14.7 Thrombosis in pregnancy 2606

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ESSENTIALS Pregnancy and the puerperium are associated with a 10-fold increase in the risk of venous thromboembolism, comprising deep vein throm- bosis and pulmonary embolism, compared to the nonpregnant state. Pulmonary embolism has been the leading direct cause of maternal mortality in most of the United Kingdom’s triennial Confidential Enquiries into Maternal Deaths over the past 30 years, attesting to the importance of prevention and prompt diagnosis and treatment of venous thromboembolism during pregnancy and following delivery. The diagnosis of venous thromboembolism is challenging in preg- nancy because it can be difficult to distinguish features of venous thromboembolism, such as leg swelling and breathlessness, from those of normal pregnancy, and there are no validated clinical scoring sys- tems. It is therefore important to have a high index of suspicion and initiate treatment with low-molecular-weight heparin when the diag- nosis is considered, and to objectively confirm or exclude the diagnosis as soon as possible. Compression duplex ultrasonography is required when deep vein thrombosis is suspected. In those with suspected pul- monary embolism and no features of deep vein thrombosis, either ven- tilation/perfusion lung scanning (provided a chest X-ray is normal) or computerized tomography pulmonary angiography can be used. Treatment with low-molecular-weight heparin should continue for a minimum of three months and until at least six weeks post-partum. Management around the time of labour and delivery requires close collaboration between obstetricians and anaesthetists, and is particu- larly important when regional anaesthesia is used. Warfarin and direct oral anticoagulants should not be used in pregnancy, but warfarin and heparin can be used in women who are breastfeeding. All women should undergo risk assessment for venous thrombo- embolism in early pregnancy, at the time of hospital admission or change in clinical condition, and after delivery. Women with identi- fied risk factors should be considered for thromboprophylaxis with low-molecular-weight heparin in line with national guidelines. Introduction Pregnancy and the puerperium are associated with a 10-fold in- crease in the risk of venous thromboembolism, comprising deep vein thrombosis and pulmonary embolism, compared to the non- pregnant state. Pulmonary embolism has been the leading direct cause of maternal mortality in most of the United Kingdom’s tri- ennial Confidential Enquiries into Maternal Deaths over the past 30 years (Table 14.7.1). The prevention, diagnosis, and treatment of venous thromboembolism are therefore

important concerns in obstetric practice. This is reflected in a series of guidelines on venous thromboembolism prevention and management from the Royal College of Obstetricians and Gynaecologists. Overall there has been a welcome reduction in the annual incidence of fatal pulmonary embolism in pregnancy and the puerperium in recent years despite an increase in the prevalence of common risk factors for venous thromboembolism such as increasing maternal age and ma- ternal comorbidities, body mass index, and caesarean section. This suggests that changes in obstetric care have been beneficial. Likely 14.7 Thrombosis in pregnancy Peter K. MacCallum and Louise Bowles Table 14.7.1 Direct deaths from thrombosis and thromboembolism and rates per 100 000 maternities (United Kingdom, 1985–2013) Thrombosis and thromboembolism Number Rate 95% CI 1985–1987 32 1.41 1.00 1.99 1988–1990 33 1.40 1.00 1.96 1991–1993 35 1.51 1.09 2.10 1994–1996 48 2.18 1.65 2.90 1997–1999 35 1.65 1.19 2.29 2000–2002 30 1.50 1.05 2.14 2003–2005 41 1.94 1.43 2.63 2006–2008 18 0.79 0.49 1.25 2009–2011 30 1.26 0.85 1.8 2010–2012 26 1.08 0.71 1.59 2011–2013 24 1.01 0.65 1.5 2012–2014 20 0.85 0.52 1.32 2013–2015 26 1.13 0.74 1.65 Data from Knight M, Nair M, Tuffnell D, Shakespeare J, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013–15. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2017.

14.7 Thrombosis in pregnancy 2607 important improvements include: routine risk assessment of women during pregnancy and after delivery, and use of thromboprophylaxis with low-molecular-weight heparin (LMWH) in those perceived to be at increased risk of venous thromboembolism; a high index of clinical suspicion for venous thromboembolism in symptomatic women; adoption of LMWH as the preferred modality of treatment for venous thromboembolism; and advances in general obstetric care (e.g. early mobilization after delivery). Aetiology and pathogenesis The increased risk of venous thromboembolism in pregnancy is the result of alteration in the components of Virchow's triad of venous stasis, prothrombotic changes in the blood, and vessel wall injury. Reduced blood flow in the veins of the lower limbs and pelvis arises from the vasodilator effects of progesterone and other pregnancy-related hormones, also the obstruction resulting from the gravid uterus. Pregnancy itself is a prothrombotic state, pre- sumably arising as the body prepares for delivery and its attendant bleeding risks. Well described procoagulant changes (increases in fibrinogen, factor VII, factor VIII, and von Willebrand factor), re- duced fibrinolytic activity (elevated plasminogen activator inhibi- tors) and reduced protein S (a naturally occurring anticoagulant) occur during pregnancy and likely predispose to venous thrombo-embolism. These changes can take some weeks to fully correct postnatally, and the risk of venous thromboembolism is further enhanced in the puerperium by the injury to the pelvic veins that occurs during delivery. Many pregnancy-related deep vein thromboses are ileofemoral, whereas in the nonpregnant setting most are thought to originate in the distal veins before extending to the popliteal and femoral veins. Deep vein thrombosis in pregnancy affects the left leg in 80–90% of cases compared to around 50% in the nonpregnant state, and this likely reflects additional compression in pregnancy of the left common iliac vein by the right common iliac artery. Epidemiology The absolute risk of venous thromboembolism in pregnancy and the puerperium is approximately one event per 1000 pregnancies com- pared to the nonpregnant state where the risk of venous thrombo- embolism is approximately 1 in 10 000 annually. The risk of venous thromboembolism increases in early pregnancy (when UK maternal mortality data suggest fatal pulmonary embolism may be more fre- quent), increases further towards term, and peaks in the

first three weeks post-partum. The venous thromboembolism risk is increased around 5-fold during pregnancy and 20-fold or more during the puerperium. The risk per day is therefore higher in the puerperium, with up to 50% of events occurring post-partum. Over the past 10 years, the number of maternal deaths from pulmonary embolism in the United Kingdom has ranged from around 5–10 annually (Table 14.7.1). Taking account of the number of births per year in the UK (approximately 800 000) and therefore the number of expected episodes of venous thromboembolism (approximately 800), this sug- gests an overall case fatality rate for venous thromboembolism in pregnancy of around 1%. Risk factors for venous thromboembolism in pregnancy and the puerperium are shown in Table 14.7.2. Clinical features One of the difficulties with the diagnosis of deep vein throm- bosis or pulmonary embolism is that the characteristic features of these conditions (e.g. leg swelling, breathlessness), are common in normal pregnancy (Table 14.7.3). The standard predictive clinical tools widely used in the initial assessment of nonpregnant patients, such as the Wells scores for deep vein thrombosis and pulmonary embolism, have not been validated in pregnancy, and the clinical diagnosis of venous thromboembolism in pregnancy is particularly unreliable. The condition should be suspected with leg swelling that is unilateral (particularly if left-sided) and associated with pain, Table 14.7.2 Risk factors for venous thromboembolism in pregnancy and the puerperium Pre-existing New onset or transient Previous episode of VTE Age over 35 years Obesity (BMI >30 kg/m2) either pre-pregnancy or in early pregnancy Parity >3 Known thrombophilia or family history of unprovoked or oestrogen-related VTE in a first-degree relative Smoker Gross varicose veins with phlebitis Paraplegia Medical comorbidities, e.g. cancer, heart disease; metabolic, endocrine, or respiratory pathologies; inflammatory conditions (e.g. inflammatory bowel disease, active systemic lupus erythematosis); sickle cell disease; nephrotic syndrome; current intravenous drug user Caesarean section Surgical procedure in pregnancy or puerperium, except immediate repair of the perineum Hospital admission Hyperemesis Dehydration Ovarian hyperstimulation syndrome Multiple pregnancy or assisted conception Current systemic infection (e.g. pyelonephritis) Immobility (e.g. SPD, significantly reduced mobility for three or more days; long distance travel >4 hours during pregnancy and up to six weeks post-partum) Preeclampsia in current pregnancy Post-partum haemorrhage (>1 litre or transfusion) Prolonged labour (>24 hours) Stillbirth in current pregnancy Preterm delivery (<37 weeks in current pregnancy) Mid-cavity instrumental delivery Immobility after delivery Critical care admission PPH >1 litre or blood transfusion SPD, symphysis pubis dysfunction; VTE, venous thromboembolism.

 lower abdominal pain, or back pain (especially if unilateral), or sudden onset of breathlessness, chest pain, haemoptysis, dizziness or collapse. Low grade pyrexia may be present. Differential diagnosis Some of the features of deep vein thrombosis and pulmonary em- bolism described here may occur in normal pregnancy. In common with the nonpregnant state, other conditions that may present with similar features to deep vein thrombosis include superficial vein thrombosis, a ruptured Baker’s cyst, and muscle tears. The differ- ential diagnosis of pulmonary embolism includes musculoskel- etal pain, chest infection (particularly pneumonia with pleurisy), pneumothorax, acute coronary syndrome, and heart failure. Clinical investigations Because the clinical diagnosis of venous thromboembolism is unre- liable and anticoagulant treatment carries significant risks, it is very Table 14.7.3 Symptoms and signs of venous thromboembolism in pregnancy Deep vein thrombosis Painful swollen leg (lower leg or whole leg) Redness/oedema of leg Left iliac fossa/groin/buttock pain Nonspecific lower abdominal pain Pulmonary embolism Chest pain (sudden onset) Breathlessness (sudden onset) Dizziness

Syncope or collapse Haemoptysis Tachypnoea Tachycardia Hypoxia Raised jugular venous pressure

1. Investigations should be completed within 24 hours of admission with suspected pulmonary embolism (PE).
2. Chest X-ray signs of PE may include small effusion, prominent pulmonary vasculature and regional oligemia, but the chest X-ray is most often normal in PE. Clinical assessment and initial investigations. Chest X-ray, ECG, and arterial blood gas. FBC, U&E, LFTs Do not perform a D-dimer test CXR Normal Commence LMWH if suspect PE1 Abnormal Treat LMWH High probability of PE V/Q scan Treat other disorder CTPA Other diagnosis likely based on chest X-ray and initial investigations PE remains likely diagnosis2 No further investigations necessary (if good quality scan and clear report) Stop LMWH Demonstrates PE Normal Low/ intermediate probability of PE Stop LMWH Does not demonstrate PE Treat LMWH Fig. 14.7.1 Algorithm for the investigation and initial management of suspected pulmonary embolism in pregnancy and the puerperium (from Royal College of Obstetricians and Gynaecologists (RCOG) green-top guideline 37b) in haemodynamically stable women without symptoms or signs of deep vein thrombosis.

14.7 Thrombosis in pregnancy 2609 important that the diagnosis of venous thromboembolism is object- ively confirmed as expeditiously as possible. When deep vein thrombosis is suspected, compression duplex ultrasonography should be undertaken. If this is negative and there is a low index of clinical suspicion, treatment can be discontinued. If a high index of suspicion remains, treatment can be discontinued, and the ultrasound repeated on days 3 and 7. The diagnosis of iliac vein thrombosis should be considered in those with swelling of the en- tire leg plus associated back pain. Magnetic resonance (MR) or com- puted tomography (CT) venography may be required to confirm the diagnosis. If pulmonary embolism is suspected, a chest X-ray and electrocar- diogram (ECG) should be performed to exclude other conditions in the differential diagnosis. In women who also have features of deep vein thrombosis, compression duplex ultrasonography should be performed and, if positive, treatment for venous thromboembolism should continue without further investigation for pulmonary em- bolism. If the Doppler is negative, imaging to exclude a pulmonary embolism should be undertaken. In women without features of deep vein thrombosis, a ventilation/perfusion (V/Q) lung scan or compu- terized tomography pulmonary angiogram (CTPA) should be per- formed (Fig. 14.7.1). The latter is particularly preferred in women with an abnormal chest X-ray. There are potential drawbacks to both V/Q scanning (slightly increased risk of childhood cancer) and CTPA (slightly increased risk of maternal breast cancer), but the absolute risk is very small in each case and outweighed by the risk incurred by failing to establish the diagnosis of pulmonary embolism object- ively. In the case of V/Q scanning, the radiation dose can be further limited by avoiding a ventilation scan in those with a normal perfu- sion scan. Women should be involved in the decision to undergo V/ Q scanning or CTPA and give informed consent before these tests are undertaken. The value of a negative D-dimer test has not been validated in preg- nancy and it should not be used for venous thromboembolism diag- nosis. It is important, however, to perform a baseline full blood count, coagulation screen, urea and electrolytes, and liver function tests to iden- tify any comorbidities that might complicate anticoagulant treatment. Treatment Antenatal The optimal treatment of venous thromboembolism in pregnancy is with therapeutic doses of low-molecular-weight heparin based on booking or early pregnancy weight (Table 14.7.4a). Unless strongly contraindicated, treatment should commence when venous thrombo- embolism is clinically suspected and stopped if the diagnosis is ex- cluded by objective

testing. In those in whom the diagnosis of venous thromboembolism is confirmed, low-molecular-weight heparin should continue for the remainder of the pregnancy and for at least six weeks postnatally and until at least three months of treatment has been given in total. It is not necessary to monitor low-molecular-weight heparin by measurement of anti-Xa levels, except perhaps in women at extremes of body weight (less than 50 kg or more than 90 kg) or with renal im- pairment or recurrent venous thromboembolism. The risk of heparin- induced thrombocytopenia with low-molecular-weight heparin in pregnancy is low and it is not necessary to monitor the platelet count. Women should be taught to self-inject low-molecular-weight heparin and arrangements made to ensure safe disposal of needles and syringes. Elevation of the leg may reduce swelling, and mobilization should be encouraged. Graduation compression stockings may reduce pain and swelling in the affected leg, but recent evidence suggests they do not prevent the post-thrombotic syndrome. Warfarin and other vitamin K antagonists should not be used for antenatal venous thromboembolism treatment because they cross the placenta and have adverse effects on the fetus. Direct oral anti- coagulants are contraindicated in pregnancy. In women who present with massive pulmonary embolism with haemodynamic compromise characterized by systolic hypotension, a multidisciplinary team of senior clinicians including obstetricians, physicians and radiologists should be involved as a matter of ur- gency (Fig. 14.7.2). If possible an urgent portable echocardiogram or CTPA should be arranged to confirm the diagnosis. Women should be managed on an individual basis, taking account of the severity of the situation, the availability of resources such as echocardiography Table 14.7.4 (a) Calculation of initial treatment doses of low-molecular-weight heparin by early pregnancy weight <50 kg 50–69 kg 70–89 kg 90–109 kg 110–125 kg

> 125 kg Enoxaparin 1 mg/kg bd
> (or 1.5 mg/kg od) 40 mg bd
> (60 mg od) 60 mg bd
> (90 mg od) 80 mg bd
> (120 mg od) 100 mg bd
> (150 mg od) 120 mg bd
> (180 mg od) Discuss with a haematologist Dalteparin 100 IU/kg bd
> (or 200 IU/kg od) 5000 IU bd (10 000 IU od) 6000 IU bd
> (12 000 IU od) 8000 IU bd (16 000 IU od) 10 000 IU bd
> (20 000 IU od) 12 000 IU bd (24 000 IU od) Discuss with a haematologist
> Tinzaparin 175 units/kg od od, once daily; bd, twice daily. Table 14.7.4 (b) Suggested thromboprophylactic doses of low-molecular-weight heparin by early pregnancy weight <50 kg 50–90 kg 91–130 kg 131–170 kg 170 kg Enoxaparin 20 mg od 40 mg od 60 mg oda 80 mg oda 0.6 mg/kg/daya Dalteparin 2500 IU od 5000 IU od 7500 IU od 10 000 IU od 75 IU/kg/ day Tinzaparin 3500 IU od 4500 IU od 7000 IU oda 9000 IU oda 75 IU/kg/daya a May be given in two divided doses. (a) and (b) Source data from Royal College of Obstetricians and Gynaecologists (2015). Reducing the risk of venous thromboembolism during pregnancy and the Puerperium (Green- top Guideline No. 37a). https://www.rcog.org and Royal College of Obstetricians and Gynaecologists (2015). Thromboembolic disease in pregnancy and the puerperium: acute management (Green-top Guideline No. 37b). https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37b.pdf

Section 14 Medical disorders in pregnancy 2610 or CTPA, and the bleeding risks. Treatment should commence with intravenous unfractionated heparin (Table 14.7.5). Systemic or catheter directed thrombolysis should be considered in women who are hypotensive. If this is contraindicated because of bleeding, then percutaneous catheter fragmentation or thoracotomy and surgical embolectomy should be considered. During labour and delivery Women who are established on low-molecular-weight heparin should be advised to stop further injections when they are in, or think they are in, labour. When delivery is planned, either by elective caesarean section or induction of labour, low-molecular-weight heparin should be discontinued 24 hours prior to planned delivery. Regional anaesthesia should not be undertaken until at least 24 hours after the last therapeutic dose of low-molecular-weight heparin. If delivery is by caesarean section, wound drains should be considered and the skin incision closed with interrupted sutures to allow drainage of any haematoma. Following delivery, a prophylactic dose of low-molecular-weight heparin can be administered at least four hours later, providing bleeding has settled, and a therapeutic dose recommenced 8–12 hours later. At least four hours should pass after a spinal anaesthetic has been administered or after an epidural cath- eter has been removed before further low-molecular-weight heparin is given, and an epidural catheter should not be removed within 12 hours of the most recent injection. Postnatal As mentioned earlier, women who are diagnosed with venous thromboembolism antenatally need to continue treatment for at least six weeks postnatally and until at least three months of treatment has been given in total. Women who are diagnosed with venous thrombo- embolism post-partum need to continue treatment for a minimum of three months. The continuing risk of thrombosis should be assessed before treatment is stopped. Postnatally, women should be offered the choice of low-weight-molecular heparin or warfarin after discus- sion about the need for regular blood tests for monitoring warfarin, particularly during the first 10 days of treatment. Warfarin should not be commenced until at least the fifth day post-partum and after a longer delay in those at risk of post-partum haemorrhage. Neither heparin (unfractionated or low-molecular-weight heparin) nor war- farin is contraindicated in breastfeeding. Direct oral anticoagulants should not be used in those who are breastfeeding. Prognosis/outcome Anticoagulant treatment is very effective in most women with acute venous thromboembolism presenting during pregnancy or the puerperium. An overall case fatality rate of around 1% is supported by the data alluded to earlier. Although uncommon, the fatalities are more often the result of failure of diagnosis than of established treatment. The mortality rate is higher in patients presenting with pulmonary embolism and haemodynamic compromise, and thrombolytic therapy may be life-saving in this group. Around 40% of women develop the post-thrombotic syndrome after deep vein thrombosis in pregnancy. This is characterized by variable chronic swelling, pain, a feeling of heaviness, dependent cyanosis and chronic pigmentation in the leg affected by the throm- bosis, and may be a cause of considerable impairment of quality of life. Occasionally the post-thrombotic syndrome can be sufficiently severe as to lead to venous ulceration. Chronic thromboembolic pulmonary hypertension should be considered in those with persistent breathlessness. It is relatively uncommon, but identification can lead to successful pulmonary endarterectomy in those where the persisting embolus is large and central. Individuals who have had an episode of venous thrombo- embolism are at greater risk of another event in the future. The abso- lute risk is thought to be around 1–5% in the first year after stopping anticoagulant treatment and likely declines subsequently, although Multidisciplinary resuscitation team Oxygen, IV UFH, IV fluids, inotropic support Transfer to ITU Inform on call obstetric team immediately for consideration of early delivery Negative investigations –pursue other diagnoses Diagnosis of PE by emergency CTPA or echocardiogram (ECHO) If the patient becomes peri-arrest, consider thrombolysis without

imaging CTPA confirms PE or ECHO confirms right ventricular dilatation/dysfunction If persistent hypotension (systolic BP < 90 mm Hg), consider thrombolysis If thrombolysis contraindicated, consider percutaneous catheter fragmentation or surgical embolectomy Fig. 14.7.2 Management of women with clinically suspected massive pulmonary embolism. UFH, unfractionated heparin; ITU, Intensive Therapy Unit; CTPA, computerized tomography pulmonary angiogram; PE, pulmonary embolism. Reproduced from Khalil A., Bowles L., O'Brien P., Cohen H. (2015) Systemic Thromboembolism in Pregnancy: Venous Thromboembolism. In: Cohen H., O'Brien P. (eds) Disorders of Thrombosis and Hemostasis in Pregnancy. Springer with permission from Springer Nature. Table 14.7.5 Adjustments in the infusion rate of unfractionated heparin (UFH) according to the activated partial thromboplastin time (APTT) with target APTT ratio 1.5–2.5 APTT ratio Dose (units/kg/h) Additional action Next APTT (h) <1.2 +4 Re-bolus 80 units/kg 6 1.2–1.5 +2 Re-bolus 40 units/kg 6 1.5–2.5 No change 24 2.5–3.0 −2 6

> 3.0 −3 Stop infusion for 1 h 6 Loading dose of 80 units/kg followed by a continuous infusion of 18 units/kg/hour. Measure APTT 4–6 hours after the loading dose. Source data from Royal College of Obstetricians and Gynaecologists (2015). Thrombo embolic disease in pregnancy and the puerperium: acute management (Green-top Guideline No. 37b). https://www.rcog.org.uk/globalassets/documents/guidelines/ gtg-37b.pdf

14.7 Thrombosis in pregnancy 2611 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 Hospital admission Single previous VTE related to major surgery High-risk thrombophilia + no VOTE 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. appendice to my OHSS (first trimester only) 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 Transient risk factors: Dehydration/hyperemesis; current systemic infection; long-distance travel APL = antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, β2 -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 fertilization; 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. Fewer than three risk factors LOWER RISK mobilization and avoidance of dehydration Four or more risk factors: prophylaxis from first trimester Three risk factors: prophylaxis from 28 weeks HIGH RISK Refer to trust-nominated thrombosis in pregnancy expert/team Requires antenatal prophylaxis with LMWH Postnatal assessment and management (to

be assessed on delivery suite) Antenatal and postnatal prophylactic dose of LMWH Fewer than two risk factors Two or more risk factors NB If persisting or > 3 risk factors consider extending thromboprophylaxis with LMWH At least 10 days' postnatal prophylactic LMWH INTERMEDIATE RISK HIGH RISk At least 6 weeks' postnatal prophylactic LMWH LOWER RISK Early mobilization and avoidance of dehydration Weight > 170 kg = 0.6 mg/kg/day enoxaparin/75 u/kg/day dalteparin/ 75 u/kg/day tinzaparin Weight 131–170 kg = 80 mg enoxaparin/10000 units dalteparin/9000 units tinzaparin daily Weight 91–130 kg = 60 mg enoxaparin/7500 units dalteparin/7000 units tinzaparin daily Weight 50–90 kg = 40 mg enoxaparin/5000 units dalteparin/4500 units tinzaparin daily Weight < 50 kg = 20 mg enoxaparin/2500 units dalteparin/3500 units tinzaparin daily Any previous VTE Anyone requiring antenatal LMWH High-risk thrombophilia Low-risk thrombophilia + FHx 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 polyarthro- pathy; nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU 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° weeks) Stillbirth in this pregnancy Mid-cavity rotational or operative delivery Prolonged labour (>24 hours) PPH > 1 litre or blood transfusion Age > 35 years INTERMEDIATE RISK Consider antenatal prophylaxis with LMWH Fig. 14.7.3 Obstetric venous thromboembolism risk assessment and thromboprophylaxis. Reproduced from: Royal College of Obstetricians and Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy. Green-top Guideline No. 37a. London: RCOG; 2015, with the permission of the Royal College of Obstetricians and Gynaecologists.

Section 14 Medical disorders in pregnancy 2612 remaining higher than in those without a venous thromboembolism history. This size of risk is not thought to be sufficiently high to war- rant long-term anticoagulation with its attendant risks, but short- term thromboprophylaxis should be considered in future high-risk settings (e.g. surgery or prolonged immobility). The risk of venous thromboembolism is also higher during subsequent pregnancies and warrants postnatal thromboprophylaxis in all and antenatal thromboprophylaxis in most cases. Special circumstances/complications Venous thromboembolism occurring near to or during labour and delivery presents particularly acute challenges because of the dif- ficulties with anticoagulation and the risk of peripartum haemor- rhage. If possible, it is preferable to complete at least two (and ideally four) weeks of anticoagulant treatment before delivery as the risk of recurrence is highest in this period. In this setting around the time of delivery, intravenous unfractionated heparin may have advantages because of its short half-life and reversibility with protamine sul- phate. It needs to be monitored by the activated partial thrombo- plastin time (APTT) according to an approved algorithm, and this is challenging in pregnancy because of the naturally shortened APTT that occurs, which results in apparent heparin resistance. Intravenous heparin should be stopped six hours before delivery or regional anaesthesia. In those who have an operative delivery and are receiving intravenous unfractionated heparin, the platelet count should be monitored every two to three days from days 4 to 14, or until the heparin is stopped. Consideration should be given to the use of temporary inferior vena cava filters in the peripartum period where anticoagulation cannot be given, particularly for those with iliac vein thrombosis. Expert advice should be sought in this setting. In women who develop allergic skin reactions a switch in low- molecular-weight heparin may be tried. In those with heparin-induced thrombocytopenia, low-molecular-weight heparin must be stopped and replaced by nonheparin alternatives such as danaparoid or fondaparinux. In this

rare setting specialist advice should be sought. Prevention of venous thromboembolism in pregnancy and the puerperium Although pregnancy and the puerperium are associated with an in- creased risk of venous thromboembolism, the size of risk is insuffi- cient to warrant routine thromboprophylaxis. However, several risk factors for venous thromboembolism have been identified in obser- vational studies (Table 14.7.2) and women who have one or more of these factors may require consideration for thromboprophylaxis. Within the overall population of pregnant women, the most common risk factors are advanced maternal age (over 35 years), obesity (body mass index over 30 kg/m2) and caesarean section, particularly when performed as an emergency. Other groups at increased risk include those with underlying medical comorbidities including acute sys- temic infections and inflammatory conditions. Admission to hos- pital for medical, surgical, or obstetric reasons poses an additional risk. One particularly important risk factor is a previous episode of venous thromboembolism (i.e. prior to the current pregnancy). A family history of venous thromboembolism, especially affecting a first-degree relative, also indicates an increased risk whether or not a defined thrombophilic tendency is identified. It is therefore recom- mended that all women should undergo a documented assessment of risk factors for venous thromboembolism in early pregnancy and this should be repeated if a woman is admitted to hospital or de- velops intercurrent problems in pregnancy. It should be repeated again intrapartum or immediately post-partum. Women with identified venous thromboembolism risk factors should be considered for thromboprophylaxis with low-molecular- weight heparin and the risks and benefits discussed in each case. A summary of the recommendations from the Royal College of Obstetricians and Gynaecologists is shown in Fig. 14.7.3. In most women who require low-molecular-weight heparin for venous thromboembolism prevention, prophylactic doses (weight-adjusted as shown in Table 14.7.4b) should be used. In certain particu- larly high-risk women; for example, those with a previous venous thromboembolism episode and heritable antithrombin deficiency or antiphospholipid syndrome—intermediate or therapeutic doses are recommended. Women receiving antenatal thromboprophylaxis should be ad- vised to discontinue low-molecular-weight heparin if they have va- ginal bleeding or when labour begins. Regional anaesthesia should be avoided until at least 12 hours after the previous injection (and 24 hours for those on higher doses of low-molecular-weight hep- arin). Following delivery prophylactic low-molecular-weight hep- arin should be recommenced as outlined in the Treatment section earlier. Mechanical thromboprophylaxis (antiembolism stockings or intermittent pneumatic compression) should be considered in those whom low-molecular-weight heparin is contraindicated. After delivery thromboprophylaxis should be considered for 10 days in those at intermediate risk of venous thromboembolism and six weeks in those at high risk. Areas of uncertainty, controversy, and future developments Important unresolved issues include the optimal selection of women for thromboprophylaxis taking account of cost-effectiveness, also the clinical criteria used to assess whether women with often nonspecific symptoms warrant further investigation for venous thromboembolism. FURTHER READING Royal College of Obstetricians and Gynaecologists (2015). Reducing the Risk of Venus Thromboembolism during Pregnancy and the Puerperium (Green-top Guideline No. 37a). https://www.rcog.org. uk/globalassets/documents/guidelines/gtg-37a.pdf Royal College of Obstetricians and Gynaecologists (2015). Thrombo embolic disease in Pregnancy and the Puerperium: Acute Management (Green-top Guideline No. 37b). https://www.rcog.org.uk/globalassets/ documents/guidelines/gtg-37b.pdf

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