduced to its thromboprophylactic dose on the day before induction of labour and, if appropriate, continued in this dose during labour.

Regional anaesthesia or analgesia can be sited only after discussion with a senior anaesthetist, in keeping with local obstetric anaesthetic protocols.<sup>2</sup> It is important to discuss the implications of treatment with LMWH for regional anaesthesia and analgesia with the women before labour or caesarean section. This could be appropriately undertaken in an antenatal anaesthetic clinic.

In summary, to minimise or avoid the risk of epidural haematoma:

- Regional techniques should not be used until at least 12 hours after the previous prophylactic dose of LMWH.
- 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.<sup>85</sup>
- LMWH should not be given for 4 hours after use of spinal anaesthesia or after the epidural catheter has been removed; the cannula should not be removed within 10–12 hours of the most recent injection.<sup>85</sup>

For delivery by elective caesarean section in women receiving antenatal LMWH, the woman should receive a

thromboprophylactic dose of LMWH on the day before delivery. On the day of delivery, any morning dose should be omitted and the operation should be performed that morning. The thromboprophylactic dose of LMWH should be given 4 hours post-operatively or 4 hours after removal of the epidural catheter. If antenatal LMWH is routinely prescribed at 6pm, this allows for an elective caesarean section the next morning, removal of the epidural catheter before 2pm and a first postnatal dose of LMWH at 6pm the same day.

In some women (particularly those on high-dose prophylactic or treatment doses of LMWH) there may be an indication for induction of labour to help plan thromboprophylaxis around delivery. So, for example, if the woman takes the morning dose but omits the evening dose on the day before induction of labour (in a multiparous woman), she could have an early elective epidural sited the next day (when it will be 24 hours since her last dose of LMWH).

If LMWH precludes regional techniques (in, for example, the woman who presents in spontaneous labour within 12 hours of taking a LMWH dose) alternative analgesia such as opiate-based intravenous patient-controlled analgesia can be offered.

There is an increased risk of wound haematoma following caesarean section with both unfractionated heparin and LMWH of around 2%.<sup>86</sup>

Women at high risk of haemorrhage with risk factors including major antepartum haemorrhage, coagulopathy, progressive wound haematoma, suspected intra-abdominal bleeding and postpartum haemorrhage may be more conveniently managed with unfractionated heparin or graduated compression stockings (see sections 8.2 and 9). If a woman develops a haemorrhagic problem while on LMWH, the treatment should be stopped and expert haematological advice sought.<sup>1</sup> It should be remembered that excess blood loss and blood transfusion is a risk factor for VTE,<sup>13,23,26</sup> so thromboprophylaxis should be begun or reinstated as soon as the immediate risk of haemorrhage is reduced.

## 7. Thromboprophylaxis after delivery

*For how long should thromboprophylaxis be continued after delivery?*

**Thromboprophylaxis should be continued for 6 weeks in women at high risk of postpartum VTE and for 1 week in women with intermediate risk.**



The prothrombotic changes of pregnancy do not revert completely to normal until several weeks after delivery. Indeed the time of greatest risk for VTE associated with pregnancy is the early puerperium and, although most VTE occurs antenatally, the risk/day is greatest in the weeks immediately after delivery.<sup>39,41,82</sup>

For women at high risk of postpartum VTE, the recommended duration of thromboprophylaxis is 6 weeks. Although laboratory evidence from thromboelastography suggests correction of hypercoagulability by 4 weeks,<sup>87</sup> clinical data from observational studies in Sweden,<sup>88</sup> the USA,<sup>11</sup> Norway<sup>89</sup> and the Netherlands<sup>10</sup> suggest that the increased risk of VTE persists for 6 weeks postpartum, albeit with fewer cases reported during weeks 5 and 6. The Norwegian case-controlled study showed that 96% (303/314) of the postpartum VTEs occurred in the first 6 weeks after delivery, of which 18 (5.7%) were in postnatal week 5 and nine (3%) in postnatal week 6.<sup>89</sup> Additionally, the triennial UK Confidential Enquiries into Maternal Deaths over the past 12 years also suggest that the increased risk of fatal pulmonary embolism is still present in weeks 5 and 6 (a total of 15 deaths compared with 21 in weeks 3 and 4), whereas fatal events after that are very uncommon.<sup>5,90-92</sup> Other guidelines also recommend 6 weeks of postpartum thromboprophylaxis.<sup>2,16</sup>

In women at intermediate risk of VTE, there has been much debate as to the optimal duration of thromboprophylaxis. There is little evidence to support recommendations regarding duration of thromboprophylaxis in such women and research in this area is needed. Thromboelastography data from 71 women following normal delivery showed that all parameters remained abnormal at 1 week postpartum and the authors suggested that 3–5 days of thromboprophylaxis may be insufficient.<sup>87</sup> Clinical data suggest that

the highest risk lies in the first week postpartum. In an American population-based study,<sup>11</sup> 34 of the 64 (53%) VTE occurred in the first week postpartum. Thus, a minimum of 7 days of thromboprophylaxis is recommended. This is in recognition of the increased risk of VTE during the first postpartum week but also the likelihood that by this stage the majority of women will be ambulant. This is not, however, synonymous with discharge from hospital and it is important that risk assessment is performed in each woman at least once following delivery and before discharge and arrangements made for LMWH prescription and administration (usually by the woman herself) in the community where necessary. In addition, women with continuing additional risk factors should be considered potentially at high risk and it may be necessary to extend the 7-day period of prophylaxis for up to 6 weeks.

The first thromboprophylactic dose of LMWH should be given as soon as possible after delivery provided that there is no postpartum haemorrhage or there has been regional analgesia, in which case LMWH should be given by 4 hours after delivery or 4 hours after removal of the epidural catheter, if it is removed immediately or shortly after delivery. If the epidural catheter is left in place after delivery for the purpose of postpartum analgesia, it should be removed 12 hours after a dose and 4 hours before the next dose of LMWH.

### 7.1 Assessment of risk

#### *What are the risk factors for VTE after delivery?*

The risks of VTE following delivery are summarised in Figure 1, Table 1, Appendix 1 and Appendix V.

Nearly all women (seven of eight) dying from VTE following vaginal delivery in the last Confidential Enquiries into Maternal Deaths in the UK were overweight or obese or over the age of 40 years. Three had class-3 obesity (BMI greater than 40kg/m<sup>2</sup>).<sup>5</sup>

Women with two or more persisting risk factors listed in Table 1 should receive LMWH in prophylactic doses appropriate for their weight for 7 days after delivery.

It is important to make an individual risk assessment, since occasionally one risk factor may be extreme without the presence of other risk factors. For example, young women with class 3 obesity (BMI greater than 40 kg/m<sup>2</sup>, World Health Organization international obesity standards)<sup>93,94</sup> should be offered thromboprophylaxis with LMWH postpartum even after a normal delivery and in the absence of other risk factors.

**All women with class-3 obesity (BMI greater than 40 kg/m<sup>2</sup>) should be considered for prophylactic LMWH for 7 days after delivery.**



Additional risk factors relevant for postpartum thromboprophylaxis after delivery include prolonged labour, immobility, infection, haemorrhage and blood transfusion (see Figure 1, Table 1 Appendix I and Appendix V).

Just as circumstances and risk factors can change antenatally, such changes can also occur in the puerperium. For this reason, women undergoing surgery for any reason during the puerperium, those who develop severe infection, those who are readmitted or who choose to travel long distance are at increased risk of VTE, even though they may have been discharged from hospital following normal vaginal delivery several weeks before.

**In women who have additional persistent (lasting more than 7 days postpartum) risk factors, such as prolonged admission or wound infection, thromboprophylaxis should be extended for up to 6 weeks or until the additional risk factors are no longer present.**



### 7.2 Previous VTE

#### *Which women with previous VTE need postpartum thromboprophylaxis?*

**All women with a previous history of confirmed VTE should be offered thromboprophylaxis with LMWH or warfarin for 6 weeks postpartum, regardless of the mode of delivery.**



### 7.3 Thrombophilia

*Which women with thrombophilia without previous VTE need postpartum thromboprophylaxis?*

**All women with known heritable or acquired thrombophilia should be considered for LMWH for at least 7 days following delivery, even if they were not receiving antenatal thromboprophylaxis. This could be extended to 6 weeks if there is a family history or other risk factors present.**



### 7.4 Caesarean section

*What is the magnitude of risk of VTE after caesarean section?*

**All women who have had an emergency caesarean section (category 1–3) should be considered for thromboprophylaxis with LMWH for 7 days after delivery.**



**All women who have had an elective caesarean section (category 4) who have one or more additional risk factors (such as age over 35 years, BMI greater than 30) should be considered for thromboprophylaxis with LMWH for 7 days after delivery.**



Women delivered by elective caesarean section have at least double the postpartum risk of VTE compared with vaginal birth. Women delivered by emergency caesarean section have double the risk of postpartum VTE compared with elective caesarean section. Women delivered by emergency caesarean section have a roughly four-fold increased risk of postpartum VTE compared with women delivered vaginally.

In a retrospective population-based cohort study from Canada healthy women who underwent a primary caesarean delivery for breech presentation were compared with an otherwise similar group of women who had planned to deliver vaginally. The planned caesarean group (46 766 women) had an increased postpartum risk of VTE (OR 2.2, 95% CI 1.5–3.2)<sup>12</sup> compared with the 2 292 420 women in the planned vaginal delivery group. The relative risk for caesarean section is higher if all caesarean sections rather than just elective are included. A Swedish study found a relative risk of VTE of 6.7 (95% CI 4.5–10.0) for caesarean versus vaginal delivery<sup>95</sup> and a Scottish study found that emergency caesarean was associated with double the risk of VTE compared to elective caesarean.<sup>96</sup> A 2004 cohort study from Norway<sup>97</sup> found that all women who suffered a VTE after caesarean section also had other risk factors, including twin pregnancy, obesity, severe pre-eclampsia, reoperation, immobilisation and placenta praevia. A 2008 case-control study from the same group<sup>13</sup> revealed an adjusted odds ratio (AOR) of 2.7 (95% CI 1.8–4.1) for postnatal VTE after emergency caesarean section. The AOR was 6.2 (2.4–16.2) for any caesarean section plus infection. The risks associated with caesarean section in this study may well be underestimated because most women received thromboprophylaxis for 3–7 days after caesarean section thereby probably reducing thrombotic events. The numbers of VTE after elective and emergency caesarean sections were also similar in weeks 1, 2 and 3 and thus it is important to extend the duration of prophylaxis in the presence of additional persistent (lasting more than 7 days postpartum) risk factors, such as prolonged admission or wound infection, for up to 6 weeks or until the additional risk factors are no longer present (see Figure 1).

Further, in the last three Confidential Enquiries into Maternal Deaths in the UK (1997–2005)<sup>5,91,92</sup> published since the 1995 RCOG guidelines recommending thromboprophylaxis after emergency caesarean section, there have been 21 deaths following caesarean section compared with 25 following vaginal delivery, yet the latter make up approximately 70–80% of all deliveries. This suggests that despite the previous recommendations, caesarean section continues to be a significant risk factor for fatal pulmonary embolism and argues in favour of extending routine thromboprophylaxis following emergency caesarean section to 7 days and extending this further in women with continuing risk factors.

Given the above data, it would seem reasonable to recommend that all women undergoing an emergency (category 1, 2 or 3) caesarean section receive postpartum prophylactic LMWH and that women having elective (category 4) caesarean sections receive postpartum prophylactic LMWH if they have additional risk factors (see Figure 1 and Table 1).

## 8. Which agents should be used for thromboprophylaxis?

### 8.1 Low-molecular-weight heparin

**LMWHs are the agents of choice for antenatal thromboprophylaxis. They are at least as effective as and safer than unfractionated heparin.**

**B**

LMWHs are at least as effective as unfractionated heparin for the prevention of VTE in non-pregnant patients undergoing surgery and in other high risk non-pregnant patients.<sup>98,99</sup> Systematic reviews and NICE have concluded that LMWH is a safe alternative to unfractionated heparin as an anticoagulant during pregnancy,<sup>1,86,100,101</sup> and, from a safety perspective, LMWH is preferred.<sup>86</sup>

Evidence level 1++ supported by level 2

LMWHs are as effective as and safer than unfractionated heparin when used to prevent VTE in pregnancy.<sup>86,100-102</sup> The risk of heparin-induced thrombocytopenia is substantially lower with LMWH.<sup>86,100,103</sup> Indeed, current guidelines recommend against monitoring platelet count where LMWH is used and where there is no previous exposure to unfractionated heparin.<sup>104</sup> It is only necessary to check the platelet count if the woman has had prior exposure to unfractionated heparin.<sup>2</sup> In a systematic review of 2777 pregnancies, there were no cases of heparin-induced thrombocytopenia.<sup>86</sup> Prolonged unfractionated heparin use during pregnancy may result in osteoporosis and fractures<sup>105</sup> but this risk is very low with LMWH.<sup>86,106-109</sup> In the systematic review of LMWH use in pregnancy by Greer and Nelson-Piercy,<sup>86</sup> the incidence of osteoporotic fractures was 0.04% (95% CI 0.01-0.2), and of allergic skin reactions was 1.8% (95% CI 1.34-2.37). Significant bleeding, usually related primarily to obstetric causes, occurred in 1.98% (95% CI 1.5-2.57).<sup>86</sup> This related to both treatment and prophylactic doses of LMWH and therefore the risk of bleeding is likely to be less than 2% with prophylactic doses.

Table 3 gives appropriate suggested prophylactic and therapeutic subcutaneous doses of LMWH in pregnancy and postpartum. Doses of LMWH are based on weight, not BMI. For thromboprophylaxis, the booking weight is used to guide dosing. It is also important to avoid 'dose capping' but there are no data to guide appropriate doses of LMWH for pregnant women who are obese or puerperal. The doses in Table 3 are only suggestions and doses for women who are obese are not evidence-based. It is noted that, in the UKOSS antenatal pulmonary embolism study,<sup>6</sup> some women who were overweight and obese suffered a pulmonary embolism while receiving doses of LMWH prophylaxis appropriate for women weighing 50-90 kg. It is agreed that women of higher weights should receive higher doses but the appropriate dose and weight ranges are not agreed. Some units may prefer to prescribe the usual prophylactic dose twice daily for women over 90 kg.

AntiXa levels provide only a rough guide of the concentration of heparin present and levels provide little or no evidence on the efficacy in relation to prevention of thrombosis. Experience indicates that monitoring of anti-Xa levels is not required when LMWH is used for thromboprophylaxis,<sup>110</sup> provided that the woman has normal

**Table 3:** Suggested thromboprophylactic doses for antenatal and postnatal LMWH

Weight (kg)	Enoxaparin	Dalteparin	Tinzaparin (75u/kg/day)
< 50	20 mg daily	2500 units daily	3500 units daily
50-90	40 mg daily	5000 units daily	4500 units daily
91-130	60 mg daily*	7500 units daily*	7000 units daily*
131-170	80 mg daily*	10 000 units daily*	9000 units daily*
> 170	0.6 mg/kg/day*	75 units/kg/day*	75 u/kg/day*
High prophylactic (intermediate) dose for women weighing 50-90 kg	40 mg 12-hourly	5000 units 12-hourly	4500 units 12-hourly
Treatment dose	1 mg/kg/12 hourly antenatal; 1.5 mg/kg/daily postnatal	100 units/kg/12 hourly or 200 units/kg/daily postnatal	175 u/kg/daily (antenatal and postnatal)

\* may be given in two divided doses

renal function. Lower doses of enoxaparin and dalteparin should be employed if the creatinine clearance is less than 30 ml/minute. This would equate to a serum creatinine of about 200 µmol/l for a 30-year-old woman weighing 70 kg.<sup>110</sup> For tinzaparin, dose reductions are required if the creatinine clearance is < 20 ml/minute.

Where antenatal thromboprophylaxis with LMWH is given to women who are usually on long-term oral anticoagulants, most commonly because of previous recurrent VTE or a thrombophilia, higher prophylactic doses or therapeutic doses of LMWH may be appropriate:

- high prophylactic/intermediate dose subcutaneous LMWH (e.g. 40 mg enoxaparin 12-hourly or 5000 iu dalteparin 12-hourly, or tinzaparin 4500 iu 12-hourly)
- therapeutic dose subcutaneous LMWH<sup>2</sup> (e.g. 1 mg/kg enoxaparin 12-hourly or 100 iu/kg dalteparin 12-hourly or tinzaparin 175 iu/kg daily)
- in antithrombin deficiency, higher doses of LMWH (weight-adjusted: either 75% or 100% of treatment dose)<sup>16,46</sup> may be necessary, as judged by anti-Xa levels and monitoring should be by a haemostasis expert.

## 8.2 *Unfractionated heparin*

Unfractionated heparin has a shorter half-life than LMWH and there is more complete reversal of its activity by protamine sulphate. Occasionally, unfractionated heparin may be used around the time of delivery in women at very high risk of thrombosis (when there may be reluctance to use LMWH in case regional anaesthetic techniques are required) or in women at increased risk of haemorrhage (see section 6). So, for example, if no LMWH has been given for 24 hours but the woman has not yet delivered and there is concern about delaying further given and repeated every 12 hours until LMWH can be resumed after delivery. The required interval between a prophylactic dose of unfractionated heparin and regional analgesia or anaesthesia is less (4 hours) than with LMWH (12 hours) and there is less concern regarding neuraxial haematomas with unfractionated heparin.<sup>85</sup> Any exposure to unfractionated heparin is associated with an increased risk of heparin-induced thrombocytopenia.

## 8.3 *Danaparoid*

Danaparoid is a heparinoid that is mostly used in patients intolerant of heparin, either because of heparin-induced thrombocytopenia or a skin allergy to heparins. It is administered by intravenous or subcutaneous injection and, like heparin, has both anti-IIa and anti-Xa effects, predominantly the latter with a long anti-Xa half-life of about 24 hours. The experience in the use of this agent in a total of 51 pregnancies was reviewed in 2002.<sup>111</sup> The women had either heparin-induced thrombocytopenia (32 cases) or skin allergy to heparin (19 cases) and the median duration of danaparoid exposure was 10 weeks. Dosing varied between prophylactic and treatment ranges. There were four maternal bleeding events, two of which were fatal owing to placental problems (praevia and abruption). No anti-Xa was detected in the cord blood of five infants tested and no anti-Xa activity was found in breast milk in three lactating women, despite measureable plasma levels. There were no adverse fetal outcomes attributed to danaparoid. Potential use of this agent should be in conjunction with a consultant haematologist with expertise in this area.

## 8.4 *Fondaparinux*

Fondaparinux is a synthetic pentasaccharide that functions as an anticoagulant through specific inhibition of factor Xa via antithrombin. It is licensed in the UK for the prevention and treatment of VTE outside pregnancy and has a broadly similar efficacy to LMWH. There is limited experience of its use in pregnancy but it has been used in the setting of heparin intolerance.<sup>112</sup> No placental passage of fondaparinux was found in a human cotyledon model<sup>113</sup> but anti-factor Xa activity about 10% of that in maternal plasma was found in the umbilical cord plasma in newborns of five mothers being treated with fondaparinux.<sup>114</sup> Although no adverse effects were observed in the newborns, it is premature to conclude that it is safe and its role in pregnancy at this time should be reserved for women intolerant of heparin compounds. The regular prophylactic dose is 2.5 mg subcutaneously daily and it does not seem necessary to alter this dose in pregnancy.<sup>115</sup> Potential use of this agent in pregnancy should be in conjunction with a consultant haematologist with expertise in this area.

## 8.5 *Lepirudin*

Lepirudin is a direct thrombin inhibitor that, like danaparoid, is used in the management of patients with heparin-induced thrombocytopenia. There are few reports of its use in pregnancy but it can cross the placenta and has been reported to produce embryopathy when given in high doses to rabbits.<sup>104</sup> Its use is best avoided in pregnancy unless there is no acceptable alternative.

## 8.6 *Low-dose aspirin*

There are no controlled trials on the use of aspirin for thromboprophylaxis in pregnancy. Conclusions about its efficacy have been extrapolated from other trials in the nonpregnant population. A meta-analysis of trials of short-term antiplatelet therapy in surgical and medical patients showed a significant reduction in DVT and pulmonary embolism with antiplatelet prophylaxis.<sup>116</sup> Another meta-analysis, focusing on patients at high risk for occlusive vascular events, found a statistically significant 25% reduction in the odds of pulmonary embolism associated with antiplatelet therapy.<sup>117</sup> A further, much criticized, trial suggested that low-dose aspirin reduced by 36% the risk of VTE after orthopaedic surgery compared with placebo, even in some patients taking concomitant heparin therapy.<sup>118</sup> However, the Women's Health Study<sup>119</sup> found aspirin no better than placebo for long-term primary prevention of VTE in older women in a secondary end-point analysis. The American College of Chest Physicians (ACCP) guideline<sup>16,120</sup> recommends against the use of aspirin for VTE prophylaxis in any patient group.

There were no adverse fetal outcomes reported in meta-analysis of large randomised control trials of low-dose aspirin for prevention of pre-eclampsia in pregnancy.<sup>121,122</sup> Aspirin is appropriate for women with antiphospholipid syndrome to improve fetal outcomes.<sup>76,77</sup>

## 8.7 *Warfarin*

Warfarin use in pregnancy is restricted to a few situations where heparin is considered unsuitable; for example, some women with mechanical heart valves. This is because warfarin crosses the placenta leading to an increased risk of congenital abnormalities including a characteristic warfarin embryopathy in approximately 5% of fetuses exposed between 6 and 12 weeks of gestation,<sup>123-129</sup> There is evidence that this incidence is dose-dependent, with a higher incidence in women taking greater than 5 mg/day.<sup>127-129</sup> Other reported complications associated with warfarin therapy during pregnancy include an increase in the risk of spontaneous miscarriage,<sup>126-128,130,131</sup> stillbirth,<sup>123,127,128,130</sup> neurological problems in the baby<sup>132,133</sup> and fetal and maternal haemorrhage.<sup>128,129</sup>

## 8.8 *Dextran*

Dextran should be avoided antenatally and intrapartum primarily because of the risk of anaphylactoid reaction, which has been associated with uterine hypertonus, fetal distress, fetal neurological abnormalities and death.<sup>134,135</sup> As there are now many alternatives, dextran is of little value in modern obstetric practice.

## 8.9 *Oral thrombin and Xa inhibitors*

Dabigatran and rivaroxaban are two new anticoagulants that work through direct inhibition of thrombin and factor Xa, respectively. They are licensed for the prevention of VTE after major orthopaedic surgery. They are not licensed for use in pregnancy where there is no experience in their use. Therefore they should be avoided in pregnant women.

## 9. **Graduated elastic compression stockings**

The British Society for Haematology guidelines give a grade C recommendation (evidence level IV) that all women with previous VTE or a thrombophilia should be encouraged to wear graduated compression stockings throughout their pregnancy and for 6-12 weeks after delivery.<sup>46</sup> There are no trials to support this practice and this expert opinion derives from extrapolation from studies using graduated elastic compression

therapy in the hospitalised nonpregnant population. A Cochrane review of graduated compression therapy for the prevention of DVT in nonpregnant hospitalised patients showed a significant reduction in incidence of DVT between the control group (29%) and treatment group (15%) (OR 0.36, 95% CI 0.26–0.49).<sup>136</sup> Small studies have shown that graduated compression stockings significantly improve venous emptying in pregnant women<sup>137</sup> and increase the blood flow, while decreasing the lumen diameter of the superficial femoral<sup>138</sup> and common femoral<sup>139</sup> veins in late pregnancy and the early postpartum period.

The advantages and limitations of graduated compression stockings and other mechanical methods of VTE prevention in the non-pregnancy setting were recently reviewed by the ACCP.<sup>120</sup> The conclusion was that such methods be used primarily for patients at high risk of bleeding (who were unable to receive pharmacological thromboprophylaxis) and as an adjunct to anticoagulant thromboprophylaxis where this had been shown to improve efficacy (essentially surgical patients). Attention should be given to their proper application. In hospitalised medical patients, their recommended use was limited to the setting where there was a contraindication to anticoagulant thromboprophylaxis.<sup>120</sup>

In the ACCP guideline on thromboprophylaxis in pregnancy, use of graduated compression stockings was recommended for women considered to be at high risk of VTE after caesarean section and antenatally and postpartum for all women with a previous DVT.<sup>16</sup> However, it should be borne in mind that following a symptomatic DVT, patients should, if possible, wear a tighter-fitted graduated elastic compression stocking during the day, with an ankle pressure gradient of 30–40 mmHg for 2 years to prevent the post-thrombotic syndrome (and continue for longer if post-thrombotic symptoms are present).<sup>43</sup> Where possible, this recommendation should apply in pregnancy as well.

In conclusion, the use of properly applied graduated compression stockings of appropriate strength is recommended in pregnancy and the puerperium for:

- those who are hospitalised and have a contraindication to LMWH
- those who are hospitalised post-caesarean section (combined with LMWH) and considered to be at particularly high risk of VTE (such as previous VTE, more than three risk factors)
- outpatients with prior VTE (usually combined with LMWH)
- women travelling long distance for more than 4 hours.<sup>33</sup>

There are few data regarding the most efficacious length of graduated compression stockings to use in pregnancy. More DVTs in pregnant women are iliofemoral compared with the nonpregnant population, where calf-vein DVTs are more common. Studies of graduated compression stockings in pregnancy have only concerned full-length stockings.<sup>139</sup> Although NICE guidelines support the use of thigh-length GCS in inpatients undergoing surgery,<sup>35</sup> other reviews outside pregnancy suggest equivalent efficacy of knee-length and thigh-length stockings<sup>140–142</sup> and higher rates of compliance with the former.<sup>143</sup> In addition, hydrostatic pressures on standing appear to overcome venous compression from graduated compression stockings<sup>144,145</sup> and, thus, stockings may be of less benefit in the ambulant population. In the obstetric population, there is the added problem of thigh-length stockings becoming bloodstained. Therefore, on balance, properly applied thigh-length stockings are advocated for pregnant women but knee-length stockings should be considered if (as is often the case) full-length stockings are ill fitting or compliance is poor.

## 10. Agents for postpartum thromboprophylaxis

*Which agents are appropriate for post partum thromboprophylaxis?*

**LMWH is appropriate for postpartum thromboprophylaxis although, if women are receiving long term anticoagulation with warfarin, this can be started when the risk of haemorrhage is low, usually 5–7 days after delivery.**

C

**Both warfarin and LMWH are safe when breastfeeding.**

B

LMWH is safe and easy to use and has the advantage of not requiring monitoring. For those women receiving LMWH antenatally (and therefore 6 weeks postpartum) or for those requiring 7 days of postpartum thrombo-

prophylaxis, it is the agent of choice. Experience of LMWH in the puerperium reports no problems during breastfeeding.<sup>86</sup>

Warfarin can be safely used following delivery and in breastfeeding mothers, although it requires close monitoring and visits to an anticoagulant clinic. It carries an increased risk of postpartum haemorrhage and perineal haematoma compared with LMWH. It is not appropriate for those women requiring 7 days of postpartum prophylaxis. However, it is appropriate for those on maintenance warfarin outside pregnancy. Conversion from LMWH back to warfarin should be delayed for at least 5–7 days after delivery to minimise the risk of haemorrhage during the period of overlap of LMWH and warfarin treatment.

It is unknown whether fondaparinux is excreted in breast milk and, although oral absorption seems unlikely, it should be avoided in this setting.

## 11. Contraindications to LMWH

*Which women should not be given thromboprophylaxis with LMWH?*

LMWH should be avoided, discontinued or postponed in women who are at risk of bleeding after careful consideration of the balance of risks of bleeding and clotting.<sup>1,16,86,146</sup> Risk factors for bleeding (see also Appendix III) are:

- women with active antenatal or postpartum bleeding
- women considered at increased risk of major haemorrhage (such as placenta previa)
- women with a bleeding diathesis, such as von Willebrand's disease, haemophilia or acquired coagulopathy
- women with thrombocytopenia (platelet count less than  $75 \times 10^9$ )
- acute stroke in the last 4 weeks (ischaemic or haemorrhagic)
- severe renal disease (glomerular filtration rate less than 30 ml/minute/1.73 m<sup>2</sup>)
- severe liver disease (prothrombin time above normal range or known varices)
- uncontrolled hypertension (blood pressure greater than 200 mmHg systolic or greater than 120 mmHg diastolic).

It should be noted that, in the absence of evidence in the pregnant population, the clinical and laboratory thresholds are in line with the Department of Health's guidelines based on evidence from the nonpregnant population.<sup>146</sup>

Further advice on the decision and the management of both VTE risk factors and bleeding risk factors may be sought from a haematologist with experience in the management of thrombosis and bleeding disorders in pregnancy.

## 12. Auditable standards

- Correct risk assessment at booking, on admission to antenatal ward and after delivery.
- Correct dose of LMWH (based on booking weight) prescribed antenatally and postpartum.
- LMWH prescribed and taken for 1 week postpartum in all women with class-3 obesity (BMI greater than 40).
- LMWH prescribed and given for 6 weeks postpartum in all women with previous VTE.

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## APPENDIX I

**Adjusted odds ratios (AOR) for risk of venous thromboembolism (VTE) in pregnant and postpartum women with different risk factors compared with pregnant and postpartum women without these risk factors (data from various case-control studies); evidence level 2+/2++**

Risk factor	AOR	95% CI	Comment
Previous VTE <sup>23</sup>	24.8	17.1–36	
Age > 35 <sup>15,22</sup>	1.3 <sup>14</sup>	1.0–1.7	n = 603
	1.4 <sup>21</sup>	1.0–2.0	pn = 256
Obesity, body mass index > 30 <sup>6,22–24</sup>	2.6 <sup>5</sup>	1.09–6.45	n = 143 an PE
	5.3 <sup>23</sup>	2.1–13.5	n = 129
	4.4 <sup>22</sup>	3.4–5.7	
	1.7 <sup>21</sup>	1.1–2.6	pn = 256
Body mass index > 25 <sup>13,22</sup>	1.8 <sup>12</sup>	1.3–2.4	an = 268
	2.4 <sup>12</sup>	1.7–3.3	pn = 291
	1.7 <sup>21</sup>	1.2–2.4	pn = 256
Weight:			
90–120 kg <sup>31</sup>	1.93	1.10–3.39	an
> 120 kg	4.32	1.26–14.84	an
Weight gain in pregnancy > 21 kg <sup>13</sup> (compared with 7–21 kg)	1.6	1.1–2.6	pn = 291
Parity:			
1 <sup>16</sup>	4.03	1.6–9.84	n = 143 an PE
2 <sup>15</sup>	1.5	1.1–1.9	n = 603
3 or more <sup>14</sup>	2.4	1.8–3.1	n = 603
Smoking:	2.1 <sup>12</sup>	1.3–3.4	an = 268
10–30/day <sup>13,15,26</sup>	3.4 <sup>12</sup>	2.0–5.5	pn = 291
	1.4 <sup>14</sup>	1.1–1.9	n = 603
	2.5 <sup>25</sup>	1.3–4.7	n = 90
‘current smoker’ <sup>24</sup>	2.7 <sup>23</sup>	1.5–4.9	n = 129
Sickle cell <sup>22,36</sup>	6.7 <sup>22</sup>	4.4–10.1	
	2.5 <sup>138</sup>	1.5–4.1	DVT
	1.7 <sup>138</sup>	0.9–3.1	PE
Heart disease <sup>22,23</sup>	7.1 <sup>22</sup>	6.2–8.3	
	5.4 <sup>21</sup>	2.6–11.3	pn = 256
Systemic lupus erythematosus <sup>23</sup>	8.7	5.8–13	
Anaemia <sup>23</sup>	2.6	2.2–2.9	
Varicose veins <sup>26</sup>	2.4	1.04–5.4	
Immobility <sup>13</sup>	7.7	3.2–19	an
	10.8	4.0–28.8	pn
Pre-eclampsia <sup>13,15</sup>	2.9 <sup>14</sup>	2.1–3.9	
	3.1 <sup>12</sup>	1.8–5.3	pn
Pre-eclampsia + fetal growth restriction <sup>13</sup>	5.8 <sup>12</sup>	2.1–16	
Hyperemesis <sup>13</sup>	2.5	2–3.2	
Assisted reproductive therapy <sup>13</sup>	4.3	2.0–9.4	an
Twins <sup>13,15</sup>	2.6 <sup>12</sup>	1.1–6.2	an
	1.8 <sup>14</sup>	1.1–3.0	n = 603
Multiple pregnancy <sup>22</sup>	4.2	1.8–9.7	an = 109
Preterm delivery < 36 weeks <sup>22</sup>	2.4	1.6–3.5	pn = 256
Antepartum haemorrhage <sup>23</sup>	2.3	1.8–2.8	
Emergency caesarean section <sup>15</sup>	2.7	1.8–4.1	
Any caesarean section <sup>15,22,23</sup>	3.6 <sup>14</sup>	3.0–4.3	
	2.1 <sup>22</sup>	1.8–2.4	
	2.0 <sup>21</sup>	1.5–2.7	pn = 256
Postpartum haemorrhage > 1 litre <sup>13</sup>	4.1	2.3–7.3	
Postpartum haemorrhage + surgery <sup>13</sup>	12	3.9–36.9	
Obstetric haemorrhage <sup>26</sup>	9	1.1–71	
Postpartum infection <sup>23</sup>	4.1	2.9–5.7	
Postpartum infection + caesarean section <sup>13</sup>	6.2	2.4–16.2	
Transfusion <sup>23</sup>	7.6	6.2–9.4	

an = antenatal; DVT = deep venous thrombosis; PE = pulmonary embolism; pn = postnatal; n = number of cases in case-control study

## APPENDIX II

### Summary of guideline for thromboprophylaxis in women with previous venous thromboembolism (VTE) and/or thrombophilia (prophylactic doses are given in Table 3; see also Figure 1)

Risk	History	Prophylaxis
<b>Very high</b>	Previous VTE on long-term warfarin Antithrombin deficiency Antiphospholipid syndrome with previous VTE	Recommend antenatal high-dose LMWH and at least 6 weeks postnatal LMWH/warfarin Requires specialist management by experts in haemostasis and pregnancy
	Previous recurrent or unprovoked VTE Previous estrogen-provoked (pill or pregnancy) VTE Previous VTE + thrombophilia Previous VTE + family history of VTE Asymptomatic thrombophilia (combined defects, homozygous FVL)	Recommend antenatal and 6 weeks postnatal prophylactic LMWH
<b>Intermediate</b>	Single previous VTE associated with transient risk factor no longer present without thrombophilia, family history or other risk factors Asymptomatic thrombophilia (except antithrombin deficiency, combined defects, homozygous FVL)	Consider antenatal LMWH (but not routinely recommended) Recommend 6 weeks postnatal prophylactic LMWH Recommend 7 days (or 6 weeks if family history or other risk factors) postnatal prophylactic LMWH

FVL = factor V Leiden; LMWH = low-molecular-weight heparin

## APPENDIX III

### Risk assessment for venous thromboembolism (VTE)

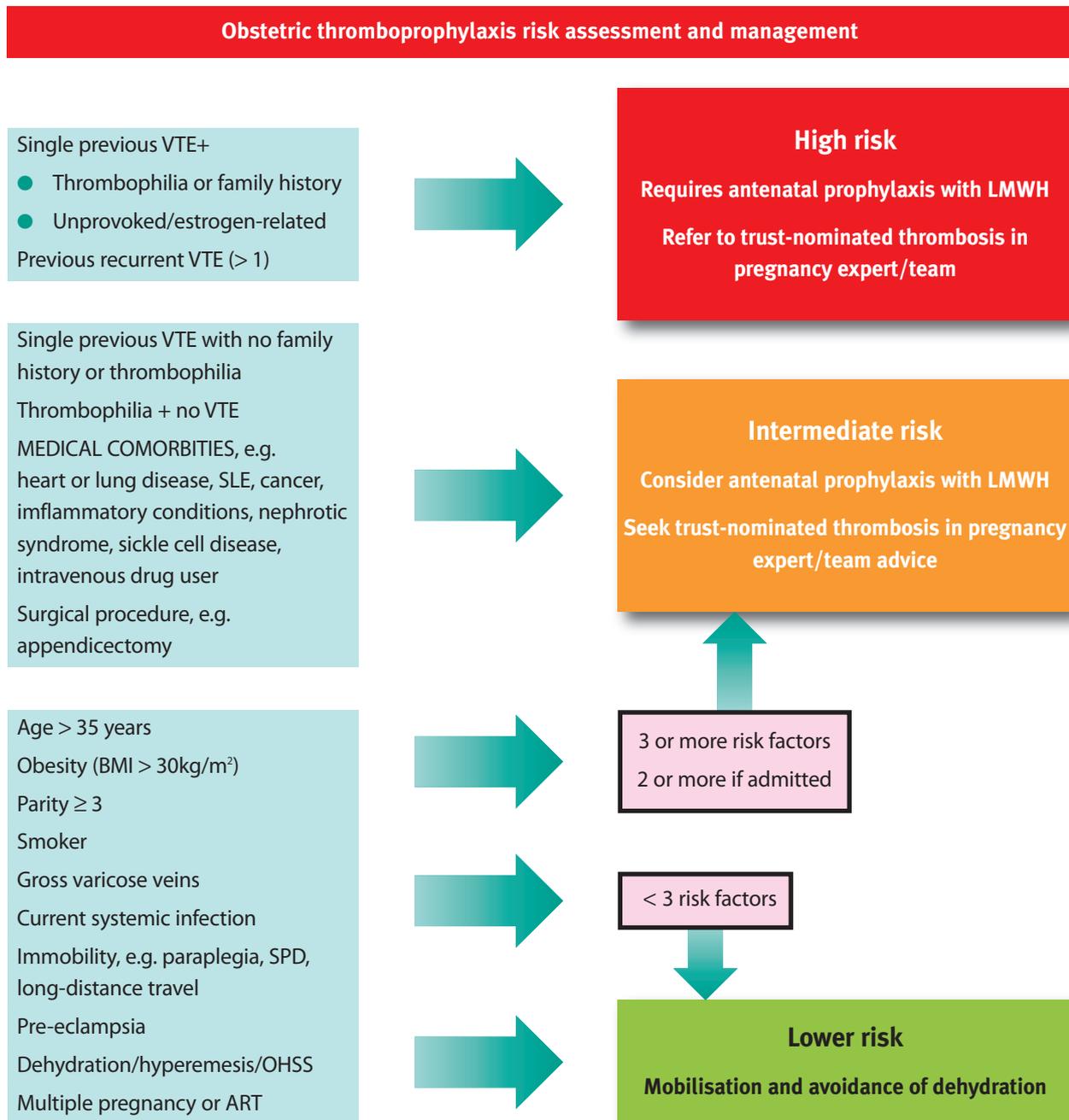
Pre-existing risk factors	Tick	Score	
Previous recurrent VTE		3	
Previous VTE – unprovoked or estrogen related		3	
Previous VTE – provoked		2	
Family history of VTE		1	
Known thrombophilia		2	
Medical comorbidities		2	
Age (> 35 years)		1	Thromboprophylaxis with LMWH should be considered if:
Obesity		1/2 <sup>a</sup>	≥ three risk factors antenatally and managed as an outpatient
Parity ≥ 3		1	
Smoker		1	≥ two risk factors antenatally and managed as an inpatient or any postnatal woman who is within 6 weeks of delivery
Gross varicose veins		1	
Obstetric risk factors			
Pre-eclampsia		1	
Dehydration/hyperemesis/OHSS		1	For women with an identified bleeding risk, the balance of risks of bleeding and clotting should be discussed in consultation with a haematologist with experience of thrombosis and bleeding in pregnancy
Multiple pregnancy or ART		1	
Caesarean section in labour		2	
Elective caesarean section		1	
Mid-cavity or rotational forceps		1	
Prolonged labour (> 24 hours)		1	
PPH (>1 litre or transfusion)		1	
Transient risk factors			
Current systemic infection		1	
Immobility		1	
Surgical procedure in pregnancy or ≤ 6 weeks postpartum		2	
<b>TOTAL</b>			

<sup>a</sup> Score 1 for BMI > 30 kg/m<sup>2</sup>; 2 for BMI > 40 kg/m<sup>2</sup> (BMI based on booking weight)

Bleeding risk	
Haemophilia or other known bleeding disorder (e.g. von Willebrand's disease or acquired coagulopathy)	
Active antenatal or postpartum bleeding	
Women considered at increased risk of major haemorrhage (e.g. placenta praevia)	
Thrombocytopenia (platelet count < 75 × 10 <sup>9</sup> )	
Acute stroke in previous 4 weeks (haemorrhagic or ischaemic)	
Severe renal disease (glomerular filtration rate < 30 ml/minute/1.73 m <sup>2</sup> )	
Severe liver disease (prothrombin time above normal range or known varices)	
Uncontrolled hypertension (blood pressure > 200 mmHg systolic or > 120 mmHg diastolic)	

## APPENDIX IV

**Antenatal assessment and management** (to be assessed at booking and repeated if admitted)



### Antenatal and postnatal prophylactic dose of LMWH

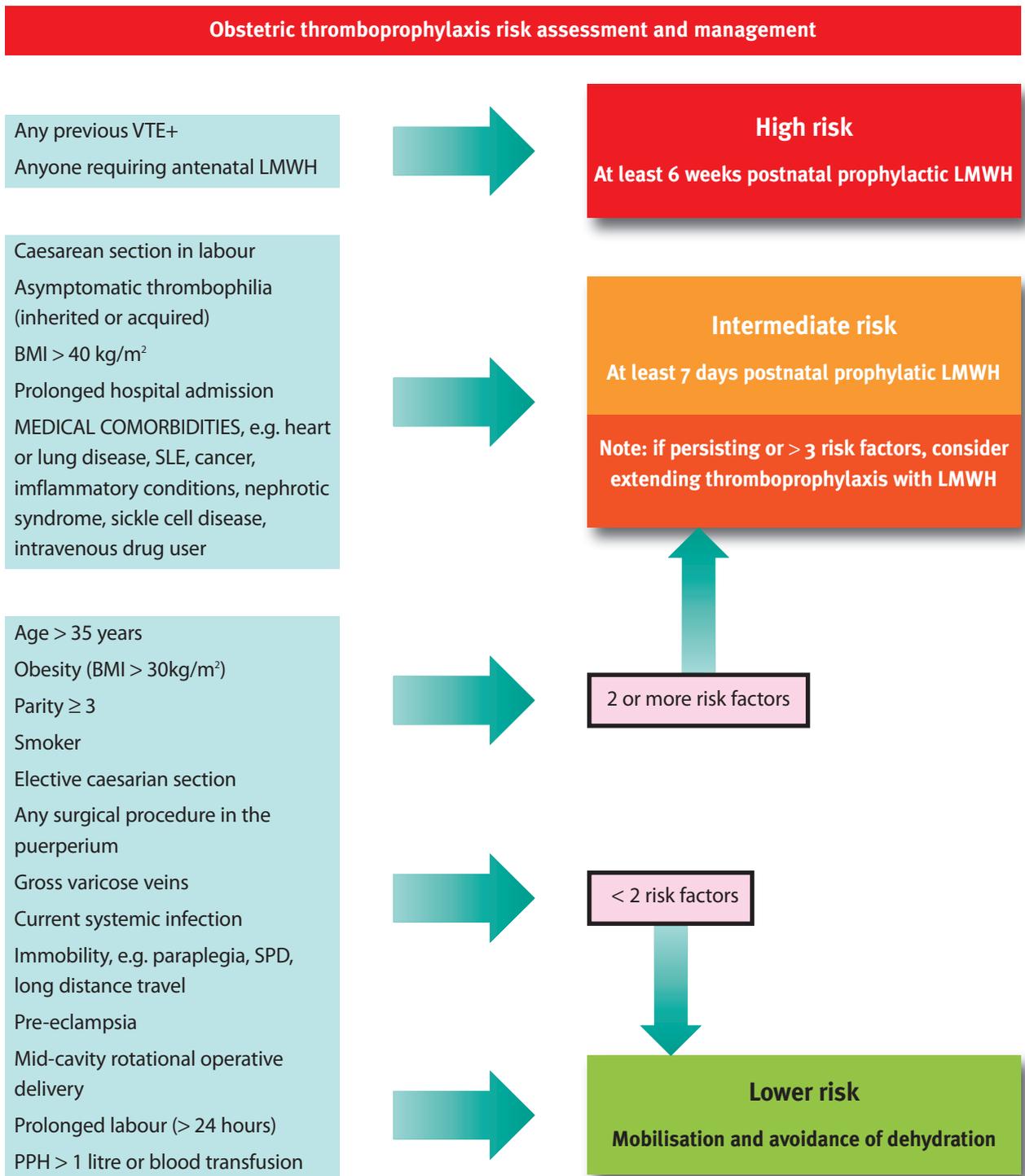
Weight < 50 kg = 20 mg enoxaparin/2500 units dalteparin/3500 units tinzaparin daily  
 Weight 50–90 kg = 40 mg enoxaparin/5000 units dalteparin/4500 units tinzaparin daily  
 Weight 91–130 kg = 60 mg enoxaparin/7500 units dalteparin/7000 units tinzaparin daily  
 Weight 131–170 kg = 80 mg enoxaparin/10000 units dalteparin/9000 units tinzaparin daily  
 Weight > 170 kg = 0.6 mg/kg/day enoxaparin; 75 units/kg/day dalteparin/75 units/kg/day tinzaparin

### Key

ART = assisted reproductive therapy, BMI = body mass index (based on booking weight), gross varicose veins = symptomatic, above the knee or associated with phlebitis/oedema/skin changes, immobility = ≥ 3 days, LMWH = low-molecular-weight heparin, OHSS = ovarian hyperstimulation syndrome, PPH = postpartum haemorrhage, SLE = systemic lupus erythematosus, SPD = symphysis pubis dysfunction with reduced mobility, thrombophilia = inherited or acquired, long-distance travel = > 4 hours, VTE = venous thromboembolism

## APPENDIX V

Postnatal assessment and management (to be assessed on delivery suite)



### Key

ART = assisted reproductive therapy, BMI = body mass index (based on booking weight), gross varicose veins = symptomatic, above the knee or associated with phlebitis/oedema/skin changes, immobility = ≥ 3 days, LMWH = low-molecular-weight heparin, OHSS = ovarian hyperstimulation syndrome, PPH = postpartum haemorrhage, SLE = systemic lupus erythematosus, SPD = symphysis pubis dysfunction with reduced mobility, thrombophilia = inherited or acquired, long-distance travel = > 4 hours, VTE = venous thromboembolism

## APPENDIX VI

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 [www.rcog.org.uk/index.asp?PageID=75](http://www.rcog.org.uk/index.asp?PageID=75)). 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
1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias	<b>A</b> 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
1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias	<b>B</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+
1- Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	<b>C</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 2++
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	<b>D</b> Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
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	<b>Good practice point</b>
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	<input checked="" type="checkbox"/> Recommended best practice based on the clinical experience of the guideline development group
3 Non-analytical studies; e.g. case reports, case series	
4 Expert opinion	

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

The Guidelines review process will commence in 2012  
unless evidence requires earlier review

#### 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.