Royal College of Obstetricians & Gynaecologists

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

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Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

This is the third edition of this guideline, first published in 2004 under the title 'Thromboprophylaxis during Pregnancy, Labour and after Vaginal Delivery' and revised in 2009 under the title 'Reducing the Risk of Thrombosis and Embolism during Pregnancy and the Puerperium'.

Executive summary of recommendations

Prepregnancy and antenatal risk assessment

What are the risk factors for venous thromboembolism (VTE) in pregnancy and the puerperium and what is the magnitude of risk for these factors?

All women should undergo a documented assessment of risk factors for VTE in early pregnancy or prepregnancy. C

Risk assessment should be repeated if the woman is admitted to hospital for any reason or develops other intercurrent problems. C

Risk assessment should be repeated again intrapartum or immediately postpartum. C

Any woman with four or more current risk factors shown in Appendix I and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic low-molecular-weight heparin (LMWH) throughout the antenatal period and will usually require prophylactic LMWH for 6 weeks postnatally but a postnatal risk reassessment should be made. [*New 2015*] D

Any woman with three current risk factors shown in Appendix I and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH from 28 weeks and will usually require prophylactic LMWH for 6 weeks postnatally but a postnatal risk reassessment should be made. [*New 2015*] D

Any woman with two current risk factors shown in Appendix I and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH for at least 10 days postpartum. [*New 2015*] D

Women admitted to hospital when pregnant (including to the gynaecology ward with hyperemesis gravidarum or ovarian hyperstimulation syndrome) should usually be offered thromboprophylaxis with LMWH unless there is a specific contraindication such as risk of labour or active bleeding. [*New 2015*] D

The risk of VTE should be discussed with women at risk and the reasons for individual recommendations explained. [*New 2015*] ✓

Previous VTE

How should women with previous VTE be managed in pregnancy? (see Appendix IV)

Single previous VTE

Women with previous VTE should be offered prepregnancy counselling and a prospective management plan for thromboprophylaxis in pregnancy made. Those who become pregnant before receiving such counselling should be referred at the earliest opportunity in pregnancy to a clinician with expertise in thrombosis in pregnancy. ✓

Women with previous VTE (except those with a single previous VTE related to major surgery and no other risk factors) should be offered thromboprophylaxis with LMWH throughout the antenatal period. [*New 2015*] C

Women with previous VTE should have a careful history documented. 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 (greater than 6 weeks) therapeutic anticoagulation. [*New 2015*] C

Thrombophilia-associated VTE

Heritable thrombophilia

Women with previous VTE associated with antithrombin deficiency (who will often be on long-term oral anticoagulation) should be offered thromboprophylaxis with higher dose LMWH (either 50%, 75% or full treatment dose) (see Appendix IV) antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery. D

Management should be undertaken in collaboration with a haematologist with expertise in thrombosis in pregnancy and consideration given to antenatal anti-Xa monitoring and the potential for antithrombin replacement at initiation of labour or prior to caesarean section. [*New 2015*] ✓

If anti-Xa levels are measured, a test that does not use exogenous antithrombin should be used and 4-hour peak levels of 0.5–1.0 iu/ml aimed for. [*New 2015*] ✓

Other heritable thrombophilic defects are lower risk and can be managed with standard doses of thromboprophylaxis. [*New 2015*] ✓

Acquired thrombophilia – see also section 4.4

Women with VTE associated with the antiphospholipid syndrome (APS) (who will often be on long-term oral anticoagulation) should be offered thromboprophylaxis with higher dose LMWH (either 50%, 75% or full treatment dose) (see Appendix IV) antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery. [*New 2015*] D

Pregnant women with APS and prior VTE or arterial thromboses should be managed in collaboration with a haematologist and/or rheumatologist with expertise in this area. [*New 2015*] ✓

Previous recurrent VTE

What extra advice is needed for women with previous recurrent VTE?

Advice regarding doses of LMWH in pregnancy should be sought from a clinician with expertise in haemostasis and pregnancy. [*New 2015*] ✓

Some women with previous recurrent VTE require higher doses of LMWH. [*New 2015*] ✓

Women on long-term warfarin or other oral anticoagulants should be counselled about the risks of these agents to the fetus (see section 8.6) and advised to stop their oral anticoagulant therapy and change to LMWH as soon as pregnancy is confirmed, ideally within 2 weeks of the missed period and before the sixth week of pregnancy. [*New 2015*] ✓

Women not on warfarin or other oral anticoagulants should be advised to start LMWH as soon as they have a positive pregnancy test. [*New 2015*] ✓

Stratification of women with previous VTE

How should women with previous VTE be stratified to determine management in pregnancy?

Women with VTE associated with either antithrombin deficiency or APS or with recurrent VTE (who will often be on long-term oral anticoagulation) should be offered thromboprophylaxis with higher dose LMWH (either 50%, 75% or full treatment dose) (see Appendix IV) antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery. These women require specialist management by experts in haemostasis and pregnancy. [*New 2015*] D

Women in whom the original VTE was unprovoked/idiopathic or related to estrogen (estrogen-containing contraception/pregnancy) or related to a transient risk factor other than major surgery or who have other risk factors should be offered thromboprophylaxis with LMWH throughout the antenatal period. D

In women in whom the original VTE was provoked by major surgery from which they have recovered and who have no other risk factors, thromboprophylaxis with LMWH can be withheld antenatally until 28 weeks provided 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. [*New 2015*] D

Testing for thrombophilia in women with prior VTE

Which women with prior VTE require thrombophilia testing?

Prior to testing for thrombophilia, women should be counselled regarding the implications for themselves and family members of a positive or negative result. The results should be interpreted by clinicians with specific expertise in the area. ✓

Women with a family history of VTE and either antithrombin deficiency or where the specific thrombophilia has not been detected should be tested for antithrombin deficiency. [*New 2015*] ✓

Women with an unprovoked VTE should be tested for the presence of antiphospholipid antibodies. [*New 2015*] ✓

Asymptomatic heritable thrombophilia

How should women with asymptomatic thrombophilia be treated? (see Appendix IV)

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. [*New 2015*] D

Women with asymptomatic antithrombin, protein C or S deficiency or those with more than one thrombophilic defect (including homozygous factor V Leiden, homozygous prothrombin gene mutation and compound heterozygotes) should be referred to a local expert and antenatal prophylaxis considered. They should be recommended for six weeks' postnatal prophylaxis even in the absence of additional risk factors. [*New 2015*] D

Heterozygosity for factor V Leiden or prothrombin gene mutation or antiphospholipid antibodies are considered as risk factors for thrombosis in asymptomatic women (see Appendix I). In the presence of three other risk factors such women may be considered for antenatal thromboprophylaxis, if there are two other risk factors thromboprophylaxis should be considered from 28 weeks and if there is one other risk factor postnatal thromboprophylaxis for 10 days should be considered. [*New 2015*] D

Women with no personal history or risk factors for VTE but who have a family history of an unprovoked or estrogen-provoked VTE in a first-degree relative when aged under 50 years should be considered for thrombophilia testing. This will be more informative if the relative has a known thrombophilia. [*New 2015*] D

Antiphospholipid antibodies

How should women with antiphospholipid antibodies be treated?

Persistent antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin and/or β_2-glycoprotein 1 antibodies) in women without previous VTE should be considered as a risk factor for thrombosis (see Appendix I) such that if she has other risk factors she may be considered for antenatal or postnatal thromboprophylaxis as above. [*New 2015*] C

Timing of initiation of thromboprophylaxis

When should thromboprophylaxis be started?

Antenatal thromboprophylaxis for those with previous VTE should begin as early in pregnancy as practical. [*New 2015*] B

Women without previous VTE and without particular first trimester risk factors or admission to hospital, but with four other risk factors, should be considered for antenatal prophylaxis throughout pregnancy. [*New 2015*] C

Women without previous VTE and without particular first trimester risk factors or admission to hospital, but with three other risk factors, can start antenatal prophylaxis at 28 weeks of gestation. [*New 2015*] C

First trimester risk factors

What are the first trimester risk factors for VTE and how should they be managed?

Women admitted with hyperemesis should be considered for thromboprophylaxis with LMWH and can discontinue thromboprophylaxis when the hyperemesis resolves. [*New 2015*] C

Women with ovarian hyperstimulation syndrome should be considered for thromboprophylaxis with LMWH in the first trimester. [*New 2015*] C

Women with an IVF pregnancy and three other risk factors should be considered for thromboprophylaxis with LMWH starting in the first trimester. [*New 2015*] C

Thromboprophylaxis during labour and delivery, including the use of regional 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. ✓

Regional techniques should be avoided if possible until at least 12 hours after the previous prophylactic dose of LMWH. ✓

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

When a woman presents while on a therapeutic regimen of LMWH, regional techniques should be avoided if possible for at least 24 hours after the last dose of LMWH. ✓

Women receiving antenatal LMWH having an elective caesarean section should receive a thromboprophylactic dose of LMWH on the day prior to delivery and, on the day of delivery, any morning dose should be omitted and the operation performed that morning. ✓

The first thromboprophylactic dose of LMWH should be given as soon as possible after delivery provided there is no postpartum haemorrhage and regional analgesia has not been used. [*New 2015*] ✓

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 managed with anti-embolism stockings (AES), foot impulse devices or intermittent pneumatic compression devices. Unfractionated heparin (UFT) may also be considered. ✓

If a woman develops a haemorrhagic problem while on LMWH the treatment should be stopped and expert haematological advice sought. ✓

Thromboprophylaxis should be started or reinstituted as soon as the immediate risk of haemorrhage is reduced. ✓

Thromboprophylaxis after delivery

Assessment of risk

What are the risk factors for VTE after delivery?

All women with class 3 obesity (BMI greater than or equal to 40 kg/m^2) should be considered for prophylactic LMWH in doses appropriate for their weight for 10 days after delivery. [*New 2015*] D

Women with two or more persisting risk factors listed in Table 1 should be considered for LMWH in prophylactic doses appropriate for their weight for 10 days after delivery. [*New 2015*] B

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 at least 6 weeks postpartum regardless of the mode of delivery. B

Asymptomatic thrombophilia

Which women with thrombophilia without previous VTE need postpartum thromboprophylaxis?

Women with thrombophilia without previous VTE 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. [*New 2015*] C

Women with a family history of VTE and an identified thrombophilia should be considered for 6 weeks' postnatal thromboprophylaxis. D

Caesarean section

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

All women who have had caesarean sections should be considered for thromboprophylaxis with LMWH for 10 days after delivery apart from those having an elective caesarean section who should be considered for thromboprophylaxis with LMWH for 10 days after delivery if they have any additional risk factors (see Appendix I and Table 1). [*New 2015*] C

For how long should thromboprophylaxis be continued after delivery?

Risk assessment should be 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. [*New 2015*] ✓

Thromboprophylaxis should be continued for 6 weeks in high-risk women and for 10 days in intermediate-risk women (see Appendix I). [*New 2015*] C

In women who have additional persistent (lasting more than 10 days postpartum) risk factors, such as prolonged admission, wound infection or surgery in the puerperium, thromboprophylaxis should be extended for up to 6 weeks or until the additional risk factor/s is/are no longer present. [*New 2015*] D

Which agents should be used for thromboprophylaxis?

Low-molecular-weight heparin (LMWH)

LMWHs are the agents of choice for antenatal and postnatal thromboprophylaxis. A

Doses of LMWH are based on weight. For thromboprophylaxis the booking or most recent weight can be used to guide dosing. [*New 2015*] B

It is only necessary to monitor the platelet count if the woman has had prior exposure to unfractionated heparin (UFH). B

Monitoring of anti-Xa levels is not required when LMWH is used for thromboprophylaxis. D

Doses of LMWH should be reduced in women with renal impairment. C

LMWH is safe in breastfeeding. A

Unfractionated heparin

In women at very high risk of thrombosis (see Appendix IV), UFH may be used peripartum in preference to LMWH where there is an increased risk of haemorrhage or where regional anaesthetic techniques may be required. D

If UFH is used after caesarean section (or other surgery), the platelet count should be monitored every 2–3 days from days 4–14 or until heparin is stopped. [*New 2015*] D

Danaparoid

Potential use of danaparoid should be in conjunction with a consultant haematologist with expertise in haemostasis and pregnancy. ✓

Fondaparinux

Fondaparinux should be reserved for women intolerant of heparin compounds. [*New 2015*] D

Fondaparinux use in pregnancy should be in conjunction with a consultant haematologist with expertise in haemostasis and pregnancy. ✓

Low-dose aspirin

Aspirin is not recommended for thromboprophylaxis in obstetric patients. [*New 2015*] D

Warfarin

Warfarin use in pregnancy is restricted to the few situations where heparin is considered unsuitable, e.g. some women with mechanical heart valves. B

Women receiving long-term anticoagulation with warfarin can be converted from LMWH to warfarin postpartum when the risk of haemorrhage is reduced, usually 5–7 days after delivery. ✓

Warfarin is safe in breastfeeding. ✓

Dextran

Dextran should be avoided antenatally and intrapartum because of the risk of anaphylactoid reaction. D

Oral thrombin and Xa inhibitors

Non-vitamin K antagonist oral anticoagulants (NOACs) should be avoided in pregnant women. [*New 2015*] ✓

Use of NOACs is not currently recommended in women who are breastfeeding. [*New 2015*] ✓

Anti-embolism stockings

The use of properly applied anti-embolism stockings (AES) of appropriate size and providing graduated compression with a calf pressure of 14–15 mmHg is recommended in pregnancy and the puerperium for women who are hospitalised and have a contraindication to LMWH. These include women who are hospitalised post-caesarean section (combined with LMWH) and considered to be at particularly high risk of VTE (e.g. previous VTE, more than four risk factors antenatally or more than two risk factors postnatally) and women travelling long distance for more than 4 hours. [*New 2015*] D

Contraindications to LMWH

Which women should not be given thromboprophylaxis with LMWH?

LMWH should be avoided, discontinued or postponed in women at risk of bleeding after careful consideration of the balance of risks of bleeding and thrombosis. D

Women with previous or current allergic reactions to LMWH should be offered an alternative preparation or alternative form of prophylaxis. [*New 2015*] D

Further advice on the management of a woman with both VTE risk factors and bleeding risk factors or LMWH allergy may be sought from a haematologist with expertise in the management of thrombosis and bleeding disorders in pregnancy. ✓

Risk scoring methodologies

A formal VTE risk assessment with numerical scoring for all pregnant and postpartum women is recommended (see Appendix III). [*New 2015*] D

1. Purpose and scope

The aim of this guideline is to provide advice, based on clinical evidence where available, regarding the prevention of venous thromboembolism (VTE) during pregnancy, birth and following delivery. For the diagnosis and management of acute VTE in pregnancy, please refer to Green-top Guideline No. 37b.[1] For anticoagulation for mechanical heart valves in pregnancy, the reader is directed to the chapter covering this within the proceedings of the RCOG study group on heart disease.[2] A summary of the guideline for antenatal and postnatal thromboprophylaxis is given in Appendix I.

2. Introduction and background epidemiology

Pulmonary embolism (PE) remains a leading direct cause of maternal death in the UK. There was a significant fall in the maternal mortality rate from PE (from 1.56 [95% CI 1.43–2.63] per 100 000 maternities in 2003–2005 [33 deaths] to 0.70 [95% CI 0.49–1.25] per 100 000 maternities in 2006–2008 [16 deaths][3,4]) due largely to reductions in deaths from antenatal VTE (which fell from 11 to 3) and deaths from VTE after vaginal delivery (which fell from 8 to 2) and attributed to the first version of this guideline published in 2004.[4]

The National Institute for Health and Care Excellence (NICE) estimates that low-molecular-weight heparin (LMWH) reduces VTE risk in medical and surgical patients by 60% and 70% respectively.[5] Therefore it is reasonable to assume that it may substantially reduce the risk of VTE in obstetric patients. A Scandinavian study[6] found a relative risk reduction of VTE of 88% in obstetric patients with one previous VTE given LMWH.

Seventy-nine percent and 89% of the women who died from PE in the UK between 2003 and 2005 and between 2006 and 2008 respectively had identifiable risk factors[3,4] and a similar proportion (70%) from the UK Obstetric Surveillance System (UKOSS) cohort (n = 143) of fatal (3.5%) and nonfatal antenatal PE also had identifiable risk factors.[7]

The UK incidence of antenatal PE calculated in the UKOSS study is 1.3 per 10 000 maternities.[7] Although the relative risk of VTE in pregnancy is increased four- to six-fold[8,9] and this is increased further postpartum,[9–11] the absolute risk is low with an overall incidence of VTE in pregnancy and the puerperium of 1–2 per 1000.[8,12–17] Absolute incidence of VTE in pregnancy and the puerperium is 107 per 100 000 person-years (95% CI 93–122 per 100 000 person-years) in the UK,[9] 107 per 100 000 pregnancy-years during pregnancy and 175 per 100 000 puerperal-years during the puerperium in Denmark,[17] and 175 per 100 000 pregnancies (deep vein thrombosis [DVT] 121 per 100 000, PE 54 per 100 000) in Canada.[16]

Many fatal antenatal VTE events occur in the first trimester and therefore prophylaxis for women with previous VTE should begin early in pregnancy.[18–20] The risk for VTE increases with gestational age, reaching a maximum just after delivery.[8–10,16,17] Caesarean section is a significant risk factor[12,21–24] but women having vaginal deliveries are also at risk.[3] The relative risk postpartum is five-fold higher compared to antepartum[8] and a systematic review of risk of postpartum VTE found that the risk varied from 21- to 84-fold from the baseline nonpregnant, nonpostpartum state in studies that included an internal reference group.[11] The absolute risk peaked in the first 3 weeks postpartum (421 per 100 000 person-years; 22-fold increase in risk).[9]

As the absolute risk of VTE in pregnancy is low, some form of risk stratification is required to determine which women warrant pharmacological thromboprophylaxis.[25] The threshold for recommending postpartum thromboprophylaxis is lower than that for recommending antenatal thromboprophylaxis because the risk per day is higher and the duration of risk is shorter.[26]

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 Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and the Database of Abstracts of Reviews of Effects [DARE]), EMBASE, the ACP Journal Club and MEDLINE, including in-process and other non-indexed citations, were searched from 2009 to 2013 to identify all relevant randomised controlled trials, systematic reviews and meta-analyses published since the previous edition of the guideline. The databases were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings. The principal search terms used were: 'venous thromboembolism', 'thrombosis', 'pregnancy', 'postpartum', 'puerperium', 'antenatal', 'prenatal'. The search was limited to humans and the English language. The National Library for Health and the National Guideline Clearinghouse were also searched for relevant guidelines and reviews. A top-up search was performed in October 2014.

Current guidelines for the prevention of VTE in pregnancy and the puerperium were reviewed.[26–28] A Cochrane systematic review[29] 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 is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period. The current guidelines are therefore drawn up recognising the limited evidence in this area.

4. Prepregnancy and antenatal risk assessment

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

All women should undergo a documented assessment of risk factors for VTE in early pregnancy or prepregnancy. C

Risk assessment should be repeated if the woman is admitted to hospital for any reason or develops other intercurrent problems. C

Risk assessment should be repeated again intrapartum or immediately postpartum. C

Any woman with four or more current risk factors shown in Appendix I and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH throughout the antenatal period and will usually require prophylactic LMWH for 6 weeks postnatally but a postnatal risk reassessment should be made. D

Any woman with three current risk factors shown in Appendix I and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH from 28 weeks and will usually require prophylactic LMWH for 6 weeks postnatally but a postnatal risk reassessment should be made. D

Any woman with two current risk factors shown in Appendix I and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH for at least 10 days postpartum. D

Women admitted to hospital when pregnant (including to the gynaecology ward with hyperemesis gravidarum or ovarian hyperstimulation syndrome) should usually be offered thromboprophylaxis with LMWH unless there is a specific contraindication such as risk of labour or active bleeding. D

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

The risk factors are listed in Table 1, Appendix II and Appendix III. 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 to be at increased risk because of the presence of one or more well-documented risk factors.[12,14–16,22–25,30–35]

Appendix II summarises the odds ratios (ORs) for VTE associated with each risk factor derived from various studies. 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, especially in the third trimester and postpartum.[9] Indeed, age greater than 35 years, obesity and caesarean section contribute most substantially to the rates of VTE because of their high and increasing prevalence.[36]

4.1.1 Previous VTE or thrombophilia

Two well-recognised significant risk factors for VTE in pregnancy, identifiable before pregnancy, are thrombophilia and previous VTE.[15,16] Heritable thrombophilia is found in 20–50% of pregnancy-related VTE.[37,38] A large retrospective study calculated an odds ratio of 24.8 (95% CI 17.1–36) for previous VTE.[32] Previous VTE and thrombophilia are discussed in more detail in sections 4.2 and 4.3 below.

Evidence level 2+

4.1.2 Obesity

Sixty percent of women who died from PE in the UK between 2003 and 2008 were obese (body mass index [BMI] 30 or higher)[3,4] compared with the 20% prevalence of obesity in women aged 16–44 in the Health Survey for England 2010.[39,40] Obesity is a risk factor for VTE in pregnancy[7,12,31–33] and the risk is higher with increasing obesity.[41] It is associated with a higher risk of PE (adjusted OR [aOR] 14.9, 95% CI 3.0–74.8) than of DVT (aOR 4.4, 95% CI 1.6–11.9).[33] Being overweight (BMI 25–29.9), too, is a weak risk factor for pregnancy-related VTE and is extremely common, with a prevalence within the childbearing population of almost 50%.[39]

Evidence level 2+

4.1.3 Age

Data for age are conflicting. Data from case–control studies (see Appendix II) have suggested a modest increased relative risk of less than two-fold for women aged over 35 years.[14,16,31] In a UK study using a large population-based cohort,[9] outside pregnancy, women in the oldest age band (35–44 years) had a 50% higher rate of VTE than women aged 25–34 years. The rate of VTE did not increase with age in the antepartum period; however, in the postpartum period women aged 35 and over had a 70% increase in risk compared to 25–34 year olds (corresponding to an excess absolute risk of 1.6 per 1000 person-years). A Korean study similarly found that increased age was not associated with VTE in pregnancy.[24] However, for simplicity we have retained age greater than 35 years as a risk factor antenatally and postpartum.

Evidence level 2+

4.1.4 Immobility and long-distance travel

For immobility and long-distance travel, data for pregnancy-related risk are limited and extrapolation from studies in nonpregnant patients is necessary.[34]

The NICE guideline on antenatal care[42] and the RCOG Scientific Impact Paper on air travel in pregnancy[43,44] state that long-haul air travel increases the risk of VTE; this guideline considers all long-distance (more than four hours) travel (not exclusively by air) to be a risk factor for VTE in pregnancy.

Evidence level 3

Some studies have demonstrated interaction between the effects of the risk factors listed in Table 1 and Appendix II. For example, in a Norwegian case–control study,[12] BMI greater than 25 and antepartum immobilisation (defined as strict bed rest 1 week or more prior to

Evidence level 2+

delivery) had a multiplicative effect on the risk for antepartum (aOR 62.3, 95% CI 11.5–337.7) and postpartum VTE (aOR 40.1, 95% CI 8.0–201.5).

Evidence level 2+

4.1.5 Admission to hospital

Admission to hospital during pregnancy is associated with an 18-fold increased risk of first VTE (adjusted incidence ratio 17.5, 95% CI 7.69–40.0) compared with time outside hospital and the risk remains increased after discharge, being six-fold higher in the 28 days after discharge. The risk is higher in the third trimester and in women over 35 years old. The risk of VTE during hospitalisation and after discharge are four-fold higher for admissions lasting less than 3 days but 12-fold higher if 3 days or longer.[45]

Evidence level 2+

4.1.6 Other risk factors

Examples of comorbidities which have been shown to be associated with an increase in the risk of VTE in pregnancy include active inflammatory bowel disease (IBD),[22,46] urinary tract infection,[22] systemic lupus erythematosus (SLE), heart disease,[16] pregnancy-induced hypertension/pre-eclampsia[15,24] and non-obstetric antenatal surgery.[47]

Recent data using a primary care database containing 376 154 pregnancies between 1995 and 2009 found that, in pregnancy, varicose veins, IBD, urinary tract infection and pre-existing diabetes were associated with an increased risk for VTE (absolute risks [ARs] ≥ 139/100 000 person-years; incidence rate ratios [IRRs] ≥ 1.8).[22] Analysing data from 1 475 301 Scottish maternity discharges, Kane et al.[15] found that risk factors for VTE included three or more previous pregnancies, obstetric haemorrhage, and pre-eclampsia.

Evidence level 2+

An individual assessment of thrombotic risk should 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. Early assessment is 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 2–3.2)[32] (see later for first trimester risk factors). This has implications for general practitioners, physicians and gynaecologists since many fatal antenatal VTE events occur in the first trimester[3,18–20] and 'booking' often does not occur until the end of the first trimester, after the stage at which thromboprophylaxis should have ideally begun.

Evidence level 3

Available evidence does not allow an accurate risk estimation of VTE to be determined from combinations of the different risk factors listed in Table 1 and Appendix II. Neither is this list exhaustive. There may be some conditions that increase the risk of VTE that are not listed. In general, active autoimmune and inflammatory conditions should be considered as risk factors. Multiple risk factors increase the risk of VTE.[12] The risk of antenatal VTE is highest in the third trimester[9,17,48] (see below under section 5).

Evidence level 2+

Therefore, as a pragmatic approach to women with risk factors (except previous VTE; see below and Appendix I and Appendix III), it is suggested that thromboprophylaxis with LMWH be considered antenatally if there are four or more risk factors, from 28 weeks if there are three risk factors and postnatally if there are only two risk factors.

Table 1. Risk factors for venous thromboembolism in pregnancy and the puerperium

See also Appendix I and Appendix II		
Pre-existing	Previous VTE	
	Thrombophilia	*Heritable* Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden Prothrombin gene mutation
		Acquired Antiphospholipid antibodies Persistent lupus anticoagulant and/or persistent moderate/high titre anticardiolipin antibodies and/or β_2-glycoprotein 1 antibodies
	Medical comorbidities e.g. cancer; heart failure; active SLE, inflammatory polyarthropathy or IBD; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease;[49] current intravenous drug user	
	Age > 35 years	
	Obesity (BMI ≥ 30 kg/m^2) either prepregnancy or in early pregnancy	
	Parity ≥ 3 (a woman becomes para 3 after her third delivery)	
	Smoking	
	Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes)	
	Paraplegia	
Obstetric risk factors	Multiple pregnancy Current pre-eclampsia	
	Caesarean section Prolonged labour (> 24 hours) Mid-cavity or rotational operative delivery Stillbirth Preterm birth Postpartum haemorrhage (> 1 litre/requiring transfusion)	
New onset/transient *These risk factors are potentially reversible and may develop at later stages in gestation than the initial risk assessment or may resolve and therefore what is important is an ongoing individual risk assessment*	Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilisation Bone fracture	
	Hyperemesis, dehydration	
	Ovarian hyperstimulation syndrome (first trimester only)	Assisted reproductive technology (ART), in vitro fertilisation (IVF)
	Admission or immobility (≥ 3 days' bed rest)	e.g. pelvic girdle pain restricting mobility
	Current systemic infection (requiring intravenous antibiotics or admission to hospital)	e.g. pneumonia, pyelonephritis, postpartum wound infection
	Long-distance travel (> 4 hours)	

4.2 Previous VTE

How should women with previous VTE be managed in pregnancy? (see Appendix IV)

4.2.1 Single previous VTE

Women with previous VTE should be offered prepregnancy counselling and a prospective management plan for thromboprophylaxis in pregnancy made. Those who become pregnant before receiving such counselling should be referred at the earliest opportunity in pregnancy to a clinician with expertise in thrombosis in pregnancy. ✓

Women with previous VTE (except those with a single previous VTE related to major surgery and no other risk factors) should be offered thromboprophylaxis with LMWH throughout the antenatal period. C

Women with previous VTE should have a careful history documented. 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 (greater than 6 weeks) therapeutic anticoagulation. C

Women with previous VTE have an increased risk of recurrence in pregnancy and postpartum[15,16,32] with reported recurrence rates of 2–11%.[27,50–53] 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).[50] The risk of recurrence appears to be constant over the whole period of pregnancy.[52,53] Evidence level 2+

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.

Evidence from prospective[51] and retrospective[53] studies 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. Outside pregnancy, the recurrence risk is lower in those with VTE complicating major surgery than in those provoked by other transient nonsurgical risk factors.[54] Evidence level 3

All women with prior VTE should receive postpartum prophylaxis[15,16,32] as this is the period of greatest risk. Evidence level 2+

4.2.2 Thrombophilia-associated VTE

Heritable thrombophilia

Women with previous VTE associated with antithrombin deficiency (who will often be on long-term oral anticoagulation) should be offered thromboprophylaxis with higher dose LMWH (either 50%, 75% or full treatment dose) (see Appendix IV) antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery. D

Management should be undertaken in collaboration with a haematologist with expertise in thrombosis in pregnancy and consideration given to antenatal anti-Xa monitoring and the potential for antithrombin replacement at initiation of labour or prior to caesarean section. ✓

If anti-Xa levels are measured, a test that does not use exogenous antithrombin should be used and 4-hour peak levels of 0.5–1.0 iu/ml aimed for. ✓

Other heritable thrombophilic defects are lower risk and can be managed with standard doses of thromboprophylaxis. ✓

The evidence on which to base guidance on the prevention of recurrent VTE during pregnancy in women with thrombophilia remains limited. However, since most women with previous VTE will be offered thromboprophylaxis anyway, the presence of a heritable thrombophilia generally makes little difference to management and, outside pregnancy, heritable thrombophilias are at best weak predictors of recurrent VTE.[55] Evidence level 4

Risks of recurrent VTE appear higher for those with a family history and deficiencies of the naturally occurring anticoagulants, particularly type 1 antithrombin deficiency (both activity and antigen reduced), than for those with heterozygous V Leiden or the prothrombin variant.[56–60] Patients with prior VTE and type 1 antithrombin deficiency typically have a family history of VTE and are often on long-term oral anticoagulant therapy. Heparins may not be as effective in antithrombin deficiency as their mode of action is antithrombin-dependent. Although evidence is limited,[61] they are likely to require intermediate or therapeutic dose Evidence level 3

LMWH throughout pregnancy and this should be continued for a minimum of 6 weeks postpartum or until converted back to long-term oral anticoagulation. 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. Antithrombin replacement around the time of delivery has been suggested[61,62] and might be considered in individual cases.

Evidence level 3

Acquired thrombophilia – see also section 4.4

Women with VTE associated with the antiphospholipid syndrome (APS) (who will often be on long-term oral anticoagulation) should be offered thromboprophylaxis with higher dose LMWH (either 50%, 75% or full treatment dose) (see Appendix IV) antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery.

D

Pregnant women with APS and prior VTE or arterial thromboses should be managed in collaboration with a haematologist and/or rheumatologist with expertise in this area.

✓

Women with antiphospholipid syndrome (APS) and previous VTE are at high risk of recurrent VTE in pregnancy. A Canadian study found that APS was associated with an adjusted odds ratio for PE of 12.9 (95% CI 4.4–38.0), and for DVT 5.1 (95% CI 1.8–14.3).[16] Many women with unprovoked or recurrent VTE diagnosed with APS will be on long-term oral anticoagulant therapy. There are no randomised controlled trial data to support recommendations for particular doses of LMWH in pregnancy. Case series support high prophylactic doses,[63,64] but some authors recommend either intermediate (75%) or therapeutic full anticoagulant doses of LMWH[26,65] and this may be appropriate for APS with recurrent previous VTE or arterial events.

Evidence level 3

4.2.3 Previous recurrent VTE

What extra advice is needed for women with previous recurrent VTE?

Advice regarding doses of LMWH in pregnancy should be sought from a clinician with expertise in haemostasis and pregnancy.

✓

Some women with previous recurrent VTE require higher doses of LMWH.

✓

Women on long-term warfarin or other oral anticoagulants should be counselled about the risks of these agents to the fetus (see section 8.6) and advised to stop their oral anticoagulant therapy and change to LMWH as soon as pregnancy is confirmed, ideally within 2 weeks of the missed period and before the sixth week of pregnancy.

✓

Women not on warfarin or other oral anticoagulants should be advised to start LMWH as soon as they have a positive pregnancy test.

✓

Individuals with recurrent VTE are at increased risk of further recurrence[66,67] and many will be on long-term oral anticoagulant therapy. Although data are lacking, it would be expected that they would have a high risk of recurrence in pregnancy.

Evidence level 4

4.2.4 Stratification of women with previous VTE

How should women with previous VTE be stratified to determine management in pregnancy?

Women with VTE associated with either antithrombin deficiency or APS or with recurrent VTE (who will often be on long-term oral anticoagulation) should be offered thromboprophylaxis with higher dose LMWH (either 50%, 75% or full treatment dose) (see Appendix IV) antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery. These women require specialist management by experts in haemostasis and pregnancy.

D

Women in whom the original VTE was unprovoked/idiopathic or related to estrogen (estrogen-containing contraception/pregnancy) or related to a transient risk factor other than major surgery or who have other risk factors should be offered thromboprophylaxis with LMWH throughout the antenatal period. D

In women in whom the original VTE was provoked by major surgery from which they have recovered and who have no other risk factors, thromboprophylaxis with LMWH can be withheld antenatally until 28 weeks provided 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. D

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 a prospective German study.[25]

Evidence level 2+

These data and recent international guidelines[5,26,68] support stratification of women with previous VTE into different risk categories requiring different levels of thromboprophylaxis (see Appendix I and Appendix IV).

4.2.5 Testing for thrombophilia in women with prior VTE

Which women with prior VTE require thrombophilia testing?

Prior to testing for thrombophilia, women should be counselled regarding the implications for themselves and family members of a positive or negative result. The results should be interpreted by clinicians with specific expertise in the area. ✓

Women with a family history of VTE and either antithrombin deficiency or where the specific thrombophilia has not been detected should be tested for antithrombin deficiency. ✓

Women with an unprovoked VTE should be tested for the presence of antiphospholipid antibodies. ✓

It is important to be aware of the effects of pregnancy on the results of thrombophilia tests. These are described in another guideline.[1] Thrombophilia testing should not be requested inappropriately and only if the finding of a thrombophilia would alter the proposed management. All women with prior VTE (see above) should be considered for thromboprophylaxis and hence testing for heritable thrombophilia is not routinely required.

Recent reviews of risk assessment for recurrent venous thrombosis recommend against testing routinely for thrombophilia.[69,70] However, if thrombophilia testing is performed following an episode of VTE (e.g. following an unprovoked VTE episode and with a family history), it is preferable that this is done before pregnancy, both because pregnancy itself affects the estimation of protein S in particular and because it allows decisions on thromboprophylaxis to be considered in advance of pregnancy.

Evidence level 4

Women with previous VTE should not be screened for thrombophilia in pregnancy unless the result will influence recommendations regarding thromboprophylaxis. Detection of antithrombin deficiency or APS will alter the dose of thromboprophylaxis offered in pregnancy and therefore screening for the former is indicated in women with previous VTE and a family history of VTE and either antithrombin deficiency or where the specific thrombophilia has not been detected and for APS in those with an unprovoked VTE. APS is not diagnosed unless lupus anticoagulant and/or anticardiolipin and/or β_2-glycoprotein 1 antibodies are positive on two occasions 12 weeks apart.[71]

4.3 Asymptomatic heritable thrombophilia

How should women with asymptomatic thrombophilia be treated? (see Appendix IV)

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. D

Women with asymptomatic antithrombin, protein C or S deficiency or those with more than one thrombophilic defect (including homozygous factor V Leiden, homozygous prothrombin gene mutation and compound heterozygotes) should be referred to a local expert and antenatal prophylaxis considered. They should be recommended for six weeks' postnatal prophylaxis even in the absence of additional risk factors. D

Heterozygosity for factor V Leiden or prothrombin gene mutation or antiphospholipid antibodies are considered as risk factors for thrombosis in asymptomatic women (see Appendix I). In the presence of three other risk factors such women may be considered for antenatal thromboprophylaxis, if there are two other risk factors thromboprophylaxis should be considered from 28 weeks and if there is one other risk factor postnatal thromboprophylaxis for 10 days should be considered. D

Women with no personal history or risk factors for VTE but who have a family history of an unprovoked or estrogen-provoked VTE in a first-degree relative when aged under 50 years should be considered for thrombophilia testing. This will be more informative if the relative has a known thrombophilia. D

The role of testing for heritable thrombophilias in women with a family history but no personal history of VTE remains controversial, as does the management in pregnancy and following childbirth of any thrombophilic tendency that is thereby identified.[26,68,72] Evidence level 4

Family history itself in the absence of an identifiable thrombophilic tendency is associated with an increased risk of VTE.[73–75] It may be reasonable to consider case finding in high-risk thrombophilic families and in asymptomatic pregnant women with a family history of VTE in a first-degree relative aged under 50 years where the episode has been unprovoked or provoked by pregnancy, combined oral contraceptive exposure or the presence of a minor risk factor.[55,68] Testing is more informative if the thrombophilic tendency in the proband is known. In contrast, thrombophilia testing is not required in pregnant women with other clinical risk factors indicating a need for thromboprophylaxis.

Recent prospective and retrospective family studies support the view that deficiencies of the naturally occurring anticoagulants (antithrombin, protein C and protein S) are of greater clinical significance than heterozygous carriage of factor V Leiden or the prothrombin gene mutation.[59,76] Recent studies have been consistent with a higher risk of pregnancy-related VTE in women who are antithrombin deficient or who are homozygous for factor V Leiden, the prothrombin gene mutation or are compound heterozygotes for factor V Leiden and the prothrombin gene mutation.[61,62,77,78] Evidence level 3

Women should be stratified according to both the level of risk associated with their thrombophilia (see Table 2) and the presence or absence of a family history or other risk factors.[79] The decision to offer antenatal thromboprophylaxis should be based on an estimate of the absolute risk of VTE during the pregnancy (and of the bleeding risk of prophylaxis) and this depends on the individual thrombophilic tendency, the details of the family history (number of affected relatives, age at which thrombosis developed, whether it was pregnancy- or estrogen-associated and the presence or absence of additional risk factors in the affected relatives),[80] the presence of additional clinical risk factors and the wishes of the individual woman.

When LMWH is used for thromboprophylaxis in pregnancy in women with asymptomatic thrombophilias, standard doses can be used, with the exception of antithrombin deficiency where intermediate doses may be required.[61]

Evidence level 4

Antenatal thromboprophylaxis is not routinely required in women with a low-risk thrombophilic tendency (heterozygosity of factor V Leiden or the prothrombin gene mutation) unless there are additional clinical risk factors including a strong family history particularly of pregnancy-related VTE.

Homozygosity for a thermolabile variant of the gene for methylenetetrahydrofolate 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 and it should be ignored.[81]

Evidence level 4

Table 2. Estimated absolute risk of pregnancy-associated VTE with different thrombophilic defects in women with one or more symptomatic first-degree relative

Thrombophilic defect	Pregnancy (%/pregnancy, 95% CI)	Antenatal (%/pregnancy, 95% CI)	Postpartum (%/pregnancy, 95% CI)
Antithrombin, protein C or protein S deficiency[82]	4.1 (1.7–8.3)	1.2 (0.3–4.2)	3.0 (1.3–6.7)
Antithrombin deficiency type 1 (range)[83–87]*	15–50	0–40	11–28
V Leiden heterozygous[82]	2.1 (0.7–4.9)	0.4 (0.1–2.4)	1.7 (0.7–4.3)
Prothrombin gene mutation heterozygous[82]	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 gene mutation (range)[88,89]	1.8–15.8	0–5	1–10

*These data are from a population-based study, not a family-based study

4.4 Antiphospholipid antibodies

How should women with antiphospholipid antibodies be treated?

Persistent antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin and/or β_2-glycoprotein 1 antibodies) in women without previous VTE should be considered as a risk factor for thrombosis (see Appendix I) such that if she has other risk factors she may be considered for antenatal or postnatal thromboprophylaxis as above.

C

Diagnostic criteria for APS, an acquired thrombophilic tendency, have been agreed.[71] Management recommendations in this guideline are limited to the prevention of VTE and not that of other adverse pregnancy outcomes.

The risk of VTE in women with obstetric APS characterised by recurrent miscarriage or fetal loss without prior VTE is unclear, but data from randomised trials suggest that the risk is low. Antenatal heparin therapy administered to improve pregnancy outcome in these trials was typically stopped between 35 weeks and delivery and no maternal VTE events were reported.[90,91] In a series of 33 women with primary APS, there were no thromboses in women with APS but without previous VTE given 3–5 days' thromboprophylaxis postpartum only.[63]

Evidence level 3

Antiphospholipid antibodies are sometimes detected because of a coagulation disturbance or connective tissue disorder in the absence of a history of thrombosis or obstetric problems. The risks of VTE in women with a persistent lupus anticoagulant and/or anticardiolipin and/or β_2-glycoprotein 1 antibodies without prior thrombosis or recurrent miscarriage or fetal loss (i.e. without APS)[92,93] are small but it is reasonable to consider this as a risk factor in the same

Evidence level 2+

way as V Leiden or the prothrombin variant and consider LMWH thromboprophylaxis if other risk factors are present.

Evidence level 2+

5. Timing of initiation of thromboprophylaxis

5.1 When should thromboprophylaxis be started?

Antenatal thromboprophylaxis for those with previous VTE should begin as early in pregnancy as practical.

B

Women without previous VTE and without particular first trimester risk factors or admission to hospital, but with four other risk factors, should be considered for antenatal prophylaxis throughout pregnancy.

C

Women without previous VTE and without particular first trimester risk factors or admission to hospital, but with three other risk factors, can start antenatal prophylaxis at 28 weeks of gestation.

C

Meta-analysis has shown that most VTE occurs antenatally with an equal distribution throughout gestation,[94] but two-thirds of antenatal fatal pulmonary VTE in 2003–2005 occurred in the first trimester.[3] Several studies have found that 40–50% of antenatal VTE occurred before 15 weeks of gestation.[18–20] These data emphasise the need for risk assessment prepregnancy and institution of prophylaxis if appropriate in early pregnancy.

Evidence level 1+

However, recent studies have demonstrated that the risk of antenatal VTE is highest in the third trimester. A Norwegian study[48] found that, of all VTEs associated with pregnancy and postpartum, 10% occurred in each of the first and second trimesters and 28% in the third trimester; a UK study found that the rate of VTE during the third trimester was six times higher than outside pregnancy (IRR 6.1, 95% CI 4.7–7.9). In contrast, both the first (IRR 1.6) and second (IRR 2.1) trimesters conferred little increase in risk.[9] In a Danish cohort study,[17] the absolute risk of VTE per 10 000 pregnancy-years increased from 4.1 (95% CI 3.2–5.2) during the first trimester to 59.0 (95% CI 46.1–76.4) by week 40.

Evidence level 2++

5.2 First trimester risk factors

What are the first trimester risk factors for VTE and how should they be managed?

Women admitted with hyperemesis should be considered for thromboprophylaxis with LMWH and can discontinue thromboprophylaxis when the hyperemesis resolves.

C

Women with ovarian hyperstimulation syndrome should be considered for thromboprophylaxis with LMWH in the first trimester.

C

Women with an IVF pregnancy and three other risk factors should be considered for thromboprophylaxis with LMWH starting in the first trimester.

C

Certain additional risk factors may complicate the first trimester (Table 1 and Appendix II), such as hyperemesis,[16,32] ovarian hyperstimulation syndrome and IVF.[12,24,95,96] In a Norwegian case–control study[12] assisted reproduction and multiple pregnancies had additive effects. Evidence from a Swedish study suggests that not only does IVF double the risk of VTE compared to natural conception, but the risk in the first trimester was four-fold higher and the risk of PE during the first trimester was seven times higher.[97] Women with ovarian hyperstimulation syndrome are particularly prone to VTE in the upper body.[95,96] At present it is unclear whether women undergoing surgical management of miscarriage and surgical termination of pregnancy are at increased risk of VTE.

Evidence level 2+

6. Thromboprophylaxis during labour and delivery, including the use of regional 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. ✓

Regional techniques should be avoided if possible until at least 12 hours after the previous prophylactic dose of LMWH. ✓

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

When a woman presents while on a therapeutic regimen of LMWH, regional techniques should be avoided if possible for at least 24 hours after the last dose of LMWH. ✓

Women receiving antenatal LMWH having an elective caesarean section should receive a thromboprophylactic dose of LMWH on the day prior to delivery and, on the day of delivery, any morning dose should be omitted and the operation performed that morning. ✓

The first thromboprophylactic dose of LMWH should be given as soon as possible after delivery provided there is no postpartum haemorrhage and regional analgesia has not been used. ✓

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 managed with anti-embolism stockings (AES), foot impulse devices or intermittent pneumatic compression devices. Unfractionated heparin (UFT) may also be considered. ✓

If a woman develops a haemorrhagic problem while on LMWH the treatment should be stopped and expert haematological advice sought. ✓

Thromboprophylaxis should be started or reinstituted as soon as the immediate risk of haemorrhage is reduced. ✓

The pregnancy-associated prothrombotic changes in the coagulation system are maximal immediately following delivery. However, in order to allow for use of regional analgesia or anaesthesia and minimise the risk of epidural haematoma,[98] women are advised to discontinue LMWH at the onset of labour or prior to planned delivery. Regional analgesia can be sited only after discussion with a senior anaesthetist, in keeping with local obstetric anaesthetic protocols.[1] It is important to discuss the implications of treatment with LMWH for regional analgesia with the woman prior to labour or caesarean section. This could be undertaken in an antenatal anaesthetic clinic.

Evidence level 4

If LMWH is routinely prescribed at 6 p.m., this allows for an elective caesarean section the next morning, removal of the epidural catheter before 2 p.m. and a first postnatal dose of LMWH at 6 p.m. 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 and facilitate a 24-hour window between the last dose of LMWH and regional analgesia.[99] 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.

Evidence level 4

7. Thromboprophylaxis after delivery

7.1 Assessment of risk

What are the risk factors for VTE after delivery?

All women with class 3 obesity (BMI greater than or equal to 40 kg/m²) should be considered for prophylactic LMWH in doses appropriate for their weight for 10 days after delivery. **D**

Women with two or more persisting risk factors listed in Table 1 should be considered for LMWH in prophylactic doses appropriate for their weight for 10 days after delivery. **B**

Risk factors for VTE after delivery are summarised in Table 1, Appendix I and Appendix II.

Nearly all women[7,8] dying from VTE following vaginal delivery in the 2003–2005 Confidential Enquiry were overweight or obese or over the age of 40 years. Evidence level 3

Additional risk factors relevant for postpartum thromboprophylaxis after delivery include prolonged labour, immobility, infection, haemorrhage and blood transfusion (see Appendix I, Table 1, Appendix II and Appendix III). Recent evidence supporting these obstetric complications as risk factors for VTE comes from several large population-based studies.[15,16,22] A Canadian population-based cohort study of around 7000 women with pregnancy-related hospitalisations for VTE from 1991–1992 to 2005–2006[16] identified major puerperal infection (aOR for PE 4.1, 95% CI 3.0–5.6; aOR for DVT 6.1, 95% CI 5.0–7.5) and blood transfusion (aOR for PE = 4.5, 95% CI 3.3–6.2; aOR for DVT 3.6, 95% CI 2.8–4.7) as risk factors for VTE. The study by Sultan et al.[22] found that the strongest risk factor was stillbirth (AR 2444/100 000 person-years; IRR 6.2) and the risk was also significantly increased with preterm birth (AR 854/100 000 person-years, 95% CI 649–1124; IRR 2.69, 95% CI 1.99–3.65). These have therefore been added as risk factors in this edition of the guideline. Evidence level 2++

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 at least 6 weeks postpartum regardless of the mode of delivery. **B**

Since the risk of VTE is higher postpartum[8,9,17,52,53,94] than antenatally, all women with previous VTE need to continue their LMWH prophylaxis for 6 weeks postpartum. Those with recurrent VTE on long-term oral anticoagulant therapy need to continue their LMWH until switched back to warfarin or another oral agent. Evidence level 2++

7.3 Asymptomatic thrombophilia

Which women with thrombophilia without previous VTE need postpartum thromboprophylaxis?

Women with thrombophilia without previous VTE 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. **C**

Women with a family history of VTE and an identified thrombophilia should be considered for 6 weeks' postnatal thromboprophylaxis. **D**

See section 4.3 above.

7.4 Caesarean section

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

All women who have had caesarean sections should be considered for thromboprophylaxis with LMWH for 10 days after delivery apart from those having an elective caesarean section who should be considered for thromboprophylaxis with LMWH for 10 days after delivery if they have any additional risk factors (see Appendix I and Table 1). C

Most women who suffer a VTE after caesarean section have other risk factors including twin pregnancy, obesity, severe pre-eclampsia, reoperation, immobilisation and placenta praevia.[100] Caesarean section is a risk factor for death from PE.[3,4,101,102] Women delivered by elective caesarean section have at least double the postpartum risk of VTE compared with vaginal birth.[21] The risk of postpartum VTE after an emergency caesarean section is twice that after an elective caesarean section and four times that after a vaginal delivery.[12,103] Studies exploring the risk of VTE comparing all caesarean sections with vaginal delivery have found relative risks of 2–6.7.[16,22,24,104] Evidence level 2+

7.5 For how long should thromboprophylaxis be continued after delivery?

Risk assessment should be 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. ✓

Thromboprophylaxis should be continued for 6 weeks in high-risk women and for 10 days in intermediate-risk women (see Appendix I). C

In women who have additional persistent (lasting more than 10 days postpartum) risk factors, such as prolonged admission, wound infection or surgery in the puerperium, thromboprophylaxis should be extended for up to 6 weeks or until the additional risk factor/s is/are no longer present. D

The prothrombotic changes of pregnancy do not revert completely to normal until several weeks after delivery. The time of greatest risk for VTE is the early puerperium and, although most VTE occurs antenatally, the risk per day is greatest in the weeks immediately after delivery.[8,9,17,52,53,94,105]

For women at high risk of postpartum VTE, the recommended duration of thromboprophylaxis is 6 weeks. Although laboratory evidence from thromboelastography (TEG) suggests correction of hypercoagulability by 4 weeks,[106] clinical data from observational studies in Sweden,[107] the USA,[8,105] Norway[48] and the Netherlands[10] suggest that the increased risk of VTE persists for 6 weeks postpartum, albeit less during weeks 5 and 6. The triennial UK confidential enquiries into maternal mortality between 1994 and 2005 suggest that the increased risk of fatal PE is still present in weeks 5 and 6 (a total of 15 deaths compared to 21 in weeks 3 and 4) and all six women who died from PE after caesarean section (2006–2008) died between 2 and 6 weeks after delivery, whereas fatal events after that are very rare.[3,4,101,102,108] Evidence level 2+

There is little evidence to support recommendations regarding duration of postpartum thromboprophylaxis in women at intermediate risk of VTE. TEG data from 71 women post normal delivery showed that all parameters remained abnormal at 1 week postpartum and the authors suggested that 3–5 days' thromboprophylaxis may be insufficient.[106] The numbers of VTEs after caesarean sections were similar in weeks 1, 2 and 3 in one study.[12] This suggests that caesarean section continues to be a significant risk factor for fatal PE and therefore it is important to extend the duration of prophylaxis in the presence of additional persistent (lasting more than 10 days postpartum) risk factors, such as prolonged admission (more than or equal to 3 days) or wound infection, for up to 6 weeks or until the additional risk factor/s is/are no longer present (see Appendix I).

8. Which agents should be used for thromboprophylaxis?

8.1 Low-molecular-weight heparin (LMWH)

LMWHs are the agents of choice for antenatal and postnatal thromboprophylaxis. A

Doses of LMWH are based on weight. For thromboprophylaxis the booking or most recent weight can be used to guide dosing. B

It is only necessary to monitor the platelet count if the woman has had prior exposure to unfractionated heparin (UFH). B

Monitoring of anti-Xa levels is not required when LMWH is used for thromboprophylaxis. D

Doses of LMWH should be reduced in women with renal impairment. C

LMWH is safe in breastfeeding. A

LMWHs are as effective as and safer than unfractionated heparin (UFH) when used to prevent VTE in pregnancy.[21,109-112] The risk of heparin-induced thrombocytopenia (HIT) is substantially lower with LMWH.[109,110,113] Guidelines recommend against monitoring platelet count where LMWH is used and where there is no previous exposure to UFH.[1,114] In a systematic review of 2777 pregnancies there were no cases of HIT.[109] Prolonged UFH use during pregnancy may result in osteoporosis and fractures,[115] but this risk is very low with LMWH.[109,116–119] A systematic review of LMWH[109] showed the incidence of osteoporotic fractures was 0.04% (95% CI 0.01–0.2) and that of allergic skin reactions was 1.8% (95% CI 1.34–2.37). More recent studies provide further evidence for the safety and efficacy of dalteparin,[120] enoxaparin[120] and tinzaparin[121] for prophylaxis in pregnancy. In the study of tinzaparin,[121] three women developed bone fractures, but all had prior risk factors for osteoporosis (such as low BMI, previous osteoporosis, smoking, long-term steroid and/or other UFH/LMWH use). Evidence level 1++

Evidence for an increased risk of bleeding is more controversial. A systematic review found significant bleeding, usually related primarily to obstetric causes, occurred in 1.98% (95% CI 1.5–2.57).[109] 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.[109] There is an increased risk of wound haematoma following caesarean section with LMWH of around 2%.[6,109,122] Some have found an increased risk of postpartum haemorrhage[6] but this is not supported by other studies.[123] A Cochrane review[29] of UFH or LMWH for thromboprophylaxis in women undergoing caesarean section found more bleeding or bruising episodes compared to women not receiving heparin (risk ratio 5.15).

Table 3 gives suggested prophylactic and therapeutic subcutaneous doses of LMWH in pregnancy and postpartum. There are no data to guide appropriate doses of LMWH for obese pregnant or puerperal women. The doses in Table 3 are only suggestions and doses for obese women are not evidence-based. In the UKOSS study,[7] some overweight and obese women suffered a PE while receiving doses of LMWH prophylaxis appropriate for women of weights 50–90 kg.

Anti-Xa levels provide only a rough guide of the concentration of heparin present and provide little or no evidence on the efficacy in relation to prevention of thrombosis.[124] Evidence level 3

Lower doses of LMWH should be employed if the creatinine clearance is less than 30 ml/minute (enoxaparin and dalteparin) or less than 20 ml/minute with tinzaparin.[124] A creatinine clearance of 30 ml/minute equates to a serum creatinine of about 200 µmol/l for a 30-year-old woman weighing 70 kg. Evidence level 2+

Table 3. Suggested thromboprophylactic doses for antenatal and postnatal LMWH

Weight	Enoxaparin	Dalteparin	Tinzaparin (75 u/kg/day)
< 50 kg	20 mg daily	2500 units daily	3500 units daily
50–90 kg	40 mg daily	5000 units daily	4500 units daily
91–130 kg	60 mg daily*	7500 units daily	7000 units daily*
131–170 kg	80 mg daily*	10 000 units daily	9000 units daily*
> 170 kg	0.6 mg/kg/day*	75 u/kg/day	75 u/kg/day*
High prophylactic dose for women weighing 50–90 kg	40 mg 12 hourly	5000 units 12 hourly	4500 units 12 hourly

*may be given in 2 divided doses

LMWH is safe and easy to use postpartum and has the advantage of not requiring monitoring. For those women receiving LMWH antenatally (and therefore for 6 weeks postpartum) or for those requiring 10 days' postpartum thromboprophylaxis, it is the agent of choice. Experience of LMWH in the puerperium reports no problems during breastfeeding.[109]

Evidence level 1+

8.2 Unfractionated heparin

In women at very high risk of thrombosis (see Appendix IV), UFH may be used peripartum in preference to LMWH where there is an increased risk of haemorrhage or where regional anaesthetic techniques may be required.

D

If UFH is used after caesarean section (or other surgery), the platelet count should be monitored every 2–3 days from days 4–14 or until heparin is stopped.

D

The benefits of UFH are that it has a shorter half-life than LMWH and there is more complete reversal of its activity by protamine sulfate.[125] 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 doses of anticoagulants, a prophylactic dose of 5000 iu subcutaneously of UFH could be used and repeated every 12 hours until LMWH can be resumed after delivery. The required interval between a prophylactic dose of UFH and regional analgesia or anaesthesia is less (4 hours) than with LMWH (12 hours)[99] and there is less concern regarding neuraxial haematomas with UFH.[98] Any exposure to UFH is associated with an increased risk of HIT.[126]

Evidence level 3

8.3 Danaparoid

Potential use of danaparoid should be in conjunction with a consultant haematologist with expertise in haemostasis and pregnancy.

✓

Danaparoid is a heparinoid that is mostly used in patients intolerant of heparin, either because of HIT or a skin allergy to heparins. Experience in the use of this agent in a total of 91 pregnancies has been reviewed.[127,128] There were six maternal bleeding events, two of which were fatal due to placental problems (praevia and abruption). Additionally there were seven early miscarriages and one neonatal death following emergency caesarean section at 28 weeks for fetal growth restriction. There were no adverse fetal outcomes attributed to danaparoid. Danaparoid seems reasonable to use in pregnancy when there is a requirement for anticoagulant prophylaxis or treatment and heparins cannot be used. The half-life of danaparoid is long (24 hours) and regional anaesthesia should be avoided in women receiving it for thromboprophylaxis.[99] Although direct evidence is limited, it seems likely that breastfeeding would be safe while on danaparoid since little if any appears in breast milk[129] and oral absorption is unlikely.

Evidence level 4

8.4 *Fondaparinux*

Fondaparinux should be reserved for women intolerant of heparin compounds. D

Fondaparinux use in pregnancy should be in conjunction with a consultant haematologist with expertise in haemostasis and pregnancy. ✓

Fondaparinux is a synthetic pentasaccharide that acts through 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 with no reported hypersensitivity reactions or adverse effects on the fetus.[130–137] No placental passage of fondaparinux was found in a human cotyledon model[138] but anti-factor Xa activity about 10% of that in maternal plasma was found in the umbilical cord plasma in newborns of four of five mothers being treated with fondaparinux.[139] No adverse effects were observed in the newborns. It does not seem necessary to alter the dose in pregnancy.[131] It is unknown whether fondaparinux is excreted in breast milk but oral absorption seems unlikely. The half-life of fondaparinux is long (18 hours) and 36–42 hours should pass following the previous dose before it becomes acceptable to consider regional anaesthesia.[99] Thus, although experience is limited, it seems likely that fondaparinux would be a reasonable alternative when there is a need for anticoagulant prophylaxis or treatment in pregnancy and heparins cannot be used.

Evidence level 4

8.5 *Low-dose aspirin*

Aspirin is not recommended for thromboprophylaxis in obstetric patients. D

There are no controlled trials on the use of aspirin for thromboprophylaxis in pregnancy. Conclusions about its efficacy have been extrapolated from trials in the nonpregnant population. In the NICE guideline reviewing VTE prevention in hospitalised patients,[5] 300 mg or more of aspirin daily reduced the risk of postoperative DVT in patients undergoing a variety of surgical procedures. However, the benefit was modest in comparison to heparin and aspirin was not recommended for postoperative thromboprophylaxis. The Women's Health Study[140] found low-dose aspirin no better than placebo for long-term primary prevention of VTE in older women. In contrast, two recent trials outside pregnancy suggested that after completion of treatment with warfarin, low-dose aspirin conferred a modest reduction compared to placebo in the risk of recurrent VTE in patients with a first unprovoked event.[141,142] Overall, any benefit of aspirin in VTE prevention appears uncertain and significantly less than that of LMWH.

Evidence level 3

8.6 *Warfarin*

Warfarin use in pregnancy is restricted to the few situations where heparin is considered unsuitable, e.g. some women with mechanical heart valves. B

Women receiving long-term anticoagulation with warfarin can be converted from LMWH to warfarin postpartum when the risk of haemorrhage is reduced, usually 5–7 days after delivery. ✓

Warfarin is safe in breastfeeding. ✓

Warfarin crosses the placenta leading to an increased risk of congenital abnormalities including a characteristic warfarin embryopathy (hypoplasia of nasal bridge, congenital heart defects, ventriculomegaly, agenesis of the corpus callosum, stippled epiphyses) in approximately 5% of fetuses exposed between 6 and 12 weeks of gestation.[143–150] There is evidence that this incidence is dose-dependent with a higher incidence in women taking greater than 5 mg/day.[147–149] Other reported complications associated with warfarin therapy during pregnancy

Evidence level 2++

include an increase in the risk of spontaneous miscarriage,[146–148,151,152] stillbirth,[145,147,148,151] neurological problems in the baby[153,154] and fetal and maternal haemorrhage.[148,149]

Evidence level 2++

Warfarin can be safely used following delivery and in breastfeeding mothers, although it requires close monitoring and visits to an anticoagulant clinic and carries an increased risk of postpartum haemorrhage and perineal haematoma compared with LMWH. It is not appropriate for those women requiring only 10 days' 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.

8.7 Dextran

Dextran should be avoided antenatally and intrapartum because of the risk of anaphylactoid reaction. D

Although dextran may reduce the risk of postoperative DVT outside pregnancy, the evidence is weak, it is less effective than LMWH and it appears to increase the risk of bleeding.[155] Anaphylaxis to dextran has been associated with uterine hypertonus, fetal distress, fetal neurological abnormalities and death.[156,157]

Evidence level 3

8.8 Oral thrombin and Xa inhibitors

Non-vitamin K antagonist oral anticoagulants (NOACs) should be avoided in pregnant women. ✓

Use of NOACs is not currently recommended in women who are breastfeeding. ✓

Non-vitamin K antagonist oral anticoagulants (NOACs, previously known as new/novel oral anticoagulants) such as dabigatran, rivaroxaban and apixaban work through direct inhibition of thrombin or factor Xa. They are not licensed for use in pregnancy where there is no experience in their use.

9. Anti-embolism stockings

The use of properly applied anti-embolism stockings (AES) of appropriate size and providing graduated compression with a calf pressure of 14–15 mmHg is recommended in pregnancy and the puerperium for women who are hospitalised and have a contraindication to LMWH. These include women who are hospitalised post-caesarean section (combined with LMWH) and considered to be at particularly high risk of VTE (e.g. previous VTE, more than four risk factors antenatally or more than two risk factors postnatally) and women travelling long distance for more than 4 hours. D

There are no trials to support the use of AES in pregnancy and the puerperium and recommendations are largely derived from extrapolation from studies using AES in the hospitalised nonpregnant population[158,159] Small studies have shown that AES significantly improve venous emptying in pregnant women[160] and increase the blood flow while decreasing the lumen diameter of the superficial femoral[161] and common femoral[162] veins in late pregnancy and early postpartum patients.

Evidence level 3

Evidence from nonpregnant patients and other guidelines support the use of AES for patients at high risk of bleeding (unable to receive pharmacological thromboprophylaxis), or where there is a contraindication to anticoagulant thromboprophylaxis,[26,163] or as an adjunct to anticoagulant thromboprophylaxis in surgical patients.

There are few data regarding the most efficacious length of AES to use in pregnancy and advice in the nonpregnant population is contradictory.[26,164–167] More DVTs in pregnant women are iliofemoral compared to the nonpregnant population where calf vein DVTs are more

Evidence level 4

common. Studies of AES in pregnancy have only concerned full-length stockings.[162] However, in the obstetric population, there is the added problem of full-length stockings becoming bloodstained. Therefore, on balance, properly applied full-length AES are advocated for pregnant women but knee-length AES should be considered if (as is often the case) full-length AES are ill-fitting or compliance is poor.

Evidence level 4

The role of graduated compression stockings providing greater than 23 mmHg support at the ankle for the prevention and/or treatment of the post-thrombotic syndrome rather than VTE prevention is discussed in Green-top Guideline No. 37b.

10. Contraindications to LMWH

Which women should not be given thromboprophylaxis with LMWH?

LMWH should be avoided, discontinued or postponed in women at risk of bleeding after careful consideration of the balance of risks of bleeding and thrombosis. D

Women with previous or current allergic reactions to LMWH should be offered an alternative preparation or alternative form of prophylaxis. D

Further advice on the management of a woman with both VTE risk factors and bleeding risk factors or LMWH allergy may be sought from a haematologist with expertise in the management of thrombosis and bleeding disorders in pregnancy. ✓

Risk factors for bleeding are summarised in Appendix III. LMWHs can increase bleeding if it occurs and therefore should be delayed in women with active bleeding, coagulopathy or low platelets (fewer than 75 x 10^9/l). LMWH is contraindicated in women with HIT. Women who develop allergic reactions to one LMWH will often be allergic to other LMWHs.[5,26,109,115]

Evidence level 4

11. Risk scoring methodologies

A formal VTE risk assessment with numerical scoring for all pregnant and postpartum women is recommended (see Appendix III). D

Compared with not using a formal assessment system, Shoenbeck et al. found there was a significant increase in the rate of risk assessment, earlier treatment and greater consistency in clinical decision making with the use of a numerical scoring system. This approach maintains a highly individualised assessment of VTE risk while achieving consistency in management.[168]

Evidence level 3

12. Recommendations for future research

- Doses of LMWH required in obese pregnant and puerperal women.
- At present it is unclear whether women undergoing surgical management of miscarriage and surgical termination of pregnancy are at increased risk of VTE.
- How do risk factors for VTE interact in the antenatal and postpartum periods?
- How do we reduce/avoid the prevalence of risk factors for VTE?
- Should thromboprophylaxis vary with different heritable thrombophilias?

13. Auditable topics

- Correct risk assessment at booking, on admission to antenatal ward, after delivery and at discharge (100%).
- Correct dose of LMWH (based on weight) prescribed antenatally and postpartum (100%).

- LMWH prescribed and taken for 10 days postpartum in all women with class 3 obesity (BMI greater than or equal to 40) (100%).
- LMWH prescribed and given for 6 weeks postpartum in all women with previous VTE (100%).

14. Useful links and support groups

- Royal College of Obstetricians and Gynaecologists. *Information for you: Reducing the risk of venous thrombosis in pregnancy and after birth*. London: RCOG; 2011 [https://www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/pregnancy/pi-reducing-the-risk-of-venous-thrombosis-in-pregnancy-and-after-birth.pdf].

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Appendix I: Obstetric thromboprophylaxis risk assessment and management

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

Any previous VTE except a single event related to major surgery

→ **HIGH RISK**
Requires antenatal prophylaxis with LMWH
Refer to trust-nominated thrombosis in pregnancy expert/team

Hospital admission
Single previous VTE related to major surgery
High-risk thrombophilia + no VTE
Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU
Any surgical procedure e.g. appendicectomy
OHSS (first trimester only)

→ **INTERMEDIATE RISK**
Consider antenatal prophylaxis with LMWH

Obesity (BMI > 30 kg/m²)
Age > 35
Parity ≥ 3
Smoker
Gross varicose veins
Current pre-eclampsia
Immobility, e.g. paraplegia, PGP
Family history of unprovoked or estrogen-provoked VTE in first-degree relative
Low-risk thrombophilia
Multiple pregnancy
IVF/ART

→ **Four or more risk factors: prophylaxis from first trimester**

Three risk factors: prophylaxis from 28 weeks

Fewer than three risk factors →

Transient risk factors:
Dehydration/hyperemesis; current systemic infection; long-distance travel

→ **LOWER RISK**
Mobilisation and avoidance of dehydration

APL = antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, β_2-glycoprotein 1 antibodies); ART = assisted reproductive technology; BMI based on booking weight; DM = diabetes mellitus; FHx = family history; gross varicose veins = symptomatic, above knee or associated with phlebitis/oedema/skin changes; high-risk thrombophilia = antithrombin deficiency, protein C or S deficiency, compound or homozygous for low-risk thrombophilias; IBD = inflammatory bowel disease; immobility = ≥ 3 days; IVDU = intravenous drug user; IVF = in vitro fertilisation; LMWH = low-molecular-weight heparin; long-distance travel = > 4 hours; low-risk thrombophilia = heterozygous for factor V Leiden or prothrombin G20210A mutations; OHSS = ovarian hyperstimulation syndrome; PGP = pelvic girdle pain with reduced mobility; PPH = postpartum haemorrhage; thrombophilia = inherited or acquired; VTE = venous thromboembolism.

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

Any previous VTE
Anyone requiring antenatal LMWH
High-risk thrombophilia
Low-risk thrombophilia + FHx

→ **HIGH RISK**
At least 6 weeks' postnatal prophylactic LMWH

Caesarean section in labour
BMI ≥ 40 kg/m²
Readmission or prolonged admission (≥ 3 days) in the puerperium
Any surgical procedure in the puerperium except immediate repair of the perineum
Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy; nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU

→ **INTERMEDIATE RISK**
At least 10 days' postnatal prophylactic LMWH

NB If persisting or > 3 risk factors consider extending thromboprophylaxis with LMWH

Age > 35 years
Obesity (BMI ≥ 30 kg/m²)
Parity ≥ 3
Smoker
Elective caesarean section
Family history of VTE
Low-risk thrombophilia
Gross varicose veins
Current systemic infection
Immobility, e.g. paraplegia, PGP, long-distance travel
Current pre-eclampsia
Multiple pregnancy
Preterm delivery in this pregnancy (< 37+0 weeks)
Stillbirth in this pregnancy
Mid-cavity rotational or operative delivery
Prolonged labour (> 24 hours)
PPH > 1 litre or blood transfusion

Two or more risk factors →

Fewer than two risk factors →

→ **LOWER RISK**
Early mobilisation and avoidance of dehydration

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 u/kg/day dalteparin/ 75 u/kg/day tinzaparin

Appendix II: Adjusted odds ratios for risk factors for VTE

Risk factor	aOR	95% CI	Comment
Previous VTE[15,32]	24.8	17.1–36	
Age > 35[14,16,31]	1.3[14]	1.0–1.7	n = 603
	1.4[31]	1.0–2.0	pn = 256
	1.2[16]	1.1–1.4	DVT
Obesity	2.65[7]	1.09–6.45	n = 143 an PE
BMI >/≥ 30[7,16,31–33]	5.3[33]	2.1–13.5	n = 129
	4.4[32]	3.4–5.7	
	1.7[31]	1.1–2.6	pn = 256
	1.8[16]	1.2–2.6	DVT
	2.7[16]	1.6–4.4	PE
BMI >/≥ 25[12,31]	1.8[12]	1.3–2.4	an n = 268
	2.4[12]	1.7–3.3	pn n = 291
	1.7[31]	1.2–2.4	pn = 256
Weight 90–120 kg[41]	1.93	1.10–3.39	an
Weight > 120 kg	4.32	1.26–14.84	
Weight gain in pregnancy > 21 kg[12] (compared to 7–21 kg)	1.6	1.1–2.6	pn n = 291
Parity 1[7]	4.03	1.6–9.84	n = 143 an PE
2[14]	1.5	1.1–1.9	n = 603
≥3[14]	2.4	1.8–3.1	n = 603
Smoking	2.1[12]	1.3–3.4	an n = 268
10–30/day[12,14,35]	3.4[12]	2.0–5.5	pn n = 291
	1.4[14]	1.1–1.9	n = 603
	2.5[35]	1.3–4.7	n = 90
Current smoker[33]	2.7[33]	1.5–4.9	n = 129
Sickle cell[32,49]	6.7[32]	4.4–10.1	
	2.5[49]	1.5–4.1	DVT
	1.7[49]	0.9–3.1	PE
Heart disease[16,31,32]	7.1[32]	6.2–8.3	
	5.4[31]	2.6–11.3	pn n = 256
	3.2[16]	2.2–4.6	DVT
	43.4[16]	35.0–53.9	PE
Systemic lupus erythematosus[16,32]	8.7[32]	5.8–13	
	2.3[16]	1.1–4.8	DVT
	3.9[16]	1.9–7.8	PE
Anaemia[16,32]	2.6[32]	2.2–2.9	
	1.6[16]	1.4–1.9	DVT
	1.7[16]	1.3–2.2	PE
Varicose veins[35]	2.4	1.04–5.4	
Immobility[12]	7.7	3.2–19	an
	10.8	4.0–28.8	pn
Pre-eclampsia[12,14]	2.9[14]	2.1–3.9	
	3.1[12]	1.8–5.3	pn
Pre-eclampsia plus FGR[12]	5.8[12]	2.1–16	
Hyperemesis[16,32]	2.5[32]	2–3.2	
	4.4[16]	2.4–8.4	DVT

Assisted reproductive technology[12,24,97]	4.3[12]	2.0–9.4	an
	4.2[24]	1.5–11	
	1.8[97]	1.4–2.2	
Twins[12,14]	2.6[12]	1.1–6.2	an
	1.8[14]	1.1–3.0	n = 603
Multiple pregnancy[16,31]	4.2[31]	1.8–9.7	an n = 109
	1.7[16]	1.3–2.2	DVT
Preterm delivery < 37 weeks[22,31]	2.4[31]	1.6–3.5	pn n = 256
	2.69[22]	1.99–3.65	
Stillbirth (IRR)[22]	6.24	2.77–14.1	
Antepartum haemorrhage[32]	2.3	1.8–2.8	
Emergency caesarean section[14]	2.7	1.8–4.1	
Any caesarean section[14,16,24,31,32]	3.6[14]	3.0–4.3	
	2.1[32]	1.8–2.4	
	2.0[31]	1.5–2.7	pn n = 256
	1.8[16]	1.6–2.0	DVT
	2.9[16]	2.4–3.5	PE
	3.4[24]	1.3–9.0	
PPH > 1 litre[12]	4.1	2.3–7.3	
PPH unspecified[16]	1.2[16]	1.0–1.4	DVT
	1.3[16]	1.0–1.7	PE
PPH + surgery[12]	12	3.9–36.9	
Obstetric haemorrhage[35]	9	1.1–71	
Postpartum infection[16,32]	4.1[32]	2.9–5.7	
	6.1[16]	5.0–7.5	DVT
	4.1[16]	3.0–5.6	PE
Postpartum infection + caesarean section[12]	6.2	2.4–16.2	
Transfusion[16,32]	7.6[32]	6.2–9.4	
	3.6[16]	2.8–4.7	DVT
	4.5[16]	3.3–6.2	PE

Abbreviations: an antenatal; aOR adjusted odds ratio; CI confidence interval; DVT deep venous thrombosis; FGR fetal growth restriction; IRR incidence rate ratio; n number of cases in case–control study; PE pulmonary embolism; pn postnatal; PPH postpartum haemorrhage; VTE venous thromboembolism.

Appendix III: Risk assessment for venous thromboembolism (VTE)

- If total score ≥ 4 antenatally, consider thromboprophylaxis from the first trimester.
- If total score 3 antenatally, consider thromboprophylaxis from 28 weeks.
- If total score ≥ 2 postnatally, consider thromboprophylaxis for at least 10 days.
- If admitted to hospital antenatally consider thromboprophylaxis.
- If prolonged admission (≥ 3 days) or readmission to hospital within the puerperium consider thromboprophylaxis.

For patients with an identified bleeding risk, the balance of risks of bleeding and thrombosis should be discussed in consultation with a haematologist with expertise in thrombosis and bleeding in pregnancy.

Risk factors for VTE

Pre-existing risk factors	Tick	Score
Previous VTE (except a single event related to major surgery)		4
Previous VTE provoked by major surgery		3
Known high-risk thrombophilia		3
Medical comorbidities e.g. cancer, heart failure; active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user		3
Family history of unprovoked or estrogen-related VTE in first-degree relative		1
Known low-risk thrombophilia (no VTE)		1[a]
Age (> 35 years)		1
Obesity		1 or 2[b]
Parity ≥ 3		1
Smoker		1
Gross varicose veins		1
Obstetric risk factors		
Pre-eclampsia in current pregnancy		1
ART/IVF (antenatal only)		1
Multiple pregnancy		1
Caesarean section in labour		2
Elective caesarean section		1
Mid-cavity or rotational operative delivery		1
Prolonged labour (> 24 hours)		1
PPH (> 1 litre or transfusion)		1
Preterm birth < 37^{+0} weeks in current pregnancy		1
Stillbirth in current pregnancy		1
Transient risk factors		
Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilisation		3
Hyperemesis		3
OHSS (first trimester only)		4
Current systemic infection		1
Immobility, dehydration		1
TOTAL		

Abbreviations: ART assisted reproductive technology; IVF in vitro fertilisation; OHSS ovarian hyperstimulation syndrome; VTE venous thromboembolism.

[a] If the known low-risk thrombophilia is in a woman with a family history of VTE in a first-degree relative postpartum thromboprophylaxis should be continued for 6 weeks.

[b] BMI ≥ 30 = 1; BMI ≥ 40 = 2

Contraindications/cautions to LMWH use	
Known bleeding disorder (e.g. haemophilia, 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 < 75×10^9/l)	
Acute stroke in previous 4 weeks (haemorrhagic or ischaemic)	
Severe renal disease (glomerular filtration rate [GFR] < 30 ml/minute/1.73m^2)	
Severe liver disease (prothrombin time above normal range or known varices)	
Uncontrolled hypertension (blood pressure > 200 mmHg systolic or > 120 mmHg diastolic)	

Clinical and laboratory thresholds are taken from the Department of Health's guidelines based on evidence from the nonpregnant population.[5]

Appendix IV: Summary of guideline for thromboprophylaxis in women with previous VTE and/or thrombophilia (also see Appendix I)

Very high risk	Previous VTE on long-term oral anticoagulant therapy	Recommend antenatal high-dose LMWH and at least 6 weeks' postnatal LMWH or until switched back to oral anticoagulant therapy
	Antithrombin deficiency Antiphospholipid syndrome with previous VTE	*These women require specialist management by experts in haemostasis and pregnancy*
High risk	Any previous VTE (except a single VTE related to major surgery)	Recommend antenatal and 6 weeks' postnatal prophylactic LMWH
Intermediate risk	Asymptomatic high-risk thrombophilia homozygous factor V Leiden/compound heterozygote Protein C or S deficiency	Refer to local expert Consider antenatal LMWH Recommend postnatal prophylactic LMWH for 6 weeks
	Single previous VTE associated with major surgery without thrombophilia, family history or other risk factors	Consider antenatal LMWH (but not routinely recommended) Recommend LMWH from 28 weeks of gestation and 6 weeks' postnatal prophylactic LMWH
Low risk	Asymptomatic low-risk thrombophilia (prothrombin gene mutation or factor V Leiden)	Consider as a risk factor and score appropriately (see Appendix III) Recommend 10 days' if other risk factor postpartum (or 6 weeks' if significant family history) postnatal prophylactic LMWH

Appendix V: Explanation of guidelines and evidence levels

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

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

Classification of evidence levels

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

Grades of recommendations

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

Good practice point

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

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Conflicts of interest:
Professor Nelson-Piercy is a trustee for APEC, Action on Pre-eclampsia, and a patron of the Lauren Page Trust, supporting the work of obstetric physicians. She is co-Editor-in-Chief of *Obstetric Medicine: The Medicine of Pregnancy*, a quarterly journal published by SAGE, and receives an editorial stipend for this work. Professor Nelson-Piercy has received commercial support for attending meetings/conferences from LEO Pharma and Sanofi-Aventis (manufacturers of low-molecular-weight heparin).

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Dr Mackillop has received fees for reports as an expert witness and small honoraria for lectures.

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

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