

Venous thromboembolism in pregnancy

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Pregnancy-related venous thromboembolic events are important preventable causes of morbidity and mortality in South Africa. All pregnant patients should be evaluated for thrombotic risk at different stages of their pregnancy and appropriate preventive steps taken. Maternal and fetal wellbeing must be kept in mind, as well as physiological changes leading to altered drug pharmacokinetics. Managing the patient with thrombotic risk in pregnancy, diagnosing venous thromboembolism (VTE) during pregnancy and treatment of venous thromboembolic events should be managed by a team. Excellent recent reviews on this subject are available, including risk factor stratification in anticoagulant therapy; managing the patient at time of labour; diagnosing VTE; and managing neuraxial anaesthesia in the pregnant patient on anticoagulant therapy.

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The risk of venous thromboembolism (VTE) increases 5 - 10-fold during pregnancy, and 15 - 35-fold postpartum compared with that in non-pregnant women of the same age.^[1] High-quality data specific to the pregnant patient are lacking, as pregnancy is an exclusion criterion in most randomised clinical VTE trials. Most guidelines are therefore based on expert opinion and observational studies. Pregnancy also deals with maternal and fetal wellbeing. Despite these issues, several excellent publications have appeared in the past year. The aim of this review is not to replace any of these papers, but rather summarise some of the points made. The interested reader is advised to read some (if not all) of these recommendations, which include those on thromboprophylaxis in obstetrics and gynaecology; management of thromboembolism in pregnancy; and evidence-based anticoagulation in pregnancy (see references 12, 13 and 14).

Why are patients prone to VTE during pregnancy?

Various physiological changes^[2] that prevent haemorrhage during birth and in the weeks after pregnancy lead to a natural hypercoagulable state in the pregnant patient (Table 1). Pregnant women also experience venous stasis (the enlarging uterus compresses the inferior vena cava and pelvic veins). Another VTE risk factor (in the well-known Virchow's triad) is also present, with endothelial changes described in pregnancy^[4] (including endothelial trauma during delivery).

How many patients develop VTE in pregnancy?

Depending on the population studied, VTE complicates 0.5 - 2.2 per 1 000 deliveries.^[1] Pregnancy-related VTE is one of the 10 most important potentially preventable causes of maternal death in South Africa (SA).^[5] In the UK, VTE is the leading direct cause of maternal death (12.9% of patients between 2013 and 2015) and the fifth most common cause of death overall in pregnancy.^[6] Approximately 80% of venous thrombotic events are deep-vein thrombosis (DVT) and 20% pulmonary embolism.^[7] The risk of VTE increases from the time of conception, with the highest risk at the time of delivery and immediately thereafter, especially in the first 3 - 6 postpartum weeks, with approximately half of VTE events occurring during that period. Arterial thrombotic events also increase during pregnancy, but are 4 times less common than VTE.^[8]

How do we identify pregnant patients at risk of VTE?

All patients should be risk stratified for VTE early in pregnancy if admitted to hospital or confined to bedrest during pregnancy, as well as in the postpartum period. Various risk factors have been classified as high, intermediate or low.^[9] Complex scoring systems^[9,10] have been developed, but no randomised clinical trials have been performed to validate these. Patients at high risk of VTE in pregnancy should be managed by a team, including a clinical haematologist. The risk of bleeding should always be evaluated prior to prescribing thromboprophylaxis.

Table 1. Physiological changes involving coagulation during pregnancy

Increased clotting factors	Decreased circulating anticoagulants	Reduced fibrinolysis
↑ Factor VIII	↓ Protein S (40 - 60% decrease) ^[3]	↑ Activity of PAI-1 and PAI-2
↑ Factor X	Acquired protein C resistance	↓ Activity of t-PA
↑ Von Willebrand factor	-	↑ TAFI levels in third trimester
↑ Factor I (fibrinogen)	-	-
↑ Factor II	-	-
↑ Factor VII	-	-

PAI-1 = plasminogen activator inhibitor-1; PAI-2 = plasminogen activator inhibitor-2; t-PA = tissue plasminogen activator; TAFI = thrombin activatable fibrinolysis inhibitor.

VTE events are classified as unprovoked events (~50%), indicating that there is no known clinical risk factor (e.g. trauma, surgery, active cancer, immobility, pregnancy or hormonal usage). Provoked events, however, may be due to a transient factor or persistent risk factor. Risk of recurrence is highest with provoked persistent risk factors, very high with unprovoked risk factors, and lower with transient risk factors.^[11] In pregnancy, this means that a previous oestrogen-related VTE event (persistent provoked risk) and previous unprovoked VTE event have a very high risk of recurrence during pregnancy.

Evaluation of risk factors at time of first consultation or antepartum

The patient can be assessed according to risk factors mentioned in Royal College of Obstetricians and Gynaecologists (RCOG)^[9] and/or South African Society of Thrombosis and Haemostasis (SASTH)^[12] articles (Table 2).

Three important questions must be answered (Fig. 1):

Has the patient previously experienced VTE?

If confirmative, at least 6 weeks' postpartum VTE prophylaxis should be given. If the event was oestrogen related, unprovoked or more than one event occurred, antepartum and postpartum prophylaxis are required.^[9] Another approach to the recurrent risk in cases of a previous VTE, is that all pregnant patients with a previous VTE event should receive antepartum and postpartum prophylaxis, unless the single previous VTE event was due to a major risk factor.

A familial or acquired clotting tendency (thrombophilia) represents a consistent relative increased risk for a first VTE. There is much controversy regarding managing patients with known thrombophilia and whether they should undergo thrombophilia testing. The second question is therefore:

Does the patient have a family history (first degree) of thrombosis or known thrombophilia? Which specific thrombophilia is present (including acquired antiphospholipid syndrome)?

One approach has been to grade the different types of thrombophilia as severe, intermediate or minor types, and to look at events in other family members with the same thrombophilic abnormality. Table 3^[13,14] summarises the recommendations by various authors. It is imperative that the total patient 'package' must be evaluated, e.g. even though carriers of the factor V Leiden mutation may only need careful observation antepartum, the patient may have additional risk factors, such as a high body mass index (BMI), thus also putting them into a higher risk grade and need for antepartum prophylaxis.

The question arises whether patients should be tested for thrombophilia before pregnancy if there is a family history of VTE. A positive family history of VTE is a poor predictor of the presence of thrombophilia.^[15] In any patient with a first-degree relative with VTE, whether a thrombophilic tendency has been proven or not, the VTE risk doubles, and in cases where the VTE event occurred in a family member <50 years of age, the risk rises up to 3-fold.^[15] The RCOG guideline^[9] therefore suggests testing the patient with a first-degree relative who had an unprovoked or oestrogen-related VTE before the age of 50 years. Patients may choose to undergo thrombophilia screening or specific testing for a thrombophilic abnormality that has been diagnosed in their family. Pretest counselling is necessary, because of the implications for the patient and her family. The RCOG guideline^[9] suggests testing for antiphospholipid syndrome if an unprovoked VTE has occurred in a pregnant patient in the past (this may influence management of anticoagulation).

Table 2. Risk factors to consider antepartum^[12]

High risk	Intermediate risk	Low risk
<ul style="list-style-type: none"> • Previous unprovoked or pregnancy- or oestrogen-related VTE • High-risk hereditary thrombophilia (compound heterozygous or homozygous for factor V Leiden or prothrombin gene mutation and some deficiencies of antithrombin) and a positive family history of VTE • Antiphospholipid syndrome and previous VTE 	<ul style="list-style-type: none"> • Single VTE related to a transient risk factor (not related to pregnancy or oestrogen use) • Low- and intermediate-risk hereditary thrombophilia (some antithrombin deficiencies, protein S deficiency, protein C deficiency; heterozygous for factor V Leiden or prothrombin gene mutation) and a positive family history of VTE • High-risk hereditary thrombophilia and no positive family history of VTE • Antiphospholipid syndrome • Non-obstetric surgery during pregnancy • Medical comorbidities, e.g. cancer, heart failure, peripartum cardiomyopathy, active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease; nephrotic syndrome; type 1 diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user • Ovarian hyperstimulation syndrome (3 months after resolution) • Clinical monitoring indicated 	<ul style="list-style-type: none"> • Age >35 years • BMI ≥30 kg/m² • Parity ≥3 • Smoker (at least 10 cigarettes per day) • Family history of unprovoked or oestrogen-related VTE in first-degree relative • Low-risk thrombophilia • Gross varicose veins • Current systemic infection or perioperative infection • Immobility, e.g. paraplegia, long-distance travel (>8 h), strict bedrest ≥7 d • Pre-eclampsia with intrauterine growth restriction • Multiple pregnancy • <i>In vitro</i> fertilisation • Dehydration/hyperemesis
<ul style="list-style-type: none"> • Antepartum • Thromboprophylaxis indicated 		<ul style="list-style-type: none"> • Early mobilisation and avoid dehydration • Thromboprophylaxis if multiple (≥4) risk factors present

VTE = venous thromboembolism; BMI = body mass index.

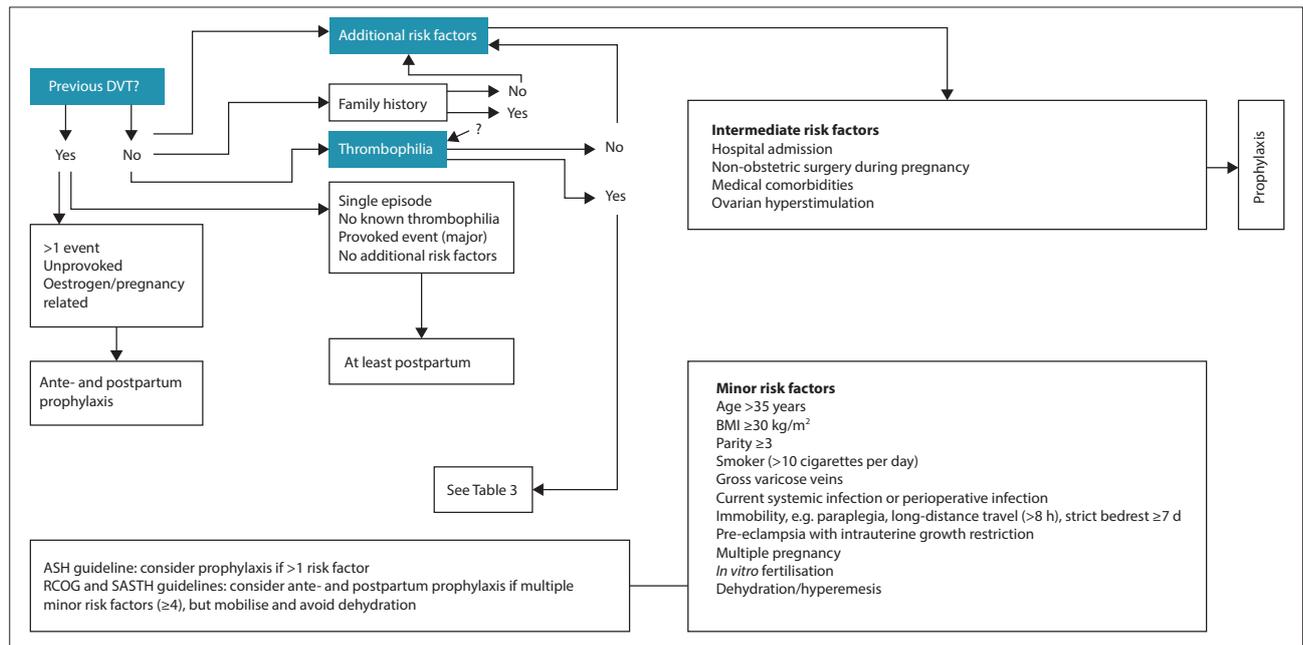


Fig. 1. Approach to initial assessment of venous thromboembolism risk in pregnancy. (DVT = deep-vein thrombosis; BMI = body mass index; ASH = American Society of Hematology; RCOG = Royal College of Obstetricians and Gynaecologists; SASTH = South African Society of Thrombosis and Haemostasis.)

Table 3. Thrombophilia in pregnancy

Type of thrombophilia	Risk	Family history (1st degree)	ASH, 2018 ^[13]		Blood Reviews, 2018 ^[14]	
			AP	PP	AP	PP
Factor V Leiden heterozygous	Low risk	Negative	No*	No*	No	No
		Positive	No*	No*	No	Yes
Prothrombin mutation heterozygous	Low risk	Negative	No*	No*	No	No
		Positive	No*	No*	No	Yes
Protein C deficiency	Intermediate risk	Negative	No*	No*	No	No
		Positive	No*	Yes*	No	Yes
Protein S deficiency	Intermediate risk	Negative	No*	No*	No	No
		Positive	No*	Yes*	No	Yes
Antithrombin deficiency	Intermediate risk	Negative	No*	No*	No	No
		Positive	Yes*	Yes*	No	Yes
Combined factor V Leiden and prothrombin mutation	High risk	Negative	Yes*	Yes*	Yes	Yes
		Positive	Yes*	Yes*	Yes	Yes
Factor V Leiden homozygous	High risk	Negative	Yes*	Yes*	No	Yes
		Positive	Yes*	Yes*	Yes	Yes
Prothrombin mutation homozygous	High risk	Negative	No*	Yes*	No	Yes
		Positive	Yes*	Yes*	Yes	Yes
Antiphospholipid syndrome	High risk		Yes,	Yes,	Yes,	Yes,
			add aspirin	add aspirin	add aspirin	add aspirin

ASH = American Society of Hematology; AP = antepartum prophylaxis; PP = postpartum prophylaxis.
 *Conditional recommendation, low evidence.

Various other risk factors (personal risks (e.g. BMI, smoking), pregnancy-related risks (e.g. caesarean section) and medical comorbidities (e.g. autoimmune disorder)) are known to increase the risk of developing VTE, and thus the third question to ask the patient is the following:

Are there additional risk factors present?

The magnitude of this last group depends on the number of risk factors present, as well as the nature of the specific risk

factors. Assigning weight to factors has been attempted, but not validated. It is also unclear whether risk factors have an additional or multiplicative role.^[13] The 2018 American Society of Hematology (ASH) guideline^[13] suggests considering (without previous VTE or thrombophilia) prophylaxis – only if more than one additional risk factor is present. The RCOG Green-top guideline^[9] and the SASTH guideline^[12] suggest considering thromboprophylaxis in intermediate risk factors (hospital admission, non-obstetric surgery during

pregnancy, medical comorbidities and ovarian hyperstimulation syndrome (first-trimester-only prophylaxis) and when multiple (≥ 4) minor risk factors (age >35 years, BMI ≥ 30 kg/m², parity ≥ 3 , smoker (at least 10 cigarettes per day), gross varicose veins, current systemic infection or perioperative infection, immobility, e.g. paraplegia, long-distance travel (>8 hours), strict bedrest ≥ 7 days, pre-eclampsia with intrauterine growth restriction, multiple pregnancy, *in vitro* fertilisation and dehydration/hyperemesis) are present.

Evaluation of risk factors at the time of delivery/postpartum

There are three groups of risk factors that should be considered at this time of pregnancy (Table 4 and Fig. 2).

Which anticoagulant drugs are safe in pregnancy and during breastfeeding?^[14]

Drugs that are safe during pregnancy and breastfeeding are listed in Table 5.

How are patients on anticoagulation managed if they are contemplating pregnancy?

When contemplating pregnancy, preconception counselling regarding risks for mother and baby is essential. The International Society on Thrombosis and Haemostasis (ISTH) specifically recommends that women of childbearing age be counselled regarding risk of novel oral anticoagulants (NOACs) (dabigatran, rivaroxaban, apixaban) in pregnancy owing to possible teratogenic effects.^[16] The suggested

Table 4. Risk factors to consider at time of delivery/postpartum^[9]

High risk	Intermediate risk	Additional factors
<ul style="list-style-type: none"> Anyone requiring antenatal prophylaxis Any previous VTE 	<ul style="list-style-type: none"> Caesarean section in labour Asymptomatic thrombophilia (inherited or acquired) BMI >40 kg/m² Prolonged hospital admission Medical comorbidities, e.g. heart or lung disease, SLE, cancer, inflammatory conditions, nephrotic syndrome, sickle cell disease, intravenous drug user 	<ul style="list-style-type: none"> Age >35 years Obesity (BMI >30 kg/m²) Parity ≥ 3 Smoker Elective caesarean section Any surgical procedure in the puerperium Gross varicose veins Current systemic infection Immobility, e.g. paraplegia, symphysis pubis dysfunction, long-distance travel Pre-eclampsia Mid-cavity rotational operative delivery Prolonged labour (>24 h) PPH >1 L or blood transfusion
<ul style="list-style-type: none"> At least 6 weeks' postpartum prophylaxis 	<ul style="list-style-type: none"> At least 7 days' postpartum prophylaxis; if persisting or >3 risk factors, consider extending thromboprophylaxis 	<ul style="list-style-type: none"> ≥ 2: at least 7 days' postpartum prophylaxis, if persisting or >3 risk factors, consider extending thromboprophylaxis <2: early mobilisation and avoid dehydration

VTE = thromboembolism; BMI = body mass index; SLE = systemic lupus erythematosus; PPH = postpartum haemorrhage.

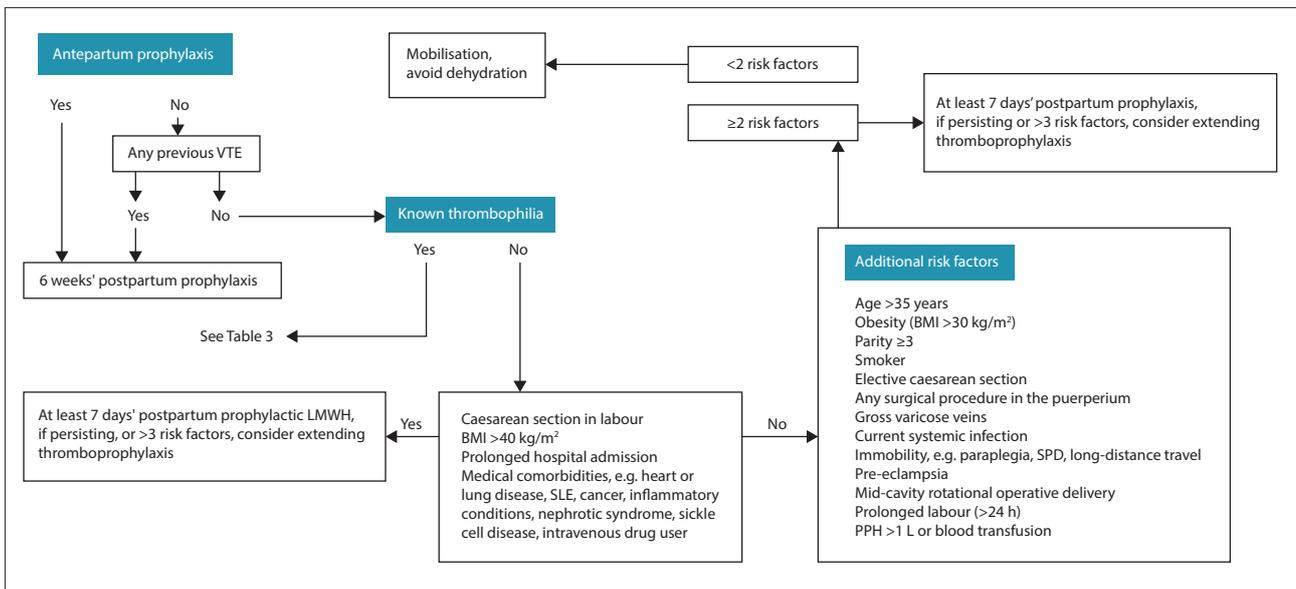


Fig. 2. Approach to assessment of venous thromboembolism risk in pregnancy at delivery/postpartum.^[9] (VTE = venous thromboembolism; LMWH = low-molecular-weight heparin; BMI = body mass index; SLE = systemic lupus erythematosus; SPD = symphysis pubis dysfunction; PPH = postpartum haemorrhage.)

Table 5. Anticoagulants used in pregnancy

Drug	Drug passes the placenta	Drug safe/unsafe in pregnancy	Drug passes into breastmilk	Drug safe/unsafe in breastfeeding
VKA	Yes	Unsafe	Yes	Safe
UFH	No	Safe	Yes	Safe
LMWH	No	Safe	Yes	Safe
Fondaparinux*	Yes	May be used*	?	Safe
NOAC	Yes	Unsafe	Yes	Unsafe
Aspirin	Yes	Yes (up to 100 mg/d)	Yes	Yes (up to 100 mg/d)

VKA = vitamin K antagonist (warfarin); UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; NOAC = novel oral anticoagulant.
*Fondaparinux should only be used if there are LMWH side-effects.

Table 6. Managing an anticoagulated patient who is planning a pregnancy

Drug	Action	Additional action
NOAC	Switch to VKA or to LMWH before the pregnancy	If switched to VKA, follow VKA path
VKA (warfarin)	Pregnancy test immediately after missed menstrual period Reassess frequently If positive pregnancy test, switch to LMWH Patient's choice to switch early	Give oral vitamin K as soon as switched to LMWH
LMWH	Continue with LMWH	-

NOAC = novel oral anticoagulant; VKA = vitamin K antagonist (warfarin); LMWH = low-molecular-weight heparin.

management of a patient on anticoagulants contemplating pregnancy is shown in Table 6.^[14]

Practical aspects of low-molecular-weight heparin prophylaxis in pregnancy

Which patients should not receive low-molecular-weight heparin as the drug of choice?

Unfractionated heparin (UFH) is indicated in patients with significant renal dysfunction and may be used if a shorter period of anticoagulation/urgent reversal is contemplated (peripartum). Fondaparinux (or danaparoid, which is currently not available South Africa (SA)) is the drug of choice in patients with heparin-induced thrombocytopenia (HIT) or a history of HIT.

What dosage of low-molecular-weight heparin should patients receive for VTE prophylaxis? Should one measure effect?

Physiological changes (increased volume of distribution and renal clearance) during pregnancy alter the pharmacokinetics of drugs,^[16] but until the study^[17] evaluating required dosages for VTE prophylaxis in pregnancy is completed, the 2018 ASH guidelines suggest against the use of intermediate dosages in antepartum prophylaxis compared with standard dosages, and for the use of standard- or intermediate-dose low-molecular-weight heparin (LMWH) for postpartum VTE prophylaxis.^[13] The SASTH guideline^[12] also suggests standard prophylactic dosages, but in view of the physiological changes in pregnancy, recommends that regular anti-factor X activity (FXa) measurement be done, especially in women at extremes of weight, with renal disease and severe pre-eclampsia. The RCOG guideline^[9] suggests that routine monitoring of the platelet count not be done in pregnant patients, unless UFH is used. Both the SASTH guideline^[12] and the Society of Obstetricians and Gynaecologists of Canada^[18] suggest that baseline platelet count be done, followed a week later with screening for HIT.

Standard dosages of LMWH are given in Table 7.

Table 7. Standard prophylactic dosages of LMWH^[1]

Drug	Standard dose	Intermediate dose*
Enoxaparin	40 mg daily	40 mg twice daily or 80 mg once daily
Nadroparin	2 850 U daily	3 800 U daily
Dalteparin	5 000 U daily	5 000 U twice daily or 10 000 U once daily
Bemiparin	40 mg daily	60 mg once daily if <50 kg; 90 mg once daily if >50 kg

LMWH = low-molecular-weight heparin.

*LMWH adjusted to peak anti-factor Xa level (3 - 4 h after administration) to 0.2 - 0.6 IU/mL.

How long should VTE prophylaxis be continued?

Patients with a high VTE risk (such as those needing antepartum prophylaxis, previous VTE event, multiple risk factors) should continue with prophylaxis for 6 weeks postpartum, and at least for 10 days if at intermediate risk, with low-risk patients receiving thromboprophylaxis until discharged from hospital.^[12]

Which patients should receive thromboprophylaxis after caesarean delivery?

There is no clear consensus regarding which patients have a low enough risk not to receive thromboprophylaxis after elective caesarean delivery (CD). Emergency CD alone puts the patient in the intermediate-risk group of the RCOG^[9] (with thromboprophylaxis indicated). This intermediate-risk group also includes patients with elective CD and an additional risk factor. Another guidance paper^[1] suggests VTE prophylaxis if one of the following is present: prior VTE, antepartum immobilisation (strict bedrest >1 week), significant postpartum infection, postpartum haemorrhage (PPH) of at least 1 000 mL that requires reoperation, pre-eclampsia with growth restriction, significant medical comorbidities (systemic lupus erythematosus (SLE), heart disease, sickle cell disease) or known thrombophilia. Thromboprophylaxis is also indicated if ≥2 of the following are present (in emergency CD ≥1): PPH >1 000 mL without

reoperation necessary, BMI >30 kg/m², fetal growth restriction, pre-eclampsia, multiple pregnancies and tobacco use during pregnancy (>10 cigarettes per day).

A practical approach is recommended by both SASTH^[12] and the European Society of Anaesthesiology (ESA) VTE guideline task force:^[19] all patients should receive thromboprophylaxis in hospital (ESA – except low-risk patients with elective CD), with the duration of thromboprophylaxis at least 6 weeks for high-risk patients and at least 7 days for low-risk patients. Mechanical prophylaxis after surgery and before starting LMWH should be left in place until the patient is mobilised and the LMWH effect is present.^[20] Managing neuraxial blockade is discussed below.

What should be done if patients on low-molecular-weight heparin develop side-effects?

- Even though the risk of HIT in pregnancy is low with the use of LMWH (estimated at <0.1%),^[21] if the diagnosis of HIT is considered (using the 4Ts score: tone of the uterus, trauma to the birth canal, tissue (retained placenta or abnormal placentation and thrombin)), the patient should be switched to a non-heparin anticoagulant (fondaparinux), and the appropriate testing done to confirm the diagnosis. If ruled out, the patient may continue receiving LMWH.
- Heparin-induced skin reaction is often seen (1.8 - 42.0% of patients)^[14] and switching to another LMWH often resolves the issue.
- Bleeding risk depends on the dosage of the anticoagulant and patient factors. Prior to prescribing thromboprophylaxis,^[22] the patient's bleeding history should always be evaluated. Risk of bleeding is highest at the time of delivery and options to reduce this risk are discussed below under management of labour.
- Osteoporosis risk is estimated to be low with prophylactic dosages of LMWH, but data are needed on therapeutic LMWH use in pregnancy. This risk is much higher with the use of UFH. Routine screening for osteoporosis in the pregnant patient is not mandatory.^[14]

Specific hypercoagulable difficult situations

- **Antithrombin (AT) deficiency.** Heparin (especially UFH) acts as an anticoagulant via AT, and VTE despite adequate LMWH prophylaxis has been described.^[23] Another problem is that some of the anti-FXa laboratory methods add AT during

testing; the laboratory value would then be unreliable in AT deficiency. These patients may need AT supplementation (not available in SA), and testing the effect of LMWH needs to be done with a method that does not add external AT in the laboratory.

- **Antiphospholipid syndrome (APLS).**^[14] This acquired thrombophilia has a high risk of pregnancy complications. Patients with APLS (even without a previous history of VTE and not on long-term prophylactic anticoagulation before pregnancy) should receive prophylactic LMWH antepartum and up to 6 weeks postpartum (there is an ongoing study to find the optimal dose).^[24] Patients receiving therapeutic anticoagulation before pregnancy should continue with therapeutic LMWH antepartum, postpartum and during pregnancy. Additional aspirin (<100 mg daily) should also be given. Catastrophic APLS, although rare, seems to be triggered in pregnancy, and a specialist team should manage these patients.

Diagnosis of VTE in pregnancy

A pregnant patient with signs or symptoms suggestive of DVT should be evaluated promptly and LMWH should be administered until the diagnosis has been excluded, unless there are contraindications

to LMWH (15 - 24% of patients with DVT develop pulmonary embolism (PE), which is fatal in almost 15% of pregnant patients).^[22] Until recently, pretest probability scoring systems (such as the modified Wells scoring system and the YEARS criteria, which include DVT present, haemoptysis and PE the most likely diagnosis) have not been used in the diagnosis of VTE during pregnancy. D-dimer testing has limited use to exclude VTE in pregnancy, as D-dimer values increase in pregnancy. Furthermore, the use of D-dimer testing in pregnancy remains controversial, as the RCOG guideline advises against such testing in this setting (a negative D-dimer is inadequate proof to exclude PE in pregnancy).^[22] Fig. 3 shows the RCOG approach: if a DVT is clinically suspected, compression duplex ultrasonography should be undertaken. If this is negative, but there is a high level of suspicion, a repeat ultrasound examination should be done after 3 and 7 days.^[22] If iliac vein thrombosis is suspected, magnetic resonance imaging (MRI) or a venogram may be done if ultrasonography is negative.

For the work-up of the pregnant woman presenting with a possible PE, the RCOG Green-top guideline^[22] suggests the following (Fig. 4): Unless contraindicated, consider giving LMWH during work-up. The patient should have a chest radiograph and electrocardiogram (ECG) done urgently. If signs and symptoms of DVT are present,

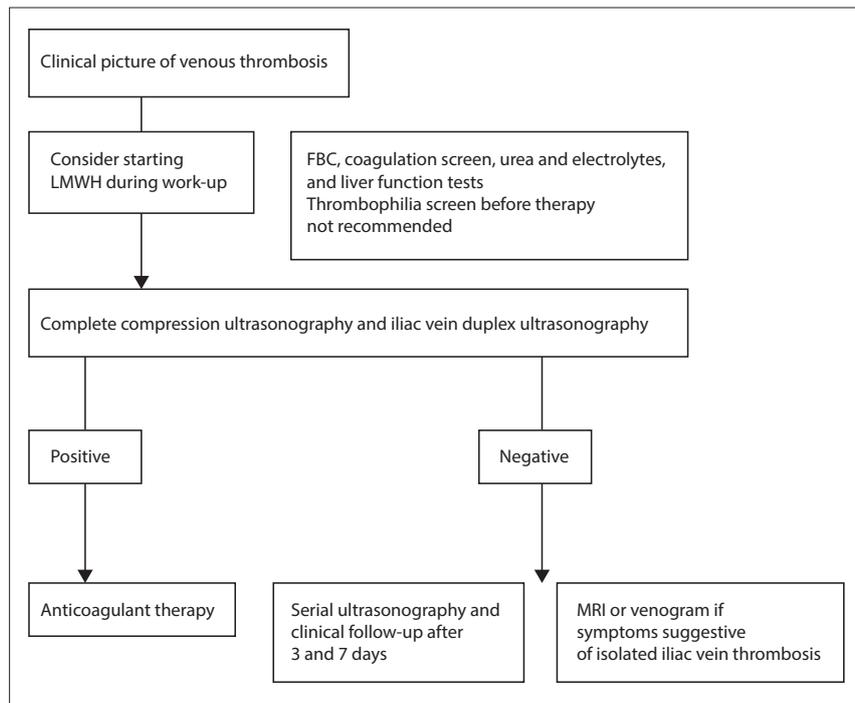


Fig. 3. Suggested flow diagram for diagnosis of venous thrombosis (adapted from the Royal College of Obstetricians and Gynaecologists guideline^[22]). (LMWH = low-molecular-weight heparin; FBC = full blood count; MRI = magnetic resonance imaging.)

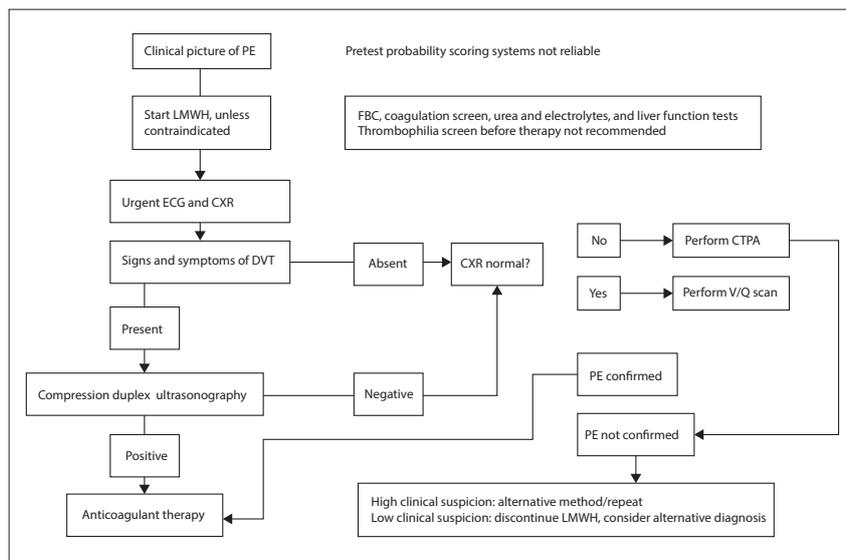


Fig. 4. Suggested flow diagram for the diagnosis of pulmonary embolism (adapted from the Royal College of Obstetricians and Gynaecologists guideline^[22]). (PE = pulmonary embolism; LMWH = low-molecular-weight heparin; FBC = full blood count; ECG = electrocardiogram; CXR = chest radiograph; DVT = deep-vein thrombosis; CTPA = computed tomography pulmonary angiogram; V/Q = ventilation/perfusion.)

an ultrasound examination should be done, and if positive, no further testing is required (but the patient must be assessed for severity of the PE). If the ultrasound findings are negative, confirmation of the PE is either with a ventilation/perfusion (V/Q) scan or computed tomography pulmonary angiogram (CTPA). Radiation risk to the mother is the highest with CTPA, and radiation risk to the fetus is highest with a V/Q scan (radiation risk below the threshold for fetal teratogenicity, death or growth restriction, but a very small increased risk of childhood cancer development). Informed consent must be obtained from the mother before performing any of these tests. If the chest radiograph is abnormal, a CTPA is suggested rather than a V/Q (more specific for other pathological conditions). If the clinical suspicion is still high after the CTPA or V/Q test, alternative testing or repeat testing may be done, but anticoagulation must be continued until the diagnosis is definitely excluded. The ASH guideline^[13] suggests a V/Q scan rather than CTPA for exclusion of PE. The European Society of Cardiology (ESC) 2019 acute pulmonary embolism management guideline,^[25] however, suggests using the assessment of clinical probability, D-dimer measurement, compression ultrasound examination, and CTPA to possibly safely exclude PE in pregnancy. With new CTPA techniques, radiation to the breasts of the mother is much less (such as reducing kilovoltage, reducing the anatomical coverage of the scan and reducing

the contrast-monitoring component of the CTPA).^[25] If a PE is diagnosed, its severity and the risk of early death should be assessed as soon as possible, and the patient referred to a multidisciplinary team with experience in the management of PE.

Treatment of VTE in pregnancy

All guidelines state that treatment of VTE in pregnancy should be with LMWH as the preferred drug.^[13] UFH may be used in massive PE (cardiovascular collapse), or when VTE occurs at term.^[3,22] Acute superficial vein thrombosis should also be treated with LMWH.^[13] The dosage of LMWH needs to be therapeutic, and although traditionally given as a twice-daily dose, the ASH guideline^[13] (low certainty) recommends that either once-daily or twice-daily LMWH may be administered. Due to the half-life of LMWH, a twice-daily dosage is a more rational choice pharmacokinetically.^[13] Doses are titrated against the patient's booking or early pregnancy weight. Routine anti-FXa measurement is not indicated (ASH guideline),^[13] but regular anti-FXa measurement is suggested in the SASTH guideline^[12] (for prophylaxis and therefore also for treatment). The RCOG Green-top guideline^[22] suggests anti-FXa measurement in cases of extremes of body weight (<50 kg or >90 kg), and in the presence of complicating factors (e.g. renal dysfunction). Recommended baseline blood measurements are full blood count, coagulation screening,

urea and electrolytes and liver function tests, but thrombophilia screening should not be done at the time of VTE.^[22] Most patients with VTE need to be admitted to hospital. Treatment should be continued with therapeutic doses during the remainder of the pregnancy and at least for 6 weeks postpartum. If the patient has a high risk of osteoporosis, bleeding or an isolated distal DVT, 1 month of full-dose therapy decreased to 75% of the therapeutic dose may be considered.^[1] If the VTE event occurred during the last trimester, at least 3 months of therapy should be given. With VTE at term, consideration should be given to UFH (much easier to use therapeutically).^[22] Thrombolysis should only be considered in life-threatening VTE (massive PE, limb-threatening DVT), and must be managed by a team of experienced clinicians.^[22] The 2018 ASH guideline^[13] states that pregnant patients with acute PE and right ventricular dysfunction in the absence of haemodynamic instability should not receive thrombolysis (systemic thrombolytic therapy only in acute PE and life-threatening haemodynamic instability). Graduated elastic compression stockings to reduce oedema are suggested.^[22] The only indication for the insertion of an inferior vena cava filter would be an acute VTE and if anticoagulation is contraindicated.^[1]

Suggested dosages of LMWH and fondaparinux according to weight are described in Tables 8 and 9.

Managing labour in patients on anticoagulation

Anticoagulation at the time of labour poses a risk of bleeding, and all pregnant patients receiving antepartum thromboprophylaxis need a delivery plan.^[12] This should be discussed early (~30 weeks' gestation)^[14] and includes mode of delivery, e.g. CD, induction of labour (scheduled delivery) or spontaneous labour and delivery. The decision should be based on obstetric indication,^[12] but mostly depends on patient and physician preference. The ASH guideline^[13] suggests scheduled delivery with prior discontinuation of anticoagulation in patients receiving therapeutic dosages of LMWH (24 hours before delivery). In patients receiving prophylactic dosages of LMWH, the ASH guideline suggests against scheduled delivery (conditional recommendation, with very little evidence), but LMWH should be discontinued 12 hours prior to delivery. If spontaneous labour occurs, the patient must be advised to discontinue LMWH at the first sign of labour (contraction, membrane

rupture) or any vaginal bleeding. Switching from LMWH to UFH closer to delivery has been suggested in the very-high-risk patient to reduce the 'time without anticoagulation period', but this showed increased bleeding risk.^[26] (UFH can be discontinued 4 - 6 hours before delivery.^[27]) Attention should be paid to the mechanism of clotting (formation of thrombin), as well as to the other haemostatic factors (known as the 4 Ts).^[3] The ESC guideline suggests active management of the third stage of labour with modified doses of oxytocin.^[28] Wound drains (abdominal and rectus sheath) should be considered with CD and skin closure should be with interrupted sutures or staple clips.^[9] Reintroduction of treatment should be started 4 - 6 hours after vaginal delivery or 6 - 12 hours after CD (American College of Obstetricians and Gynecologists)^[1] in the absence of postpartum haemorrhage and regional anaesthesia.^[9] The Royal College

of Obstetricians and Gynaecologists^[9] guideline suggests avoiding the use of warfarin in the first 5 days after delivery, and for a longer period in the patient at risk of postpartum haemorrhage. Mechanical prophylactic measures should be left *in situ* until the patient is ambulatory and on anticoagulation again.

Managing neuraxial anaesthesia

With CD, the risk for adverse intraoperative and postoperative events is lower with neuraxial anaesthesia than with general anaesthesia. It is also often the choice for anaesthesia during labour, because it contributes to minimising the urge to bear down before complete cervical dilation and decreases circulating catecholamines.^[29] If the patient is on anticoagulation, it is crucial to evaluate the specific drug, dosage and time since administration before neuraxial anaesthesia.

Table 8. Initial therapeutic dosages of LMWH^[22]

Booking or early pregnancy weight, kg	Enoxaparin dose, mg*	Dalteparin dose, IU*	Bemiparin dose, mg*
<50	40 bd or 60 once daily	5 000 bd or 10 000 once daily	60 once daily
50 - 69	60 bd or 90 once daily	6 000 bd or 12 000 once daily	90 once daily
70 - 89	80 bd or 120 once daily	8 000 bd or 16 000 once daily	120 once daily
90 - 109	100 bd or 150 once daily	10 000 bd or 20 000 once daily	90 - 100 kg: 120 once daily
110 - 125	120 bd or 180 once daily	12 000 bd or 24 000 once daily	100 - 125 kg: 180 once daily
>125	Discuss with haematologist	Discuss with haematologist	Discuss with haematologist

LMWH = low-molecular-weight heparin.
*Anti-factor Xa testing required.

Table 9. Treatment dosages of fondaparinux*^[23]

Booking or early pregnancy weight, kg	Fondaparinux, mg
<50	2.5 once daily
51 - 75	5.0 once daily
76 - 100	7.5 daily
>100	10.0 daily

*Only to be used if there is a low-molecular-weight heparin side-effect, e.g. heparin-induced thrombocytopenia.

Knowledge of the patient's platelet count and possible drugs that interfere with platelet function is necessary before administering neuraxial anaesthesia. Extreme caution is needed if any other drugs influencing coagulation are prescribed,^[12] and concomitant antiplatelet therapy (aspirin/non-steroidal anti-inflammatory drugs (NSAIDs)) should not be administered with heparin if a neuraxial catheter is left *in situ*.^[30] Aspirin should not be given for 5 - 7 days prior to neuraxial anaesthesia if the patient is receiving anticoagulant therapy. Women who have received neuraxial anaesthesia should

Table 10. Summary of most recent guidelines regarding neuraxial anaesthesia

	Low-dose LMWH	Higher-dose LMWH [†]	Low-dose UFH [†]	Higher-dose UFH [†]	Fondaparinux (prophylactic, 2.5 mg) [‡]
Period after last dose given	Wait for ≥12 h	Wait ≥24 h	Wait ≥4 - 6 h	Wait ≥24 h (intermediate dose ≥12 h)	Wait 36 - 42 h
Restarting anticoagulation after neuraxial block [§]	Wait ≥12 h	Wait ≥24 h ^[29]	Wait ≥1 h	Wait ≥1 h	Wait 12 h
Restarting anticoagulation after insertion of indwelling catheter [§]	Wait ≥4 h	Maintain anti-coagulation with low-dose LMWH; therefore, wait ≥4 h, no NSAIDs	Wait ≥1 h	Maintain with low-dose UFH; therefore, wait ≥1 h	-
Removal of catheter after last anticoagulant	Wait ≥12 h	Low-dose LMWH maintenance; therefore, wait ≥12 h	Wait ≥4 - 6 h	Low-dose UFH; therefore, wait ≥4 - 6 h	-
Restarting anticoagulant after removal of catheter	Wait ≥4 h	Wait ≥4 h	Wait ≥1 h	Wait ≥1 h	Wait 6 - 12 h

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; NSAIDs = non-steroidal anti-inflammatory drugs.

[†]Anti-factor Xa assay may be done.

[‡]Activated partial thromboplastin time to be determined.

[§]Neuraxial anaesthesia impractical with fondaparinux.

[¶]If blood is noted in the needle or neuraxial catheter, LMWH should be delayed for at least 24 h.

be monitored closely for the development of spinal haematoma (mandatory for a minimum of 12 hours; ideally for 72 hours).^[12] Table 10 shows some of the suggested guidelines that have been published in the past year, but the SOAP guideline states clearly that it 'is not intended to set out a legal standard of care and does not replace medical care or the judgment of the responsible medical professional considering all the circumstances presented by an individual patient'.^[30] It is also applicable to the patient with normal renal function in the context of pregnancy and body weight >40 kg, with no other known contraindications to neuraxial anaesthesia.^[30] The ASRA guideline^[28] is also incorporated in Table 10. It is important that each unit has an easily accessible protocol for managing these patients. If spontaneous labour occurs while the patient is on anticoagulation, neuraxial anaesthesia should not be administered if labour is within the contraindicated timeframe.

Summary

Managing VTE in the pregnant patient is complex, and although guidelines have been discussed in this article, a team approach, taking all factors in the individual patient into consideration, is essential. It is impossible to discuss all the permutations of thrombotic and bleeding risk factors in every patient. The reader is advised to read the excellent recent reviews, including the first statement by SOAP regarding anaesthetic management in pregnant patients receiving thromboprophylaxis.^[30]

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- Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis* 2016;41(1):92-128. <https://doi.org/10.1007/s11239-015-1309-0>
- Thornton P, Douglas J. Coagulation in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2010;24(3):339-352. <https://doi.org/10.1016/j.bpobgyn.2009.11.010>
- Fogerty AE. Challenges of anticoagulation therapy in pregnancy. *Curr Treat Options Cardiovasc Med* 2017;19(10):76. <https://doi.org/10.1007/s1193>
- Bravo MC, Bernstein I, McBride C, et al. Hemostatic activation and glycoalyx shedding during pregnancy. *Blood* 2018;132:3794. <https://doi.org/10.1182/blood-2018-99-119304>
- Moodley J, Fawcus S, Pattinson R. Improvements in maternal mortality in South Africa. *S Afr Med J* 2018;108(3a):s4-s8. <https://doi.org/10.7196/SAMJ.2018.v108i3.12770>
- Speed V, Roberts LN, Patel JP, Arya R. Venous thromboembolism and women's health. *Br J Haematol* 2018;183(3):346-363. <https://doi.org/10.1111/bjh.15608>
- James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: Incidence, risk factors, and mortality. *Am J Obstet Gynecol* 2006;194(5):1311-1315. <https://doi.org/10.1016/j.ajog.2005.11.008>
- McLean K, Cushman M. Venous thromboembolism and stroke in pregnancy. *Hematology* 2016;2016(1):243-250. <https://doi.org/10.1182/asheducation-2016.1.243>
- Royal College of Obstetricians and Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-Top Guideline No. 37a, 2015. <https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf> (accessed 30 September 2019).
- Dargaud Y, Rugeri L, Fleury C, et al. Personalized thromboprophylaxis using a risk score for the management of pregnancies with high risk of thrombosis: A prospective clinical study. *J Thromb Haemost* 2017;15(5):897-906. <https://doi.org/10.1111/jth.13660>
- Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing G-J, Kyrle PA, for the Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: Guidance from the SSC of ISTH. *J Thromb Haemost* 2016;14(7):1480-1483. <https://doi.org/10.1111/jth.13336>
- Schapkaite E, de Jong PR, Jacobson BF, Büller HR. Recommendations for thromboprophylaxis in obstetrics and gynaecology. *S Afr J Obstet Gynaecol* 2018;24(1):27-31. <https://doi.org/10.7196/sajog.1312>
- Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Venous thromboembolism in the context of pregnancy. *Blood Advances* 2018;2(22):3317-3359. <https://doi.org/10.1182/bloodadvances.2018024802>
- Scheres LJJ, Bistervels IM, Middeldorp S. Everything the clinician needs to know about evidence-based anticoagulation in pregnancy. *Blood Rev* 2019;33:82-97. <https://doi.org/10.1016/j.blre.2018.08.001>
- Bleker SM, Coppens M, Middeldorp S. Sex, thrombosis and inherited thrombophilia. *Blood Rev* 2014;28:123-133. <https://doi.org/10.1016/j.blre.2014.03.005>
- Anderson GD. Pregnancy-induced changes in pharmacokinetics. *Clin Pharmacokinet* 2005;44(10):989-1008. <https://doi.org/10.2165/00003088-200544100-00001>
- Bleker SM, Buchmüller A, Chauleur C, et al. Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy: Rationale and design of the Highlow study, a randomised trial of two doses. *Thromb Res* 2016;144:62-68. <https://doi.org/10.1016/j.thromres.2016.06.001>
- Chan WS, Rey E, Kent NE, et al. Venous thromboembolism and antithrombotic therapy in pregnancy. *J Obstet Gynaecol Can* 2014;36(6):527-553. [https://doi.org/10.1016/S1701-2163\(15\)30569-7](https://doi.org/10.1016/S1701-2163(15)30569-7)
- Ducloy-Bouthors A-S, Baldini A, Abdul-Kadir R, Nizard J, for the ESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis: Surgery during pregnancy and the immediate postpartum period. *Eur J Anaesthesiol* 2018;35(2):130-133. <https://doi.org/10.1097/eja.0000000000000704>
- James A, Committee on Practice Bulletins. Obstetrics Practice Bulletin No. 123: Thromboembolism in pregnancy. *Obstet Gynecol* 2011;118(3):718-729.
- Linkins L-A, Dans AL, Mores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic therapy and prevention of thrombosis. *American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*. *Chest* 2012;141(2 Suppl):e495S-e530S. <https://doi.org/10.1378/chest.11-2303>
- Royal College of Obstetricians and Gynaecologists. Thrombosis and embolism during pregnancy and the puerperium: Acute management (Green-top Guideline No. 37b). 2015. <https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37b.pdf> (accessed 30 September 2019).
- Fogerty AE. Management of venous thromboembolism in pregnancy. *Curr Treat Options Cardiovasc Med* 2018;20(8):69. <https://doi.org/10.1007/s11936-018-0658-3>
- Bleker SM, Buchmüller A, Chauleur C, et al. Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy: Rationale and design of the highlow study, a randomised trial of two doses. *Thromb Res* 2016;144:62-68. <https://doi.org/10.1016/j.thromres.2016.06.001>
- Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2019;1-61. <https://doi.org/10.1093/eurheartj/ehz405>
- Wang EHZ, Marnoch CA, Khurana R, Sia W, Yuxsel N. Haemorrhagic complications of peripartum anticoagulation: A retrospective chart review. *Obstet Med* 2014;7(2):77-83. <https://doi.org/10.1177%2F1753495X14520849>
- Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic therapy and prevention of thrombosis. *American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*. *Chest* 2012;141(2 Suppl):e691S-e736S. <https://doi.org/10.1378/chest.11-2300>
- Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;39(34):3165-3241. <https://doi.org/10.1093/eurheartj/ehy340>
- Horlocker TT, Vandermeulen E, Kopp S, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy. *Reg Anesth Pain Med* 2018;43(3):263-309. <https://doi.org/10.1097/AAP.0000000000000763>
- Leffert L, Butwick A, Carvalho B, et al. The Society for Obstetric Anesthesia and Perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. *Anesth Analg* 2018;126(3):928-944. <https://doi.org/10.1213/ane.0000000000002530>

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