Venous Thromboembolism in Pregnancy - Prevention

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1. Purpose of guideline

This guideline establishes the expected measures to prevent venous thromboembolism (VTE) during pregnancy and up to six postpartum within Te Toka Tumai Auckland.

Venous thromboembolism in pregnancy and the postpartum period remains one of the most common causes of maternal mortality in the developed world.

The overall incidence of pregnancy-associated VTE (PA-VTE) in a low-risk pregnancy is around 1 in 1500, with an equal proportion (i.e. 0.5 in 1500) of VTE occurring over the nine-month antenatal period and within the six-week postpartum period respectively. This means that the day-to-day VTE risk is greater in the postpartum compared to the antenatal period. The majority of women who develop PA-VTE have personal or pregnancy-specific risk factors for thrombosis that were either untreated or unrecognised.

Risk assessment of women and pregnant people and recommendations regarding thromboprophylaxis, are still supported only by weak clinical evidence. Most recommendations are based on expert opinion rather than from information from randomised clinical trials. Recommendations from a group of Australian and New Zealand Specialists and Green-Top Guidelines from The Royal College of Obstetricians and Gynaecologists (RCOG) in the United Kingdom, both advocate risk assessment of all pregnant women to determine their risk of PA-VTE.

The evidence correlating risk factors and the occurrence of PA-VTE is imprecise, with wide estimates of risk, and is likely to be subject to various sources of bias. The assessment of risk in an individual pregnant person has not been validated by relevant studies. The RCOG empirically recommend three or more risk factors as a threshold for prophylaxis even though this has not been formally tested in clinical trials.

There is currently no consensus on the VTE risk threshold for when to offer thromboprophylaxis. The potential risk of harm (e.g., bleeding complications), as well as patient preferences, should be taken into consideration during the risk-benefit discussion.

An assessment of the risk of thromboembolism should be carried out in all pregnant patients. Some women and pregnant people have risk factors (Table 1 and Table 2) that place them at an increased risk of VTE throughout their pregnancy and the postpartum period; that are identified before or during pregnancy and warrant extended thromboprophylaxis. Others will develop complications during pregnancy with thromboprophylaxis only recommended while they are hospitalised, especially if additional risk factors for VTE are present.

2. Guideline management principles

The management principles of this guideline are to:

- Assess the risk of VTE for all pregnant patients at the earliest opportunity (see Section 4)
- Consider whether antenatal prophylaxis is required (see Section 7)
- Consider postnatal thromboprophylaxis (see Section 8)
- Reassess risk throughout the pregnancy and puerperium
- Develop an individualised plan with the patient
- Ensure all patients mobilise early postpartum and avoid dehydration

3. Risk factors

Pregnancy is associated with a 5- to 10-fold increase in the risk of VTE due to pregnancy specific factors and maternal risk factors. Pregnancy-specific factors include venous stasis, an increase in procoagulant factor, a reduction in natural anticoagulants, and vessel wall injury that occurs during labour and following caesarean section (CS).

Increased BMI is an important and consistent risk factor for PA-VTE, especially in combination with immobilisation. Long haul air travel has not been specifically studied in pregnant women but it is associated with a two-fold increased risk in the general population. Risk factors are summarised in Table 1.

3.1 Prior history of VTE

Previous VTE is one of the most important risk factors for PA-VTE. The risk of recurrence is higher following a previous *unprovoked* event (no identified risk factors) than after a *provoked* event (associated with a risk factor). Women with previous *hormonally provoked* VTE (pregnancy or oral contraceptive associated) have an increased risk of developing a recurrent VTE in a subsequent pregnancy.

Women with a prior life-threatening provoked VTE (e.g., submassive pulmonary embolism following major surgery) will require a nuanced discussion about antenatal thromboprophylaxis – postpartum thromboprophylaxis is recommended.

The role of **hereditary thrombophilia** in PA-VTE has been extensively reviewed. Table 2 summarises the absolute risks of PA-VTE in women with thrombophilia, with data derived from studies of either unselected women or family cohort studies.

While the most common thrombophilia, factor V Leiden (fVL) and the prothrombin gene mutation, increase the relative risk of PA-VTE, the absolute risk of VTE during pregnancy with these conditions are small. For example, fVL was associated with an eight-fold increased risk of PA-VTE in a cohort of 2480 women but this represented only three cases (1.1%) among 270 fVL positive women.

There is no case for screening asymptomatic women for thrombophilia whether pregnant or not or undergoing fertility treatment. Notwithstanding this, many women have already been tested and for this reason it is necessary to include recommendations to deal with such cases. The methylenetetrahydrofolate reductase (MTHFR) polymorphism has not been shown to be more prevalent in women with PA-VTE and testing for this and homocysteine is not recommended.

3.2 Family history of VTE

Hereditary thrombophilias are only identified in around 50% of family cohorts with VTE so that in many women who have a positive family history of VTE there will be no laboratory marker that helps identify if they are at increased risk.

VTE is increasingly being recognised as a multigenic disease and the relevance of a positive family history i.e. one or more first-degree relative (parent, sibling, or child) with VTE is being increasingly recognised and has been shown to increase the risk of VTE 2-fold. The strength of the association increases if younger relatives (age) are affected [Odds ratio 2.7 (95%CI 2.2-3.4)] and if more than one relative is affected [Odds ratio 3.9 (95%CI 2.7-5.7)].

In the absence of a documented thrombophilia it will not be possible to identify which members of a family cohort are at increased risk. Therefore, all women from these families must be assumed to be at higher risk.

4. Risk factors tables

Table 1: Clinical risk factors for PA-VTE	
Risk factor	**Adjusted OR**
Previous VTE	24.8
Age >35	1.4-1.7
Obesity (BMI > 30kgm^2)*	1.7-5.3
Active medical illness	2.1-8.7
Smoking	1.7-3.46
Family history VTE	2.9-4.1
Immobility	7.7-10.1
Varicose veins	2.4
Multiparity (>2)	1.6-2.9
Multiple pregnancy	1.6-4.2
Preeclampsia	3.0-5.8
Assisted reproduction technology	2.6-4.3
Hyperemesis	2.5
Preexisting maternal medical risk factors	
Sickle cell disease	4.4-10.1
Systemic lupus erythematosus (SLE) – flare	5.8-13
Heart disease	2.6-11.3
Additional postpartum risk factors	
Planned caesarean section	1.3-2.7
Emergency caesarean section	2.7-4.0
Placental abruption	2.5-16.6
Postpartum infection	4.1-20.2
Postpartum haemorrhage	1.3-12.0

Table 2: Absolute risk of VTE with women with hereditary thrombophilias		
Thrombophilia	**Family history VTE unknown** *	**Positive family history VTE with known thrombophilia#**
Significant		
Antithrombin deficiency	0.3-4%	3.0-18.0%
Factor V Leiden homozygous	1.3-2.3%	9-17.0%
Factor V Leiden/prothrombin mutation compound heterozygous	5.20%†	1.8-5.5%
Protein C deficiency	0.5-1.8%	1.7-5.0%
Protein S deficiency	0.1-1.0%	2.0-6.6%
Weak		
Factor V Leiden heterozygous	0.2-0.5%	1.5-3.9%
Prothrombin mutation heterozygous	0.2-0.4%	1-2.8%
Family history of VTE with thrombophilia: unaffected controls		0.4-1.4%

*Derived from case control data assuming incidence of VTE 1/1500 pregnancies (0.07%).
Data from family studies of first degree relatives with VTE.
† Single study only.

Table 3: Summary of recommendations for the prevention of PA-VTE		
Patient Details	**Antenatal Recommendation**	**Postpartum Recommendation**
Positive family history VTE [§] but no personal history VTE +/- weak laboratory thrombophilia	Observation unless other risk factors	Prophylaxis favoured especially if other risk factors
Positive family history VTE [§] but no personal history VTE with significant laboratory thrombophilia	Prophylaxis favoured especially if other risk factors	Prophylaxis for six weeks postpartum
Single prior provoked VTE (excluding those associated with COCP or pregnancy)	Observation unless other risk factors	Prophylaxis for six weeks postpartum
Single prior VTE associated with COCP	Prophylaxis recommended	Prophylaxis for six weeks postpartum
Single prior unprovoked VTE Single prior pregnancy-associated VTE Prior recurrent provoked VTE	Prophylaxis recommended	Prophylaxis for six weeks postpartum

[§] Family history VTE: See Section 3.2.

5. Risk assessment

All pregnant women should have an assessment of risk of VTE at the earliest opportunity i.e. first antenatal visit or pre-conception (Table 1, Table 2, and Table 3).

Pregnant women and patients require reassessment of their risk for VTE if there is any change to their health during pregnancy, especially if admitted to hospital and also after delivery.

Commencing prophylaxis at times of additional VTE risk is clinically important and appropriate.

Decisions relating to thromboprophylaxis require detailed discussion with the individual person, during which the risks and benefits of any suggested management should be carefully explained. The final management decision should take into account the preferences of the patient.

6. Thromboprophylaxis: general

According to findings from the Highlow study [*Bistervels et al Lancet 2022]*, weight-adjusted dosing of low molecular weight heparin (LMWH) did not reduce the risk of PA-VTE recurrence in women with history of VTE when compared to standard prophylactic dose LMWH.

There remains insufficient data to recommend an increased prophylactic dose of LMWH for all patients with increased weight (> 90 kg). However, it is reasonable to consider higher doses in those patients with a BMI > 40 kg/m^2. Dosages in these patients should be discussed with an obstetric physician or obstetrician. Although there is no firm evidence on which to base dosing recommendations, but intermediate doses such as enoxaparin 40 mg twice daily (with consideration to epidural removal time as appropriate) or 60 mg daily have been used.

Thromboprophylaxis should be considered for patients with a BMI ≥ 30 kg/m^2 who are admitted to hospital especially if they have additional risk factors or are immobilised.

Any patient with a history or increased risk of VTE should be educated about the concerning symptoms suggestive of DVT and PE, to facilitate early recognition and management.

Both warfarin and LMWH are considered safe to use whilst breastfeeding.

The antenatal and postpartum flowcharts do not apply to patients requiring therapeutic doses of anticoagulation (e.g. for treatment of acute VTE in pregnancy, those on long-term anticoagulation for prior VTE, recurrent VTE or prosthetic heart valve/s, antiphospholipid syndrome, or antithrombin deficiency). Discussion with an obstetric physician or haematologist, about the management of these patients, are required.

7. Thromboprophylaxis: antenatal

Flowchart 1 outlines the recommended approach for deciding which women should have extended antenatal thromboprophylaxis. The strategy of stratifying risk based on gestation of pregnancy has not been validated by studies and should be viewed pragmatically.

Pregnancy-derived VTE risk scores have only been studied prospectively in small trials, lack precision, and therefore have limited place in current clinical practice.

Extended antenatal thromboprophylaxis, if recommended, should be started as early in pregnancy as possible. Unless otherwise stated, LMWH at prophylactic doses is recommended for antenatal thromboprophylaxis (Table 4).

7.1 Flowchart 1: Antenatal thromboprophylaxis assessment

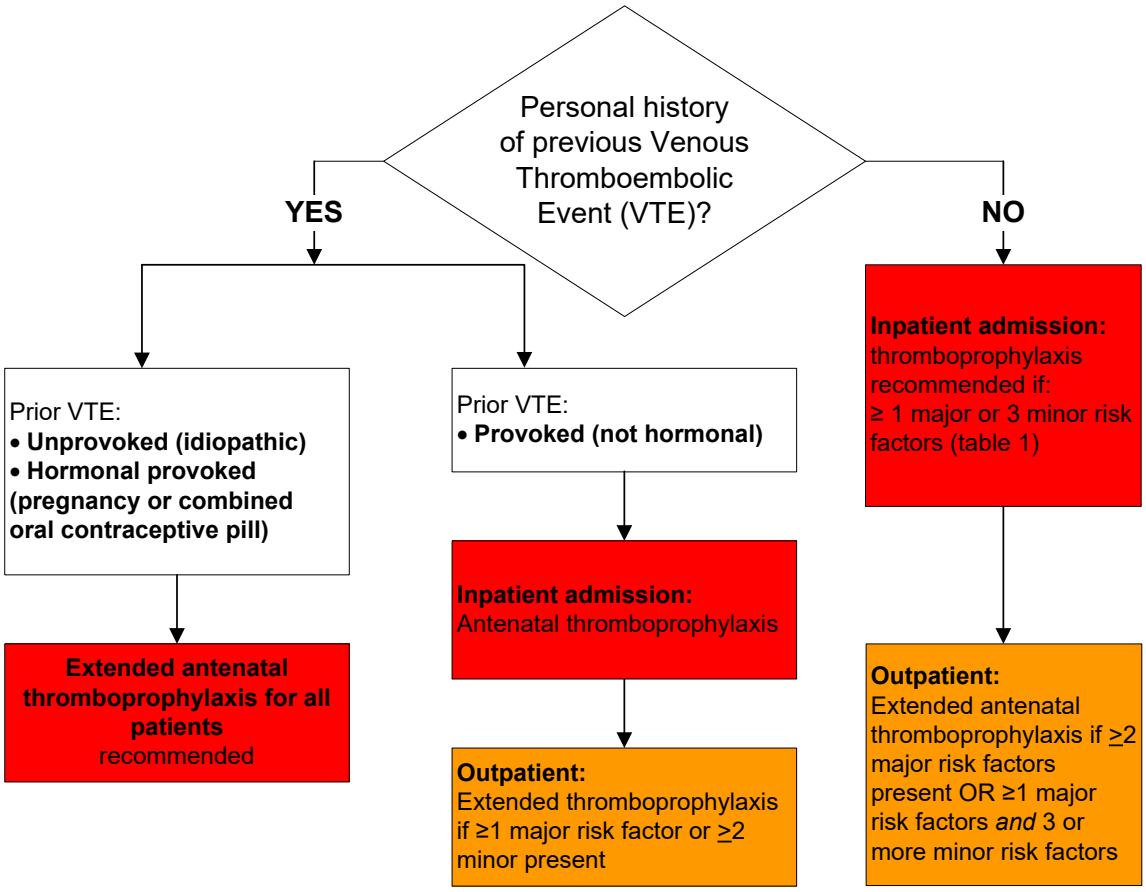

Table 1: Risk factors

Major
Body mass index ≥30 kg/m^2
Family history of VTE#
Preeclampsia
Known *significant* thrombophilia (table 2)
Active medical illness eg malignancy, nephrotic syndrome, pneumonia*

Minor
Maternal age ≥35 years
Immobilisation*
Smoker
Known *weak* thrombophilia (table 2)
Severe varicose veins
Multiple pregnancy
Severe hyperemesis
Parity (≥3)

* *eg bed rest or plaster of paris cast*
\# *event confirmed on imaging in a first degree relative*

Table 2: Hereditary thrombophilia

Significant
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Homozygous factor V Leiden
Combined hereditary defects

Weak
Heterozygous factor V Leiden
Heterozygous G20210A prothrombin mutation

* Flowchart does NOT apply to women with antithrombin deficiency, antiphospholipid syndrome, multiple prior VTE on long term warfarin or prosthetic heart valve(s). *Such women should be discussed with an obstetric physician or haematologist*

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8. Thromboprophylaxis: postnatal

Flowchart 2 outlines the recommended approach for deciding which women require postpartum thromboprophylaxis. Extended postpartum thromboprophylaxis with LMWH at prophylactic doses implies a duration of six weeks.

The approach of increasing to intermediate dose LMWH can be considered for higher risk women (after the initial peripartum bleeding has resolved) [*Bistervels et al Lancet 2022]*.When prophylaxis with unfractionated heparin or LMWH is recommended postpartum, it should generally be commenced within 6-12 hours of normal vaginal delivery and caesarean section, provided the obstetric team has no concerns about bleeding at that time.

To ensure consistent administration times and to avoid prolonged periods without chemical prophylaxis, LMWH should be prescribed and administered daily at 8 pm. However:

- If delivery occurs between 4 pm and 8 pm the dose of LMWH should be omitted on the day of delivery.
- If delivery occurred between 4 pm and 2 am an additional “Once Only” dose can be administered the next day at 8am.

Anti-thromboembolism (TED) stockings should be applied to the following patients:

- Delivery by emergency Caesarean Section
- 1 or more Major Risk Factor
- 2 or more Minor Risk Factors
- 1 Major + 1 Minor Risk Factor

These should remain insitu for at least five days postpartum or until discharge home.

Intermittent calf compression during CS should be employed for the following patients who are at particularly high risk of VTE until postpartum thromboprophylaxis can be started in the postpartum period:

- Those who have had an acute DVT or PE during pregnancy in whom anticoagulation has been temporarily discontinued for delivery.
- Those in whom initiation of postpartum thromboprophylaxis must be delayed because of bleeding complications (e.g. following major PPH).

8.1 Flowchart 2: Postnatal VTE risk assessment

*To be completed **by delivering practitioner** prior to transfer to postnatal ward*

Step 1

☐ Personal history VTE

☐ Received extended (6 weeks or more) antenatal thromboprophylaxis for ANY reason

☐ Family history of VTE and any known inherited thrombophilia (Antithrombin, Protein C and/or Protein S deficiency; homozygous Factor V Leiden or prothrombin gene mutation or compound heterozygote for FVL/prothrombin gene mutation)

☐ Family history of VTE with no known thrombophilia and other risk factors present

☐ Significant thrombophilia

↓

If YES to any of the above

6 WEEKS Enoxaparin (or other low molecular weight heparin) required ☐

Step 2

MAJOR RISK FACTORS

☐ Elective CS

☐ BMI ≥ 30

☐ Medical co-morbidity

☐ Pre-eclampsia

☐ Systemic infection

☐ Surgical procedure in puerperium (except CS)

MINOR RISK FACTORS

☐ Immobility

☐ Age >35 years

☐ Prolonged labour > 24 hours

☐ Smoker

☐ PPH > 1000 mL

☐ Extensive perineal trauma or prolonged repair

☐ Severe varicose veins

☐ Parity ≥ 3

↓

≥2 MAJOR risk factors
OR
≥1 MAJOR risk factor AND ≥2 MINOR risk factors
OR
Delivered by **emergency** CS

Enoxaparin for 5 days or until fully mobile ☐

Flowtrons should be used if Enoxaparin contraindicated due to bleeding risk

NO risk factors ☐
Or 1 minor risk factor

- TEDs not required
- Enoxaparin not required
- Early mobilisation
- Adequate hydration
- Remove flowtrons when mobilising

TED STOCKINGS ☐

Needed if:

- ≥1 MAJOR risk factor
- ≥2 MINOR risk factors
- 1 MAJOR + 1 MINOR risk factor
- Emergency CS

ENOXAPARIN PRESCRIPTION ON MEDICATION CHART, CONTINUES AT BIRTHCARE

- Regular "once daily" at 8pm
  - 60mg if >130kg
  - 40mg if 50-130kg
  - 20mg if <50kg
- Additional "once only" 20-40mg at 8am if delivers between 4pm and 2am
- Flowtrons until Enoxaparin/mobilisation

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9. Dosage for low molecular weight heparin (LMWH)

Table 4: Recommended doses for LMWHs	
Drug	**Prophylactic dose**
Enoxaparin (Clexane®)	• 40 mg once daily if patient 50-130 kg • 20 mg once daily if patient <50 kg • 60 mg once daily if patient >130 kg

10. Epidural/spinal anaesthesia/analgesia

For postpartum epidurals, prophylactic enoxaparin will be charted for 8 pm and midwives will normally remove epidurals in the morning or before 4 pm (provided a 'once-only' dose of enoxaparin has not been administered at 8 am), after they have assessed appropriateness of discontinuing the epidural as per Pain – Epidural Analgesia in Adults.

Other issues relating to timing of anticoagulant doses and epidural catheters are outlined in Table 5 (see also *Pain - Epidural Analgesia for an Adult* guideline).

Table 5: Timing of administration of LWMH and unfractionated heparin in patients with catheters for regional anaesthesia				
	Timing of dose before neuraxial block	Timing of next dose after neuraxial block	Timing of dose before epidural catheter insertion or removal	Timing of dose after epidural catheter removal
Prophylactic LMWH (Enoxaparin up to 40 mg once daily, or 60 mg once daily in patients >130 kg)	≥ 12 hours	≥ 4 hours	≥ 12 hours	≥ 4 hours
Doses > 60 mg or twice daily dosing	Only the acute pain service/on call anaesthetist should order the removal of the epidural catheter in these patients.			
Unfractionated heparin				

Note: Postpartum thromboprophylaxis should be initiated within 6 to 12 hours after vaginal delivery and caesarean section, provided the obstetric team has no concerns about bleeding at that time, but may be delayed if:

- Surgical bleeding concerns
- Renal impairment (creatinine >150), platelet count <80 or other haemostatic disorder

11. Supporting evidence

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12. Associated documents

- Thromboprophylaxis Therapy in DCCM
- Pain - Epidural Analgesia for an Adult

13. Disclaimer

No guideline can cover all variations required for specific circumstances. It is the responsibility of the health care practitioners using this Te Toka Tumai (Auckland Hospital) guideline to adapt it for safe use within their own institution, recognise the need for specialist help, and call for it without delay, when an individual patient falls outside of the boundaries of this guideline.

14. Corrections and amendments

The next scheduled review of this document is as per the document classification table (page 1). However, if the reader notices any errors or believes that the document should be reviewed ***before*** the scheduled date, they should contact the owner or Document Control without delay.