Venous Thromboembolism in Pregnancy - Prevention

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• Excluded	
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Contents

1. Purpose of guideline

This guideline establishes the expected measures to prevent venous thromboembolism (VTE) during pregnancy within Auckland District Health Board (Auckland DHB).

Venous thromboembolism in pregnancy and in postpartum remains one of the most common causes of maternal mortality in the developed world. The majority of women who develop VTE in association with pregnancy have personal or pregnancy-specific risk factors for thrombosis that were either untreated or unrecognised.

Risk assessment of women and recommendations regarding thromboprophylaxis are still supported only by weak clinical evidence and the majority of 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 (UK) both advocate risk assessment of all pregnant women to determine their risk of pregnancy-associated 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 woman not been validated by relevant studies. The Royal College of Obstetricians and Gynaecologists (RCOG) empirically recommend three or more risk factors as a threshold for prophylaxis even though this has not been formally tested in clinical trials.

An assessment of risk of thromboembolism should be carried out in all pregnant women. Some women 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:

a. Assess risk of VTE for all pregnant women at the earliest opportunity (Section 4)
b. Consider whether antenatal prophylaxis is required (Section 7)
c. Consider postnatal thromboprophylaxis (Section 8)
d. Reassess risk throughout the pregnancy and puerperium
e. Make an individualised plan with the patient
f. Ensure all women mobilise early postpartum and avoid dehydration

3. Risk factors

Pregnancy is associated with a 5-10-fold increase in the risk of VTE due to pregnancy specific factors and maternal risk factors. Pregnancy factors include venous stasis, an increase 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 previous *unprovoked* (no identified risk factors) than *provoked* (associated with a risk factor) events. Women with previous *hormonally provoked* VTE (pregnancy or oral contraceptive associated) have an increased risk of developing a recurrent VTE in a subsequent pregnancy.

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 therapy. Notwithstanding this, many women have already been tested and for this reason it was 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, so 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
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 6 weeks postpartum
Single prior provoked VTE (excluding those associated with COCP or pregnancy)	Observation unless other risk factors	Prophylaxis for 6 weeks postpartum
Single prior VTE associated with COCP	Prophylaxis recommended	Prophylaxis for 6 weeks postpartum
Single prior unprovoked VTE Single prior pregnancy-associated VTE Prior recurrent provoked VTE	Prophylaxis recommended	Prophylaxis for 6 weeks post-partum

[§] 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 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 individual women, 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

There are insufficient data to recommend an increased prophylactic dose of low molecular weight heparin (LMWH) for all women with increased weight (> 90kg) but it is reasonable to consider higher doses in women with a BMI >40kg/m^2. Dosages in these women should be discussed with an obstetric physician or obstetrician. There is no firm evidence on which to base dosing recommendations but doses of enoxaparin 40mg twice daily or 60mg daily have been used.

Thromboprophylaxis should be considered for women with a BMI of 30 or above who are admitted to hospital especially if they have additional risk factors or are immobilised.

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

Both warfarin and low molecular weight heparin are safe for breastfeeding.

The antenatal and postpartum flowcharts do not apply to women 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. 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

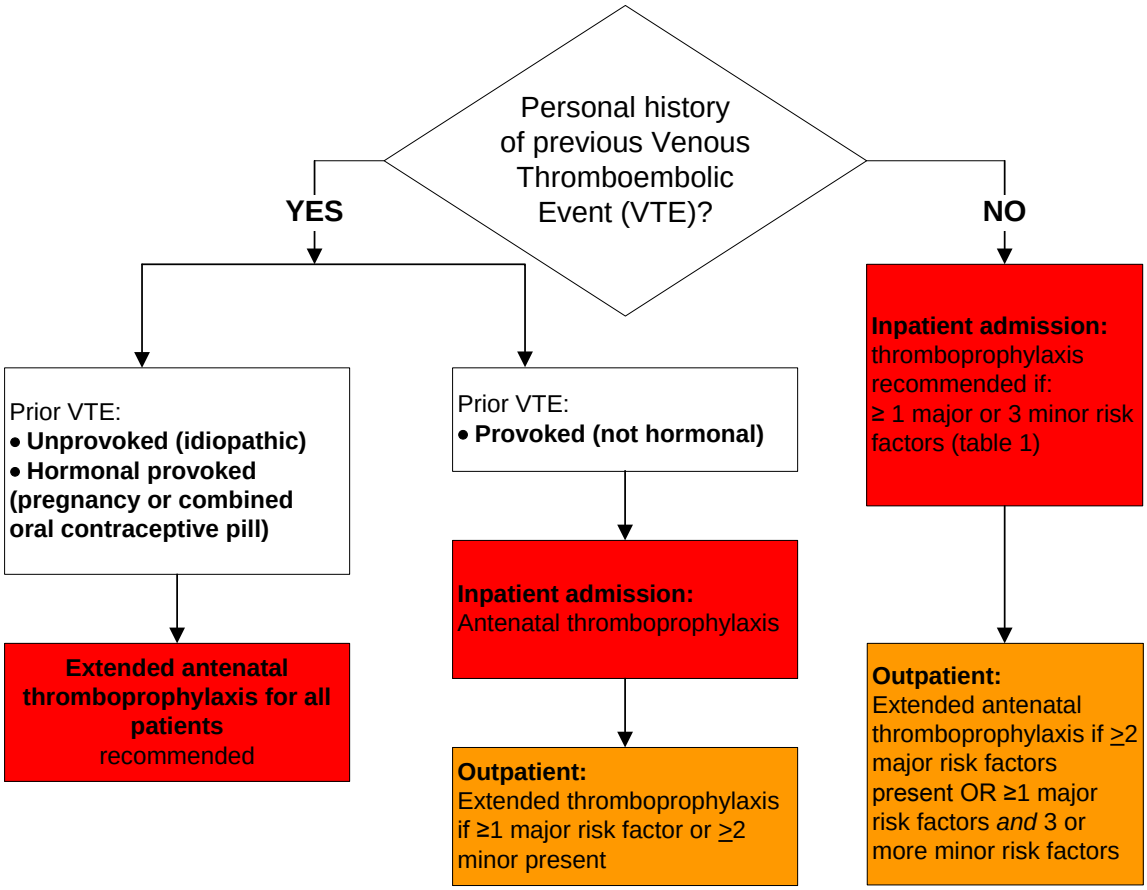

Table 1: Risk factors

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*

8. Thromboprophylaxis: postnatal

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

When prophylaxis with unfractionated heparin or LMWH is recommended postpartum, it should generally be commenced within 6-12 hours of normal vaginal delivery and CS, 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 8pm, with an additional "Once Only" administration at 8am if the woman delivers between 4pm and 2am. Women who deliver between 4pm-8pm should not receive the 8pm dose of LMWH on the day of delivery.

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 caesarean section should be employed for the following women who are at particularly high risk of VTE until postpartum thromboprophylaxis can be started in the postpartum period:

- Women who have had an acute DVT or PE during pregnancy in whom anticoagulation has been temporarily discontinued for delivery
- Women in whom initiation of postpartum thromboprophylaxis must be delayed because of bleeding complications i.e. 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

9. Dosage for low molecular weight heparin (LMWH)

Table 4: Recommended doses for LMWH	
Drug	**Prophylactic dose**
Enoxaparin (Clexane®)	40mg once daily if patient 50-130kg 20mg once daily if patient <50kg 60mg once daily if patient >130kg
Unfractionated heparin	5000 units twice daily or three times daily

10. Epidural/spinal anaesthesia/analgesia

Postpartum thromboprophylaxis doses should be given at 8pm to ensure that there are no issues relating to removal of epidural analgesia catheters.

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 40mg once daily, or 60mg once daily in patients >130kg)	≥ 12 hours	≥ 2 hours *	≥ 12 hours	≥ 2 hours
Higher or more frequent doses of LMWH	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 NVD and C/S, provided the obstetric team has no concerns about bleeding at that time.

* May be delayed if:

- Surgical bleeding concerns
- Multiple attempts to insert neuraxial block, traumatic insertion or bloody tap. (Usually delay timing of next dose of prophylactic anticoagulation to >= 4 hours)
- Uraemia, aspirin use, 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 Auckland DHB 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.