LOW MOLECULAR WEIGHT HEPARIN FOR PREVENTION OF VENOUS THROMBOEMBOLISM (VTE) IN THE POSTPARTUM

BACKGROUND

During pregnancy the risk of VTE is 5-10 fold higher than that outside pregnancy and remains one of the leading causes of direct maternal death in the developed world, with a mortality of 2/100,000 pregnancies in New Zealand. The incidence of VTE is 1-2 / 1000 pregnancies, with approximately 50% occurring antenatally and 50% postnatally. The risk for VTE increases with gestational age, reaching a maximum just after delivery. The relative risk postpartum is five-fold higher compared to antepartum and the absolute risk peaked in the first 3 weeks postpartum (421 per 100,000 person-years; 22-fold increase in risk). The threshold for recommending postpartum thromboprophylaxis is lower than that for recommending antenatal thromboprophylaxis because the risk per day is higher and the duration of risk is shorter.

Factors contributing to the increased risk of VTE in pregnancy are:

- venous stasis
- increased pro-coagulant factors and reduced natural anticoagulants (protein C and S)
- vessel wall injury occurring in both labour and during caesarean section
- Pro-inflammatory state of pregnancy with endothelial cell activation

Certain maternal factors further increase the risk and are listed below and in the postpartum VTE risk assessment scoring sheets (see Appendix 1).

There is limited data on VTE prophylaxis in pregnancy.

Published guidelines are listed in references. All of these guidelines were based on expert opinion, evidence from observational studies and evidence from studies in the non-pregnant population.

MANAGEMENT

This guideline does NOT apply to the following women:

- on treatment for acute VTE in pregnancy
- on long-term anticoagulation (for prior VTE, recurrent VTE or prosthetic heart valve/s)
- with antiphospholipid syndrome
- with antithrombin deficiency

The management of these patients must always be discussed with an obstetric physician or haematologist.

The management principles of this guideline are to:

a) **Assess risk of VTE for all pregnant women at the earliest opportunity** – 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 birth.

b) **Consider whether antenatal prophylaxis is required** – 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

c) **Consider postnatal thromboprophylaxis.**

d) **Ensure all women mobilise early postpartum and avoid dehydration**.

e) **Educate all women about the symptoms suggestive of Deep Vein Thrombosis (DVT) and Pulmonary Embolus (PE) to facilitate prompt recognition and management.**

Low molecular weight heparin (LMWH) (enoxaparin and dalteparin are subsidised by PHARMAC) is the drug of choice for antenatal thromboprophylaxis. LMWH requires a special authority number **if prescribed for more than 30 days, which can be applied for by any treating doctor.**

Both warfarin and LMWH are safe for breastfeeding, but LMWH is preferred in most circumstances for short-term thromboprophylaxis.

Information leaflets available:

- **Deep Vein Thrombosis** (Ref.6610)
- **Enoxaparin (Clexane)®** (administration information) (Ref.6972)

MATERNAL RISK FACTORS FOR PREGNANCY ASSOCIATED VTE (PA-VTE)

TABLE 1 Clinical risk factors for PA-VTE

Risk factor	Adjusted OR
Previous VTE	24.8
Age > 35	1.4 - 1.7
Obesity (BMI > 30 kgm2)*	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

- **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.
- **Immobility**
  - **In-patient care**, post-natal immobility is associated with an increase in PA-VTE and assessment of risk is an essential part the management plan of these women.
  - **Long haul air travel** (or any travel > 4 hours) has not been specifically studied in pregnant women, but is associated with a two-fold increased risk in the general population.
- The role of **hereditary thrombophilia** in PA-VTE has been extensively reviewed and **Table 2** summarises the absolute risks of PA-VTE in women with thrombophilia.

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.

  - The most common thrombophilia are factor V Leiden (fVL) deficiency and the prothrombin gene mutation, however, the absolute risk of VTE during pregnancy with these conditions remains small.
  - Screening of asymptomatic women for thrombophilia is not recommended.
  - 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.

- **Family history of VTE**
  - Hereditary thrombophilias are only identified in around 50% of family cohorts with VTE.
  - VTE is a multigenic disease and the relevance of a positive family history, ie. one or more first-degree relative (parent, sibling or child) with VTE has been shown to increase the risk of VTE 2-fold.
- **Increased BMI** is an important and consistent risk factor for PA-VTE especially in combination with immobilisation. This risk further increases as BMI increases.

TABLE 3 Additional Postpartum Risk Factors

Risk Factor	Adjusted OR
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

PRECAUTIONS AND CONTRAINDICATIONS

- **Known hypersensitivity to LMWH or prior heparin-induced thrombocytopenia:**
  - - Liaise with the obstetric physician.
  - - Discontinue therapy and consider alternative treatment if platelets are <100 x10^9/L and/or thrombosis develops.
  - - Use caution in patients with congenital or drug-induced thrombocytopenia or platelet defects.
- **Administration:** do **not** administer intramuscularly.
- **Active bleeding.**
- **Renal impairment:** Use with caution in patients with renal failure; dosage adjustment needed if Cl_{cr} < 30 mL/minute and a factor Xa measurement should be taken four hours after the dose and repeated on day 3.
- **For timing of administration following epidural or spinal insertion or removal.**

TABLE 4 Timing of administration of LWMH and UFH and placement of catheters for regional anaesthesia

	Timing of dose before neuroaxial block	Timing of dose after neuroaxial block	Timing of dose before epidural catheter removal	Timing of dose after epidural catheter removal
LMWH eg. enoxaparin (Clexane)	≥ 12 hours	≥ 4 hours*	≥ 12 hours	≥ 4 hours*
Unfractionated heparin (UFH)	≥ 6 hours	≥ 4 hours*	≥ 6 hours	≥ 4 hours*

* **Note:** Postpartum thromboprophylaxis should be initiated **within** 6 to 12 hours after birth

Reference: FDA (2013)

May be delayed if:

- Surgical bleeding concerns.
- Anaesthetic concerns during or following regional block placement, see anaesthesia assessment/indication record when available).
- Uraemia, aspirin use, platelet count < 80 x10^9/L or other haemostatic disorder.

DOCUMENTATION AND PRESCRIBING

Completion of the Thromboprophylaxis form to be undertaken by:

POSTNATALLY: (SEE APPENDIX 1)

- **Registered Doctor or Midwife** on birthing suite prior to transfer to maternity ward, primary unit or home
- **Surgeon** in operating theatre completes and scores assessment form for all women entering the operating theatre

If the score indicates Enoxaparin (Clexane)® is required, the Registered Doctor or Surgeon is to prescribe the Enoxaparin and include instruction for the entire duration this is required, according to the assessment score and related management plan.

DISPENSING

The discharging Registered Doctor will prescribe the duration of Enoxaparin following discharge in accordance with the duration entered on the inpatient prescription or by referring to the Postpartum Thromboprophylaxis Assessment form.

Special authority number to be generated electronically by the RMO **discharging** the woman and both the number and regime included on the discharge prescription with other medications, eg. Analgesia.

SELF-ADMINISTRATION

- All self-administration in the hospital setting is to be supervised by a midwife, and documented as per code on the drug chart (QM0044).
- Women should be advised sharps containers must be disposed of at their local pharmacy or GP practice.
- See Fluid & Medication Manual (Volume 12) policy document on Patient Self-Medication (Ref.4736)

REFERENCES

- **This CDHB guideline is based on the guidelines endorsed by SOMANZ / RANZCOG with the exception that we follow the dosing adjustments recommended by RCOG. The evidence has been thoroughly reviewed**.
- The Royal College of Obstetricians and Gynaecologists (RCOG) published 'Green top' guidelines in 2009, and in 2012 guidelines were published both by the American College of Chest Physicians and in ANZJOG endorsed by the Society of Obstetric Medicine Australia and New Zealand (SOMANZ) and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG).
- McLintock C, Brighton, T. Chunilal, S. et al Recommendations for the prevention of pregnancy-associated venous thromboembolism. Aust NZ J Obstet Gynaecol. 2011
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- Larsen TB, Sorensen HT, Gislum M et al. Maternal smoking, obesity, and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case-control study. Thromb Res 2007; 120: 505-9.
- Simpson EL, Lawrenson RA, Nightingale AL et al. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. BJOG 2001; **108**: 56-60.

APPENDIX 1: POSTNATAL THROMBOPROPHYLAXIS ASSESSMENT TO ONLY BE USED FOR WOMEN WHO HAVE UNDERGONE A PROCEDURE IN AN OPERATING THEATRE

Canterbury District Health Board
Te Poari Hauora ō Waitaha
CHRISTCHURCH WOMEN'S HOSPITAL
OBSTETRICS & GYNAECOLOGY

SURNAME ..... NHI .....
FIRST NAME..... DOB .....
ADDRESS .....
..... POSTCODE .....
(or affix patient label)

Postpartum Thromboprophylaxis Assessment

This scoring sheet does not apply to women on life-long anticoagulants or to women with antiphospholipid syndrome, who should be referred for specialist care (Obstetric Physician or Haematologist).

RISK FACTORS (*persistent risk factors)	Score
Received extended antenatal thromboprophylaxis	12
Prior venous thromboembolism (VTE): provoked or unprovoked	12
Significant hereditary thrombophilia (asymptomatic): • Homozygous Factor V Leiden • Homozygous Prothrombin G20210A mutation • Protein C deficiency • Protein S deficiency • Antithrombin III deficiency • Combined hereditary defects	12
Acquired thrombophilia (in the absence of clinical APLS): Lupus anticoagulant, anticardiolipin antibodies	12
Family History of VTE in a first degree relative and any known thrombophilia (significant or weak)	12
Family History of VTE in a first degree relative and no known thrombophilia	8
Weak hereditary thrombophilia (asymptomatic): • Heterozygous Factor V Leiden • Heterozygous Prothrombin G20210A mutation	8
Emergency caesarean section	6
Elective caesarean section	4
*Active medical illness: • Malignancy or myeloproliferative disorders • Nephrotic syndrome • Inflammatory conditions eg. inflammatory bowel or joint disease • Cardiac disease (congenital or acquired) • Sickle cell disease • Intravenous drug abuse	4*
Immobilisation: AOU admission, bed rest, Plaster of Paris, travel >4 hours, paraplegia	4
Current systemic Infection	4
Surgical procedure in puerperium	4
*Body Mass Index ≥ 40 kg/m^3	4*
*Body Mass Index ≥ 30 kg/m^3	2*
Postpartum haemorrhage > 1000 mL or blood transfusion	3
Pre-eclampsia	3
*Severe varicose veins	3*
*Age ≥ 35 years	2*
Prolonged labour > 24 hours	2
Mid-cavity rotational operative delivery – Keilland's forceps	2
*Smoker	2*
*Parity ≥ 3	2*
TOTAL SCORE	

Date: ...../...../..... Time: ..... Signature: .....

Ref.6643 Authorised by: Clinical Director O&G Page 1 of 2 November 2017

POSTPARTUM THROMBOPROPHYLAXIS C240296

SURNAME ..... NHI .....
FIRST NAME..... DOB .....
ADDRESS .....
..... POSTCODE .....
(or affix patient label)

Postpartum Thromboprophylaxis Assessment

MANAGEMENT

SCORE	Initial 5 days postpartum	Beyond 5 days postpartum
≥ 12	Postpartum thromboprophylaxis Early mobilisation, avoidance of dehydration	Extended postpartum thromboprophylaxis for a total of 6 weeks
7 - 11	Postpartum thromboprophylaxis Early mobilisation, avoidance of dehydration	Extended postpartum thromboprophylaxis for a total of 10 days
4 - 6	Postpartum thromboprophylaxis Early mobilisation, avoidance of dehydration	In women with persistent risk factors consider extended postpartum thromboprophylaxis for a total of 10 days Vigilance*
3	Graduated compression stockings Early mobilisation, avoidance of dehydration	Vigilance*
0 - 2	Early mobilisation, avoidance of dehydration Vigilance*	Vigilance*

* Vigilance – Ensure that the woman is aware of the symptoms and signs of VTE and that she understands the importance of seeking urgent medical attention should they arise.

POSTPARTUM THROMBOPROPHYLAXIS

Body Weight	Dose of Enoxaparin
under 50 kg	20 mg
50-90 kg	40 mg
91-130 kg	60 mg
131-170 kg	80 mg
over 170 kg	0.6 mg / kg / day

Adjust dose for severe renal impairment. Discuss with Pharmacist or Obstetric Physician.

☐ Inpatient prescription has been completed and includes duration of:

☐ 5 days ☐ 10 days ☐ 6 weeks (42 days)

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VTE in Pregnancy and Postpartum
Maternity Guidelines
Christchurch Women's Hospital
Christchurch New Zealand