

South Australian Perinatal Practice Guideline

Thromboprophylaxis and Thromboembolic Disease in Pregnancy

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Note

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Explanation of the aboriginal artwork:

The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant woman. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.



Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that Perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

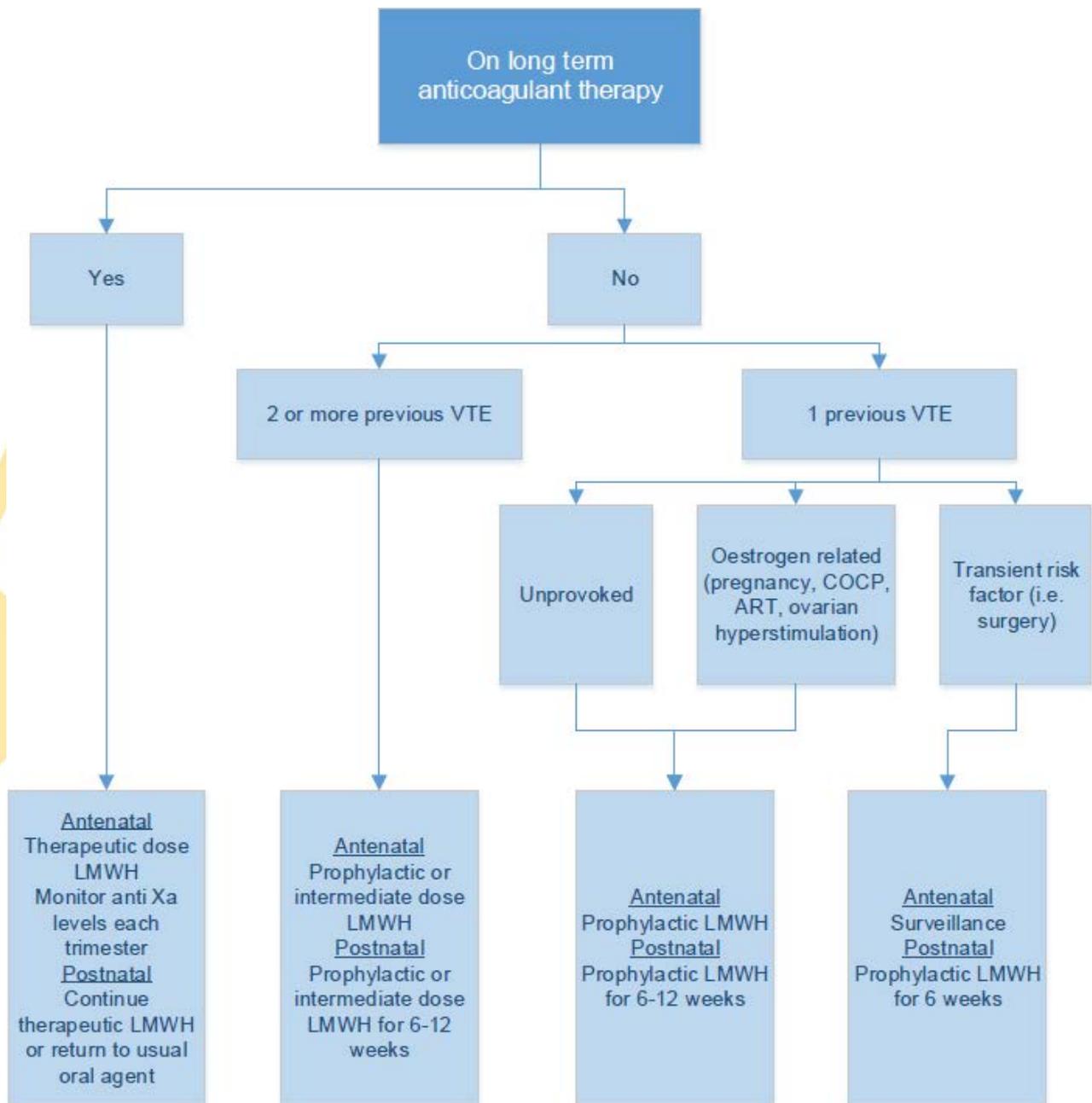
Purpose and Scope of this PPG

This PPG aims to assist clinical decision making in preventing and managing venous thromboembolic disease in pregnancy and the post-partum period. It does not cover the management of antiphospholipid syndrome, nor of anticoagulation for cardiac indications, including prosthetic cardiac valves in pregnancy; these conditions require specialist assessment and management.



Thromboprophylaxis and Thromboembolic Disease in Pregnancy

Flowchart 1: Thromboprophylaxis for women with a history of venous thromboembolic disease (VTE)



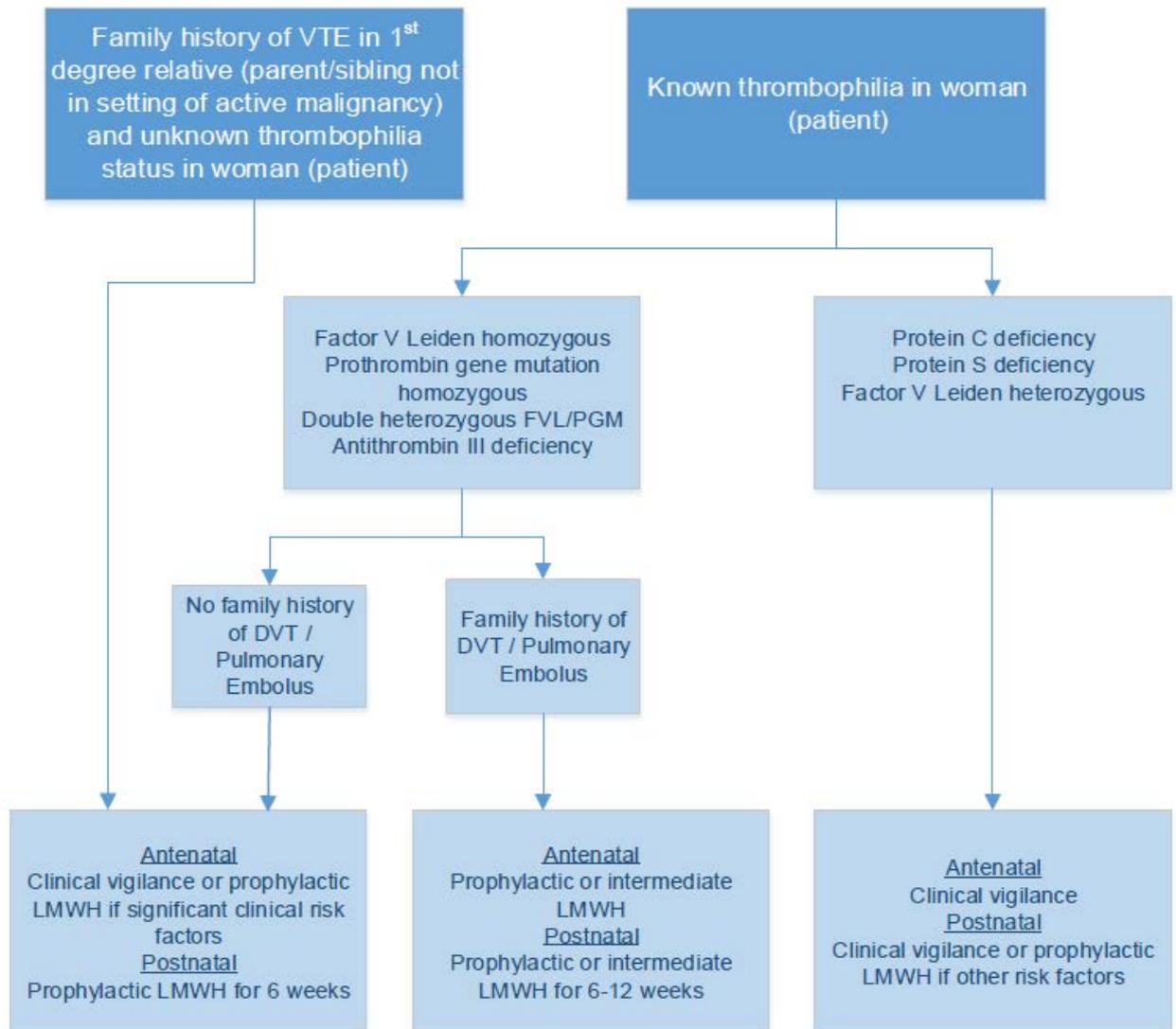
Decisions regarding the optimal dose of LMWH for antenatal and postnatal thromboprophylaxis, as well as the appropriate duration of therapy postpartum may need to be made in consultation with an Obstetric Physician or experienced Haematologist.

*Following delivery, warfarin or LMWH can be used safely by women who are breastfeeding or expressing. NOAC's such as rivaroxaban should not be used in lactating women.



Thromboprophylaxis and Thromboembolic Disease in Pregnancy

Flowchart 2: Thromboprophylaxis in women with no prior history of VTE, but family history of VTE and/or known thrombophilia



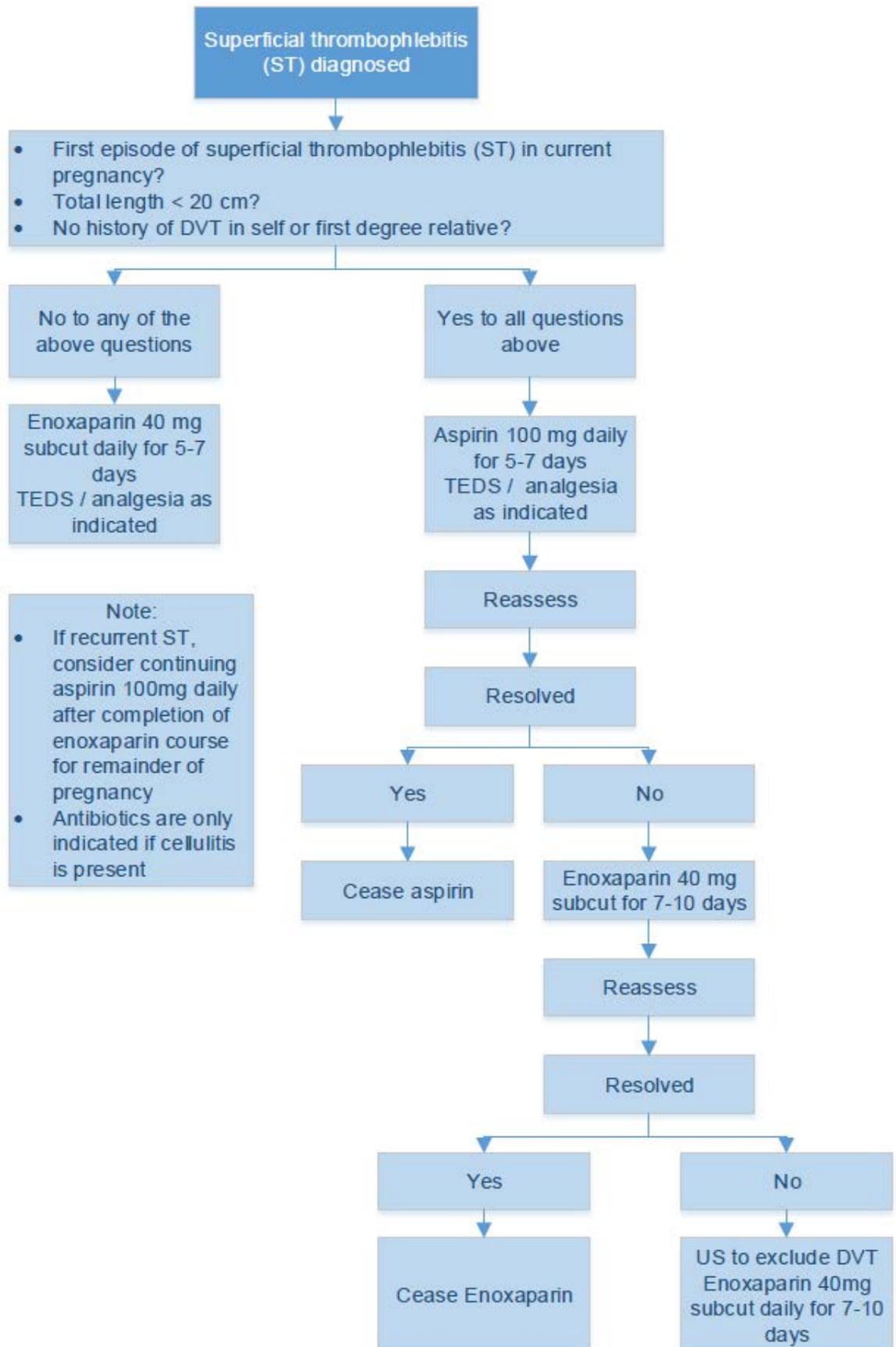
Family history of VTE is of significance if it occurs in a first degree relative (ie: parents or siblings). The context of an episode of VTE also requires assessment (ie: likely lower risk if occurred in the setting of joint replacement surgery or active malignancy).

Decisions regarding the optimal dose of LMWH for antenatal and postnatal thromboprophylaxis, as well as the appropriate duration of therapy postpartum may need to be made in consultation with an Obstetric Physician or experienced Haematologist.



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Flowchart 3: Superficial Thrombophlebitis Management



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Table 1: Antenatal Thromboprophylaxis

Antenatal thromboprophylaxis in women with clinical risk factors	
Risk factor	Prophylaxis indicated
<ul style="list-style-type: none">• Immobilisation (anticipated bed rest ≥ 7 days) + BMI $\geq 25\text{kg/m}^2$• Inpatients with prior VTE if not already on antenatal prophylaxis• Significant OHSS• Active systemic lupus erythematosus (SLE)• Nephrotic syndrome with albumin $\leq 19\text{g/L}$• Cardiac disease• Inpatient with family history of VTE (in first degree relative)• Inpatient with high risk thrombophilia not already on antenatal prophylaxis• Inpatient with active bacterial infection and reduced mobility	Prophylactic LMWH for the duration of admission or resolution of active medical condition. Reassess requirement 48-72 hours post-admission.



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Table 2: Postnatal thromboprophylaxis

Who gets post-partum thromboprophylaxis?

1. Any woman who has been on antenatal anticoagulation (LMWH) for maternal thromboprophylaxis, regardless of mode of delivery: 6-12 weeks.
2. Any woman who has a personal history of a thromboembolic event, regardless of mode of delivery or whether they were on antenatal thromboprophylaxis: 6-12 weeks.
3. Women with clinical risk factors stratified according to table.

Type of Birth	One or more of the following	Duration of treatment
Normal vaginal birth	Some hereditary thrombophilias and / or VTE in first degree relative – discuss with physician. Post-partum haemorrhage of at least 1,000mL requiring operation and / or transfusion Significant post-partum infection Antepartum immobility (bed rest > 6 days)	Generally will only need treatment while in hospital or until infection resolves, but discuss with on-call physician in tertiary centre if uncertain.
Any LSCS	Antepartum immobility (bed rest > 6 days) Significant post-partum infection Post-partum haemorrhage of at least 1,000mL requiring re-operation Pre-eclampsia with growth restriction Significant medical co-morbidities (cardiac, renal, inflammatory – including superficial thrombophlebitis) Known thrombophilia* VTE in a first degree relative**	5-14 days, or until resolution of infection or inflammatory condition. Discuss with on-call physician in tertiary centre if uncertain. High risk thrombophilias may require 6-12 weeks
Emergency LSCS	Post-partum haemorrhage of at least 1,000mL not requiring re-operation / anaemia (Hb < 100g/L) BMI > 30kg/m ² Fetal growth restriction Pre-eclampsia Multiple pregnancy Tobacco use during pregnancy (at least 10 cigs/day) Pre-existing diabetes	5-14 days, or until resolution of infection or inflammatory condition. Discuss with on-call physician in tertiary centre if uncertain
	Two or more of the following	
Elective LSCS	Post-partum haemorrhage of at least 1,000mL not requiring re-operation / anaemia (Hb < 100g/L) BMI > 30kg/m ² Fetal growth restriction Pre-eclampsia Multiple pregnancy Tobacco use during pregnancy (at least 10 cigs/day) Pre-existing diabetes	5-14 days, or until resolution of infection or inflammatory condition. Discuss with on-call physician in tertiary centre if uncertain.

* Recognised thrombophilias are: Factor V Leiden (FVL), prothrombin gene mutation (PGM), antithrombin III deficiency (ATIII), Protein C deficiency, Protein S deficiency.

High risk thrombophilias are FVL homozygosity, PGM homozygosity, FVL / PGM double heterozygosity and some types of ATIII.

MTHFR variants are not considered thrombophilias for the purpose of determining risk of VTE.

**Sibling or Parent.

Bates et al (2016)

This is not an exhaustive list: If you are caring for a patient whom you think may benefit from LMWH, but does not fall under these categories, discuss further with senior obstetric or medical staff.



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Abbreviations

ALT	Alanine aminotransferase
APH	Antepartum haemorrhage
APLS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time
ART	Assisted reproduction technology
bd	Twice a day
BMI	Body mass index
Cigs	Cigarettes
CI	Confidence interval
cm	Centimetre(s)
COCP	Combined oral contraceptive pill
DVT	Deep venous thrombosis
e.g.	For example
et al.	And others
FVL	Factor V Leiden
g	Gram(s)
HIC	Heparin induced thrombocytopenia
Hrs	Hours
IOL	induction of labour
INR	International normalised ratio
IU	International units
IV	Intravenous
kg	Kilogram(s)
LMWH	Low-molecular weight heparin
LSCS	Lower segment caesarean section
mg	Milligram(s)
mL	Millilitre(s)
min	Minute(s)
mmHg	Millimetres of mercury
MTHFR	Methylene tetrahydrofolate reductase
NaCl	Sodium Chloride
NOAC	Novel oral anticoagulant compounds
PGM	Prothrombin gene mutation
PE	Pulmonary (thrombo)embolism
PET	Pre-eclampsia
RCT	Randomised controlled trial
subcut	Subcutaneous
ST	Superficial thrombophlebitis
TEDS	Thrombo embolic deterrent stockings
%	Percentage
UK	United Kingdom
UFH	Unfractionated heparin
VTE	Venous thromboembolism



Thromboprophylaxis and Thromboembolic Disease in Pregnancy

Definitions

Deep venous thrombosis	Thrombus within deep peripheral veins (often of the lower limbs, but can include subclavian and upper limb veins).
Pulmonary embolism	Presence of thrombus in the pulmonary vasculature as a result of movement of a peripheral thrombus.
Superficial thrombophlebitis	Inflammatory thrombus in a superficial vein (also known as superficial venous thrombosis)
Thrombophilia	Refers to an inherited or acquired condition which increases an individual's risk of VTE
Venous thromboembolic disease	Development of a thrombus anywhere in the venous system

Introduction and Disclaimer

While the overall incidence of VTE is low, estimated at 0.5-2 per 1,000 pregnancies depending on the population studied, DVT and PE remain an important cause of maternal morbidity and mortality in developed nations. Approximately 25% of events are PE's, and of these, approximately 1 in 40 is fatal. It is therefore important that staff dealing with women during and after pregnancy are not only able to recognise the features of acute VTE so that prompt diagnosis and treatment can occur, but also that they are familiar with the risk factors for VTE so that preventative treatment can be offered.

The main risk factors to be assessed are:

- Past history of VTE
- History of VTE in a first degree relative
- Presence of a known thrombophilia
- Clinical risk factors (including immobility, LSCS, increased BMI, medical and obstetric comorbidities)

VTE risk increases 5-10 fold during the antenatal period, with a further increase to 15-35 fold postpartum (compared to age-matched non-pregnant women). Up to 50% of antenatal events occur in the first two trimesters, therefore both antenatal and postnatal thromboprophylaxis must be considered in high-risk women.

While risk factors for VTE are well recognised, due to the large number of clinical variables and the overall low frequency of VTE in the pregnant / postpartum population, there is a paucity of high-quality data specific to pregnancy on which to base recommendations. Published guidelines are based largely on observational studies, extrapolation from data in non-pregnant populations and consensus opinion.

With the awareness of these limitations, each woman should be assessed individually, with a discussion regarding her risks of VTE and the treatment options. For some women, clinical vigilance rather than prophylaxis may be preferable if she accepts her risk of VTE and feels that the burden of LMWH prophylaxis outweighs potential benefits.

Further discussion with an Obstetric Physician or a Haematologist with experience in pregnancy is advised if there is any uncertainty. More extensive information to assist in quantifying risk can be found in the publications listed in "Additional resources".



Thromboprophylaxis and Thromboembolic Disease in Pregnancy

Thromboprophylaxis in women with a history of VTE

The most important risk factor for the development of VTE in or after pregnancy is a prior history of VTE, regardless of the presence or absence of a recognised thrombophilia or other clinical risk factors. See [Flowchart 1](#).

Decisions regarding the optimal dose of LMWH for antenatal and postnatal thromboprophylaxis, as well as the appropriate duration of therapy postpartum may need to be made in consultation with an Obstetric Physician or experienced Haematologist.

*Following delivery, warfarin or LMWH can be used safely by women who are breastfeeding or expressing. NOAC's such as rivaroxaban should not be used in lactating women.

Thromboprophylaxis in women with no history of venous thromboembolic disease, but a family history and / or known thrombophilia

Family history of VTE is of significance if it occurs in a first degree relative (i.e. parents or siblings). The context of an episode of VTE also requires assessment (i.e. likely higher risk for the woman if a relative's VTE episode was spontaneous or oestrogen-related rather than provoked; e.g. malignancy, trauma, operation). See [Flowchart 2](#).

Decisions regarding the optimal dose of LMWH for antenatal and postnatal thromboprophylaxis, as well as the appropriate duration of therapy postpartum may need to be made in consultation with an Obstetric Physician or experienced Haematologist.

Thromboprophylaxis in women with clinical risk factors only

After previous VTE, immobility carries the highest odds ratio of all acquired risk factors. Women who have 2 or more other risk factors should be considered for anticoagulation during antenatal admission.

Antenatal thromboprophylaxis: See [Table 1](#)

Postpartum thromboprophylaxis: See [Table 2](#)

Options for thromboprophylaxis

Mechanical options for VTE prophylaxis

In hospitalised women, mechanical prophylaxis with either elastic stockings (TEDS) or intermittent pneumatic compression is an option for women with contraindications to pharmacological prophylaxis (ie during and immediately following LSCS). There is limited evidence which suggests these devices are less effective than pharmacological prophylaxis in preventing VTE.

Pharmacological options for VTE prophylaxis – low molecular weight heparins

Subcutaneously administered low molecular weight heparins (LMWH) are preferred over unfractionated heparin (UFH), due to their convenience and better adverse effect profile. Both UFH and LMWH have been demonstrated to not cross the placenta, and there are studies demonstrating their safety in pregnancy. With UFH there have been concerns regarding the potential for bleeding at the uteroplacental junction; this has not been remarked on with LMWH.



Thromboprophylaxis and Thromboembolic Disease in Pregnancy

Low Molecular Weight Heparin (LMWH) Regimens for VTE Prophylaxis

LMWH	Prophylactic dose	Intermediate dose
Enoxaparin	40mg daily	40mg bd or 80mg daily
Dalteparin	5,000units daily	5,000units bd or 10,000units daily
Tinzeparin	4,500units daily or 75units / kg daily	10,000units daily
Nadroparin	2,850units daily	

* Enoxaparin is available on the State Formulary. For access to another LMWH, please contact your hospital pharmacist.

The decision to use a prophylactic vs an intermediate dose should be made after individual assessment. Some recommend the higher intermediate dose for women with increased weight (ie > 90kg), or perceived higher risk. There are no published studies directly comparing different dosing regimens and the target anti-Xa levels for thromboprophylaxis in pregnancy are unknown (some have suggested peak level of 0.2-0.6units/mL).

Side Effects

Bruising and pain at injection site. Rate of allergic skin reactions estimated at 1.8% (95% CI 1.34-2.37) from systematic review.

Thrombocytopenia: HIT less common than with UFH – monitoring generally not indicated.

Osteoporosis (reversible) – rate of osteoporotic fractures 0.04% (95% CI 0.01-0.2).

Rise in serum transaminases (ALT)

Contraindications and cautions

LMWH's are renally cleared, and should be used with caution or avoided in women with significant renal impairment (creatinine clearance < 30mL/min). It may be appropriate to either reduce the dose or use UFH.

LMWH's should not be used in women with a history of HIT.

Advice should be sought from an Obstetric Physician or experienced Haematologist, for women with a platelet count < 80, or in the presence of a coagulopathy.

LMWH should not be used in women who are actively bleeding (e.g. APH) or at high risk (e.g. placenta praevia) or in whom delivery is expected within 24 hours.

LMWH should not be used in women with intracranial haemorrhage (including haemorrhagic stroke) or ischaemic stroke within the past four weeks.

LMWH should not be used in women with uncontrolled hypertension (systolic BP > 200mmHg or diastolic BP > 120mmHg).

Pharmacological options for VTE prophylaxis – unfractionated heparin

Unfractionated heparin (UFH) may be preferred peripartum in women with a higher risk of haemorrhage or in whom regional anaesthetic techniques may be required. UFH has a shorter half-life, and there is more complete reversal with protamine sulphate than with LMWH's. The required interval between the last prophylactic dose and neuraxial blockade is less (4-6 hours) than for LMWH (12 hours), and there is less concern regarding neuraxial haematomas. There is a higher rate of HIT, and the platelet count should be monitored; there is also an increased risk of HIT in women taking LMWH if they have previously been exposed to UFH.

The usual prophylactic dose of UFH is 5,000units 12 hourly.

Pharmacological options for VTE prophylaxis – danaparoid

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Danaparoid is a heparinoid, used in women with intolerance to heparins (ie due to skin reactions or HIT). There is limited experience with its use in pregnancy, and while there appears to be no increased risk of adverse fetal outcomes, significant maternal bleeding events (including placental bleeding) have been reported. Danaparoid has a long half-life (24hrs), and regional anaesthesia should be avoided. It appears to be safe for use in breastfeeding (although direct evidence is limited).

Pharmacological options for VTE prophylaxis – fondaparinux

Fondaparinux is a Factor Xa inhibitor used in women with intolerance to heparins. It is administered daily as a subcutaneous injection, and should be avoided within 6 hours of surgery due to an increased risk of bleeding. There is limited experience with its use in pregnancy; in one study of 65 women there was no obvious increase in the rates of pregnancy complications.

Acute venous thromboembolic disease in pregnancy and post-partum: diagnosis and investigation.

Deep venous thrombosis

Up to 90 % of deep venous thromboses in pregnant women occur in the left leg and over 70 % are iliofemoral in their location; an iliofemoral DVT is more likely to embolise than a calf vein thrombosis.

Distal deep venous thromboses are sited distal to the popliteal vein.

Proximal deep venous thromboses are in or above the popliteal vein, including pelvic vein thromboses.

Symptoms and signs

Leg pain or discomfort in the absence of trauma (especially left leg)

Swelling, tenderness and /or increased temperature and oedema of the limb

Lower abdominal pain may be the presenting feature of thrombus in the pelvis or groin

Homan's sign (pain on dorsiflexion of the calf) is unreliable as it is present in only 8 % to 30 of symptomatic women with deep venous thrombosis and can be elicited in up to 50 % of symptomatic women who do not have a deep venous thrombosis

History-taking should also include symptoms suggestive of pulmonary embolism

Investigations

Compression duplex ultrasound

When iliac vein thrombosis is suspected, (backpain and swelling of the entire limb) magnetic resonance venography or contrast venography (abdominal shielding) may be considered if ultrasound fails to visualise thrombus adequately

D dimer measurements are UNRELIABLE in pregnancy/postpartum: a negative D-dimer does not exclude VTE in a high risk woman

Pulmonary thromboembolism

Occurs in approximately 1:7,000 pregnancies

Deep venous thrombosis usually precedes pulmonary thromboembolism, but the thrombosis may be asymptomatic until embolisation occurs

Symptoms and signs

Dyspnoea with or without reduced oxygen saturation on pulse oximetry



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Chest pain (pleuritic)
Collapse with hypotension*
Haemoptysis
Faintness*
Tachycardia or arrhythmia
Raised jugular venous pressure*
Symptoms and signs associated with deep venous thromboses in peripheries

Investigations

Arterial blood gas on air
Complete blood count, electrolytes, liver function tests
Coagulation screen (a prolonged APTT should raise the suspicion of a lupus anticoagulant being present, consult the physician / haematologist)
Chest X-ray
A consultant physician opinion should be sought before proceeding to further imaging
If persistent clinical suspicion of acute pulmonary thromboembolism, a ventilation-perfusion (V / Q) lung scan or a computed tomography pulmonary angiogram (CTPA) should be performed after obtaining informed consent from the woman.
Advise that V / Q scanning carries a slightly increased risk of childhood cancer compared with CTPA (1 / 280,000 versus < 1 / 1,000,000) but carries a lower risk of maternal breast cancer (lifetime risk increased by up to 13.6 % with CTPA, background risk of 1 / 200 for study population)
Ensure the woman is aware that V / Q scanning involves the injection of albumin-bound isotope (particularly if she has declined blood products) before ordering the investigation

*If there is evidence of circulatory collapse or cardiac compromise:

ECG and cardiac enzymes
Urgent echocardiogram

This is a potentially life-threatening situation, and the patient should be stabilised while arrangements are being made for transfer to a facility with both adult intensive care and maternity services. Prompt involvement of or (if not possible) consultation with senior Medical, Obstetric and Anaesthetic staff is required.

Acute venous thromboembolic disease in pregnancy and post-partum: management.

Initial Management

Where a provisional diagnosis of deep venous thrombosis or pulmonary thromboembolism has been made, treatment should be given until the diagnosis is clarified, unless strong contraindications exist. Treatment for other differential diagnoses such as bronchopneumonia should be given concurrently whilst awaiting definitive diagnosis.

Non- pharmacological treatments

Oxygen to maintain adequate saturations in the setting of pulmonary embolism
Analgesia as required for both DVT and PE
Women with extensive DVT may require mobility aids and physiotherapy
TEDS may provide a measure of symptomatic relief, but have not been shown to alter the prognosis of DVT or reduce the incidence of post-thrombotic pain syndromes.

Massive, life threatening pulmonary thromboembolism

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Intravenous unfractionated heparin is the preferred treatment in massive pulmonary thromboembolism with cardiovascular compromise

Collapsed, shocked patients need to be assessed by a team of experienced clinicians. (See *Collapse (maternal)* PPG available at www.sahealth.sa.gov.au/perinatal). Where possible this should include the on-call consultant obstetrician, physician, consultant anaesthetist, and cardiologist / intensivist, who should decide on an individual basis whether the woman receives intravenous unfractionated heparin or thrombolytic treatment and referral to an Adult intensive care service.

Thrombolysis with tenecteplase may be required: this requires cardiac monitoring in an appropriate facility and carries a significant risk to the fetus. Further discussion of this treatment is beyond the scope of this PPG.

Pharmacological options for VTE treatment – low molecular weight heparins

Low molecular weight heparin is the Australasian (and international) medical consensus recommendation for standard initial therapeutic treatment of VTE in the absence of contraindications.

LMWH's do not cross the placenta, and are safe to use in patients who are lactating. Enoxaparin is commonly used at a therapeutic dose of 1mg/kg (max 120mg) twice daily, with consideration for dose reduction in significant renal failure.

Duration of therapy is three months for an uncomplicated distal DVT, and six months for women with either PE or significant proximal DVT. If therapy is due to finish before the end of the pregnancy, prophylactic anticoagulation should be continued for the remainder of the pregnancy and for a further six weeks post-partum.

Routine measurement of anti-Xa activity for patients on LMWH for treatment of acute VTE in pregnancy or post-partum is not generally recommended. In some patient populations (e.g. APLS) testing is indicated, and should be undertaken in consultation with specialist Obstetric Medicine or Haematology services. If testing is required, close communication with both venesection services and the laboratory is necessary to ensure prompt and appropriate transport of samples in order to obtain a useful result.

In selected women with distal DVT's, give consideration to reducing enoxaparin to a single daily dose of 1.5 mg / kg after at least six weeks on 1mg / kg twice daily.

Low Molecular Weight Heparin (LMWH) Regimens for VTE Treatment

Low molecular weight heparin	Therapeutic dose
Enoxaparin	1mg / kg every 12 hours
Dalteparin	100units / kg every 12 hours

* Enoxaparin is available on the State Formulary. For access to another LMWH, please contact your hospital pharmacist.

Side Effects

Bruising and pain at injection site. Rate of allergic skin reactions estimated at 1.8% (95% CI 1.34-2.37) from systematic review.

Thrombocytopenia: HIT less common than with UFH – monitoring generally not indicated.



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Osteoporosis (reversible) – rate of osteoporotic fractures 0.04% (95% CI 0.01-0.2).
Rise in serum transaminases (ALT)

Contraindications and cautions

LMWH's are renally cleared, and should be used with caution or avoided in women with significant renal impairment (creatinine clearance < 30mL/min). It may be appropriate to either reduce the dose or use UFH.

LMWH's should not be used in women with a history of HIT.

Advice should be sought from an Obstetric Physician or experienced Haematologist, for women with a platelet count < 80, or in the presence of a coagulopathy.

LMWH should not be used in women who are actively bleeding (e.g. APH) or at high risk (e.g. placenta praevia) or in whom delivery is expected within 24 hours.

LMWH should not be used in women with intracranial haemorrhage (including haemorrhagic stroke) or ischaemic stroke within the past four weeks.

LMWH should not be used in women with uncontrolled hypertension (systolic BP > 200mmHg or diastolic BP > 120mmHg).

Pharmacological options for VTE treatment – unfractionated heparin

Intravenous (IV) unfractionated heparin (UFH) infusion is the preferred treatment in acute venous thromboembolism and pulmonary embolism when there is haemodynamic instability.

UFH does not cross the placenta and is safe to use in women who are lactating.

Used as a substitute for therapeutic low molecular weight heparin during the 24 - 36 hour period before elective induction of labour or caesarean section

Treatment is usually commenced with a loading dose, followed by a steady IV infusion rate. Determination of both the loading dose and initial infusion rate depends on the woman's weight and is calculated according to the following nomogram. If any confusion, consult the on-call obstetric physician in a tertiary hospital.

UFH – initial bolus and infusion rate for patients with DVT / PE

Weight	< 55kg	56-65kg	66-75kg	76-85kg	86-95kg	>95kg
	Omit loading dose if clinically appropriate					
Initial IV bolus (80units/kg)	4,000units	4,800units	5,600units	6,400units	7,200units	8,000units
Initial infusion rate (18units/kg/hr)	900units/hr	1,100units/hr	1,250units/hr	1,450units/hr	1,600units/hr	1,800units/hr

Before commencing intravenous unfractionated heparin:

Take blood for group and save, Activated Partial Thromboplastin Time (APTT), complete blood picture and any thrombophilia studies that may be recommended

Identify renal impairment and consult with Obstetric Physician or Haematologist re dose adjustments.

Omit the loading dose in the following:

If the woman has received thrombolysis

If the last dose of therapeutic LMWH (e.g. Enoxaparin) has been given less than 12 hours before commencing IV unfractionated heparin infusion

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Target APTT

Check APTT 4-6 hours after bolus dose and 6 hours after any dose change. If the APTT is within the therapeutic range (65-100 seconds), maintain infusion rate and check APTT daily. Platelet count should be checked at least every alternate day. For values outside the target range, refer to the following table for appropriate adjustments for weight. For women at the extremes of weight (<50kg or > 100kg), or if therapeutic APTT not achieved within 24 hours, contact Obstetric Physician or Haematologist.

Unfractionated heparin intravenous infusion set up:

Draw up five (5) ampoules of heparin sodium 5000 units (total of 25,000 units) in 50mL syringe
Add sodium chloride 0.9% to make up to 50mL in total (resulting solution will be 500 units/mL)
Administer via syringe pump



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Nomogram for adjusting UFH infusion rate according to APTT in DVT / PE

Weight	<56kg	56-65kg	66-75kg	76-85kg	86-95kg	>95kg	Repeat APTT
Infusion adjustment according to APTT and weight							
APTT (seconds)	Administer additional bolus if clinically appropriate – do not give within 24 hours of delivery						
<50	Bolus 4000units Increase rate by 200units/hr	Bolus 4800units Increase rate by 250units/hr	Bolus 5600units Increase rate by 300units/hr	Bolus 6400units. Increase rate by 300units/hr	Bolus 7200units. Increase rate by 350units/hr	Bolus 8000units. Increase rate by 400units/hr	4-6 hours
50-64	Bolus 2,000units Increase rate by 100units/hr	Bolus 2,400units Increase rate by 100units/hr	Bolus 2,800units Increase rate by 150units/hr	Bolus 3,200units. Increase rate by 150units/hr	Bolus 3,600units. Increase rate by 200units/hr	Bolus 4,000u. Increase rate by 200units/hr	4-6 hours
65-110	Target range – no adjustment necessary, APTT next morning (within 24 hours).						
111-130	Decrease rate by 100units/hr	Decrease rate by 100units/hr	Decrease rate by 150units/hr	Decrease rate by 150units/hr	Decrease rate by 200units/hr	Decrease rate by 200units/hr	4-6 hours
130-199	Hold infusion 60 mins. Decrease rate by 150units/hr	Hold infusion 60 mins. Decrease rate by 200units/hr	Hold infusion 60 mins. Decrease rate by 200units/hr	Hold infusion 60 mins. Decrease rate by 250units/hr	Hold infusion 60 mins. Decrease rate by 250units/hr	Hold infusion 60 mins. Decrease rate by 300units/hr	4-6 hours
>200	Hold infusion; repeat APTT every 2hours. If <120, restart infusion with rate decreased by 150units/hr.	Hold infusion; repeat APTT every 2hours. If <120, restart infusion with rate decreased by 200units/hr.	Hold infusion; repeat APTT every 2hours. If <120, restart infusion with rate decreased by 200units/hr.	Hold infusion; repeat APTT every 2hours. If <120, restart infusion with rate decreased by 250units/hr.	Hold infusion; repeat APTT every 2hours. If <120, restart infusion with rate decreased by 250units/hr.	Hold infusion; repeat APTT every 2hours. If <120, restart infusion with rate decreased by 300units/hr.	2 hours

Side effects

Thrombocytopenia
Osteoporosis (reversible)
Rise in serum transaminases

Complications

If a complication occurs during treatment (e.g. thrombocytopenia or haemorrhage), the infusion should be suspended and the appropriate consultant opinion as to whether to continue, vary or discontinue the unfractionated heparin treatment should be sought



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Clinical considerations

Do not draw blood from the same line or arm as the unfractionated heparin infusion

Fill coagulation tubes to the specified mark and send to the lab urgently to avoid erroneous results or clotting and the need for a further sample to be taken

Avoid intramuscular injections and arterial stabs during anticoagulant treatment

Heparin antidote / reversal

Discuss management with consultant Physician and / or Haematologist

If anticoagulation with heparin needs to be discontinued for clinical reasons, termination of the heparin infusion within 4-6 hours will usually suffice

If an immediate effect is required, the heparin antidote protamine sulphate may be considered.

Protamine sulphate neutralises heparin by virtue of its positive charge and will take effect within 5 minutes of IV administration.

Protamine (in ampoules containing 50mg in 5mL) can be given without dilution, however as slow administration (over 10mins) is recommended; dilution in either 0.9% Sodium Chloride or 5% Glucose is advised.

The rate of protamine administration should not exceed 5mg protamine / minute; rapid administration can cause circulatory compromise with hypotension, bradycardia, systemic and pulmonary hypertension and dyspnoea, as well as anaphylaxis, flushing and fever. Management is supportive with resuscitation as required.

Women with known hypersensitivity reactions to fish (especially salmon), and those who have received previous protamine therapy, including protamine-containing insulins (NPH, protaphane – intermediate-acting insulins) may be at risk of hypersensitivity reactions.

Dosage: give up to 1mg protamine for every 100 units of heparin received in the preceding 2 hours, to a maximum of 50mg of protamine. Reduce dose of protamine according to time elapsed since last administration of heparin (see table).

Heparin Reversal Regimen

Time since last heparin dose	Protamine dose (mg) per 100units heparin received in the previous 2 hours
Less than 30mins	1mg
30-60mins	0.5-0.75mg
60-120mins	0.375-0.5mg
More than 120mins	0.25-0.375mg

APTT and Prothrombin Time should be checked 15mins after the administration of protamine sulphate.

Pharmacological options for VTE treatment – oral anticoagulants

Warfarin

Warfarin is an oral Vitamin K antagonist; it crosses the placenta, and has been associated with a range of adverse fetal outcomes, including teratogenicity (warfarin embryopathy), pregnancy loss, fetal bleeding and neurodevelopmental deficits. Warfarin is not recommended for treatment of VTE antenatally, however as it does not cross into breast milk, it can be safely used for the treatment of VTE in postnatal women.

Prior to commencing therapy with warfarin, baseline coagulation studies with International Normalised Ratio (INR) should be obtained.

Target INR for treatment of VTE in the postnatal period is 2-3; therapeutic LMWH should be continued until the INR is >1.9.

Royal Adelaide Hospital Warfarin Dosing Protocol (edited to only include ≤ 50 years old)

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Day	INR	Warfarin Dose in mg
1 (Baseline pre-dose)	≤ 1.4	10
2 (16 hrs after 1st dose)	≤ 1.5	10
	≥ 1.6	0.5
3 (16 hrs after 2 nd dose)	≤ 1.7	10
	1.8 - 2.3	5
	2.4 - 2.7	4
	2.8 - 3.1	3
	3.2 - 3.3	2
	3.4	1.5
	3.5	1
	3.6 - 4.0	0.5
	> 4.0	0
	4 (16 hrs after 3 rd dose)	≤ 1.5
1.6		8
1.7 - 1.8		7
1.9		6
2.0 - 2.6		5
2.7 - 3.0		4
3.1 - 3.5		3.5
3.6 - 4.0		3
4.1 - 4.5		Omit next dose, then use 1-2
> 4.5		Withhold dose

(adapted from Aust NZ J Med 1999; 29: 731-6 & Ann Pharmacother 2003; 37: 799-803)

If warfarin is commenced in hospital, the patient should receive warfarin counselling (e.g. from the pharmacy service) and be given a record book. The patient's usual General Practitioner should be informed via telephone of the diagnosis and treatment plan; this should then be followed with a faxed discharge letter containing a record of in-hospital warfarin doses and INR's to facilitate smooth transition from inpatient care to outpatient management by the GP.

Some women may prefer to continue therapeutic LMWH rather than commencing warfarin with the associated need for frequent INR's and review.

Novel oral anticoagulants (NOAC's)

These newer agents are increasingly used outside maternity care for the management and prevention of a range of thrombotic conditions. They are not recommended for either pregnant or lactating women, as their effects on both human pregnancy and on the breastfed infant are not known.

For postnatal women who are not breastfeeding or expressing for their infant, these agents offer an alternative to warfarin without the need for regular INR testing and with generally comparable rates of haemorrhagic complications. LMWH can be ceased after the first dose of these agents.

Dabigatran is a direct, competitive thrombin inhibitor; the dose of dabigatran for treatment of VTE is 150mg bd. Dabigatran is renally cleared; appropriate dose adjustment in renal impairment (creatinine clearance < 30mL/min) is unknown, so it should be used with caution in this setting. Adverse effects: haemorrhage, gastritis / GI ulceration, angioedema, thrombocytopenia.



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Rivaroxaban is a Factor Xa inhibitor; the dose of rivaroxaban for treatment of VTE is initially 15mg bd for 21 days, then 20mg daily for the remainder of the treatment course. It can also be used for VTE prophylaxis at a dose of 10mg daily. Rivaroxaban is not recommended for use in patients with significant hepatic or renal impairment. Adverse effects: haemorrhage, peripheral oedema, GI disturbance.

Superficial Thrombophlebitis

Superficial thrombophlebitis refers to inflammatory thrombus in the superficial veins: there is not the risk of embolization to the pulmonary circulation, but as between 6-44% of patients with superficial thrombophlebitis will either have or develop deep vein thrombosis (and potentially pulmonary embolism), they must be investigated and managed appropriately. While treatment is aimed at relieving local pain and preventing extension (including into the deep venous system), there can sometimes be associated cellulitis, which will require antibiotics.

Symptoms

Pain and inflammation over superficial vein(s) with areas of intravascular thrombus palpable

May also have erythema and oedema in surrounding area

Chills, high fever, and leucocytosis indicate septic superficial thrombophlebitis (*Staphylococcus aureus* is the most frequent cause)

Increasing swelling may indicate association with DVT

Investigations

Compression duplex ultrasound to exclude DVT

Complete blood picture

C-reactive protein

Serum urea and electrolytes

Coagulation studies

Liver function tests (to confirm normal hepatic and renal function before commencing anticoagulant therapy)

Treatment

See [Flowchart 3](#)



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Managing anticoagulation around birth

Table for Neuraxial Anaesthesia

Antepartum or intrapartum	
UFH prophylaxis ($\leq 10,000$ units/day)	Wait 4-6 hours after last dose before neuraxial blockade
UFH therapeutic	Cease infusion 4-6 hours before neuraxial blockade; Check APTT at 3-4 hours after ceasing infusion and ensure within normal range prior to insertion of neuraxial blockade.
LMWH prophylaxis	Wait 10-12 hours after last dose before neuraxial blockade
LMWH therapeutic	Wait 24 hours after last dose before neuraxial blockade; in this situation, bridging with IV UFH may be required.
Postpartum	
Wait until $> 6-8$ hours post-LSCS or NVD without excessive bleeding or other contraindications before commencing post-partum anticoagulation. Anaesthetic considerations may extend the duration of waiting, as outlined in this table.	
UFH prophylaxis ($\leq 10,000$ units/day) following removal of epidural catheter or use of spinal needle	Wait > 1 hour after epidural catheter removal or spinal needle placement to give dose
UFH prophylaxis with epidural catheter in situ	Wait 4-6 hours after the last dose of UFH to remove epidural catheter. The next dose of UFH should not be given until > 1 hour after removal of the epidural catheter.
UFH therapeutic	Wait at least 4 hours after epidural catheter removal or spinal needle placement to recommence infusion
LMWH prophylaxis following removal of epidural catheter or use of spinal needle.	Wait at least 4 hours after epidural catheter removal or spinal needle placement to give dose.
LMWH prophylaxis with epidural catheter in situ	Wait 10-12 hours after last dose of LMWH to remove epidural catheter. The next dose of LMWH should not be given until > 2 hours after removal of the epidural catheter.
LMWH therapeutic	Do not use with epidural catheter in situ; wait at least 12-4 hours after removal of epidural catheter or spinal needle to give dose.
Warfarin	Can commence at 1600 hours on the day after the day of birth.



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Additional Resources / References

Note: The references below were used to inform this PPG but are not specifically referred to in the text.

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Write Group Lead

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Write Group Members

Dr Neville Fields
Dr Bill Hague
Dr Bill Jeffries
Dr Shantha Joseph
Dr Mark Morton
Dr Lee Taylor

SAPPG Management Group Members

Sonia Angus
Dr Kris Bascomb
Lyn Bastian
Dr Feisal Chenia
John Coombas
A/Prof Rosalie Grivell
Dr Sue Kennedy-Andrews
Jackie Kitschke
Catherine Leggett
Dr Anumpam Parange
Dr Andrew McPhee
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Simone Stewart-Noble
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