Recommendations for thromboprophylaxis in obstetrics and gynaecology

E Schapkaitz,[1] FCPath (Haem), MMed (Haem); **P R de Jong**,[2] MMed, FRCOG (London), FCOG; **B F Jacobson**,[3] FRCS (Glasgow), PhD; **H R Büller**,[4] MD, PhD

[1] *Department of Molecular Medicine and Haematology, National Health Laboratory Service and University of Witwatersrand, Johannesburg, South Africa*
[2] *Dept of Obstetrics and Gynaecology, University of Cape Town and Christiaan Barnard Memorial Hospital, Cape Town, South Africa*
[3] *Department of Molecular Medicine and Haematology, National Health Laboratory Service and University of Witwatersrand, Johannesburg, South Africa*
[4] *Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands*

Corresponding author: *E Schapkaitz (elise.schapkaitz@nhls.ac.za)*

Background. Venous thromboembolism (VTE) is associated with considerable morbidity and mortality in the absence of thromboprophylaxis.
Method. The Southern African Society of Thrombosis and Haemostasis reviewed the available literature and comprehensive evidence-based guidelines on the prevention of VTE in obstetrics and gynaecology. A draft document was produced and revised by consensus agreement by a panel of professionals from various specialties. The recommendations were adjudicated by an independent international expert to avoid local bias.
Results and conclusion. We present concise, practical thromboprophylaxis guidelines for the clinical management of patients in obstetrics and gynaecology. Recommendations reflect current best practice, which it is hoped will lead to improved anticoagulation practice in this group of patients.

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Venous thromboembolism (VTE) is associated with considerable morbidity, and mortality in the absence of thromboprophylaxis. Pulmonary embolism (PE) is the leading cause of maternal death worldwide.[1] Further, PE is the cause of ~20% of deaths following hysterectomy.[2] The prevalence of deep vein thrombosis (DVT) in patients having major gynaecologic surgery ranges between 15% and 40%.[3] There are a few randomised trials to guide the management of this group of patients. Recommendations in this guideline therefore reflect current best practice. Management should be individualised according to the risk-benefit ratio and cost.

Methods

On behalf of the Southern African Society of Thrombosis and Haemostasis, a representative guideline panel of professionals from various specialities reviewed the available literature on the prevention of VTE in obstetrics and gynaecology. Recommendations presented are in accordance with the more comprehensive evidence-based guidelines namely the 9th edition of the American College of Chest Physicians (ACCP),[4] the Green Top guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG),[5] the American College of Obstetricians and Gynecologists (ACOG),[6] the Society of Obstetricians and Gynaecologists of Canada (SOGC),[7] Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)[8] and the European Society of Regional Anaesthesia (ESRA) Guidelines on Anticoagulation and Regional Anaesthesia.[9] Many of these recommendations are formulated in the absence of strong evidence and the guidelines were also prepared in conjunction with systematic reviews and observational studies. A draft document was produced and revised by consensus agreement. The guidelines were adjudicated and co-authored by an independent international expert to avoid local bias.

VTE in gynaecology

Oestrogen and VTE risk

Oestrogen use increases the risk of VTE as a class effect which is dose dependant.[10] The risk of VTE is dependent on the route of administration. There is lower associated risk with transdermal and intra-uterine hormonal therapy as well as the progesterone-only oral contraceptive.[11,12]

Gynaecological surgery and VTE risk

Table 1 provides a practical risk assessment for VTE in patients undergoing gynaecological surgery. Patient- and procedure-related risk factors should be considered when assessing the risk of VTE.

Patient-related risk factors include: age >60 years, prior history and family history of VTE, immobility, dehydration, sepsis, underlying malignancy, pregnancy, oestrogen therapy, obesity, hereditary thrombophilia, inflammatory bowel disease, human immunodeficiency virus infection, and autoimmune diseases including antiphospholipid syndrome.

Procedure-related risk factors include: duration of the procedure; degree of tissue damage; degree of immobility following surgery;

Table 1. Risk categories for gynaecological surgical patients

Risk Category	Recommendation
High Risk	
Major surgery, age >60 years with malignancy or history of VTE	Thromboprophylaxis
Major surgery, age 40 - 60 years with malignancy	Thromboprophylaxis
Major surgery with additional risk factors such as obesity (BMI >30 kg/m^2), hereditary thrombophilia, HIV, auto-immune disease, oestrogen therapy	Thromboprophylaxis
Moderate Risk	
Major surgery for benign condition without other risk factors	Consider thromboprophylaxis
Minor or laparoscopic surgery with additional risk factors such as obesity, hereditary thrombophilia, HIV, auto-immune disease, oestrogen therapy	Consider thromboprophylaxis
Low Risk	
Minor or laparoscopic surgery without other risk factors	Early mobilisation

and nature of the surgical procedure. The post-operative risk of VTE in patients on the combined oral contraceptive (COC) increases from 0.5% to 1%.[13] The risk of VTE needs to be balanced against the risk of stopping the COC prior to surgery. There is insufficient evidence at this time to recommend discontinuation of the COC prior to surgery or immobilisation. Hormonal therapy does not need to be stopped prior to surgery if appropriate thromboprophylaxis is used.[5]

Thromboprophylaxis following gynaecological surgery

- Low-molecular-weight heparin (LMWH) is the anticoagulant of choice:
  - Enoxaparin 40 mg subcutaneous (sc) once daily
  - Dalteparin 5 000 units sc once daily
  - Nadroparin 2 850 units sc once daily.
- It is recommended to use weight-adjusted LMWH dosing in patients at extremes of weight.
- It is recommended to start LMWH 6 - 12 hours after surgery, provided there is no active bleeding.
- In patients at high risk of bleeding or undergoing neuraxial anaesthesia, it is recommended to start LMWH a minimum of 12 hours postoperatively.
- LMWH prophylaxis should be continued until the patient is fully mobile.
- For major cancer surgery, 5 weeks of thromboprophylaxis is recommended.
- For major surgery, in patients with additional risk factors, at least 7 - 10 days of thromboprophylaxis is indicated.
- Avoid additional antiplatelet drugs for analgesia during anticoagulation.
- In patients at high risk of bleeding, use of mechanical prophylaxis such as intermittent pneumatic compression (IPC) should be considered.[14] There is, however, limited evidence for graduated compression stockings.

VTE in obstetrics

The risk of VTE is increased five- to tenfold in pregnancy.[15] The hypercoagulability of pregnancy persists for several weeks after delivery and the greatest risk for VTE is in the early postpartum period.[16] The recent decline in maternal deaths from VTE can be attributed to the use of thromboprophylaxis in high-risk women.[1]

There are multiple risk factors which increase the risk of VTE. Several guidelines have proposed a risk assessment score. In the absence of randomised controlled trials, there is no evidence for a complex clinical score.[17] The appropriate use of prophylaxis depends on identification of patients who are at high risk of VTE.

- Risk assessment is recommended early during pregnancy and in the postpartum period (Tables 2 and 3).
- Risk factors include previous VTE, family history of VTE, hereditary thrombophilia, antiphospholipid syndrome (APS), medical comorbidities, significant pregnancy complications, caesarean delivery (CD) prolonged antepartum immobilisation and clinical risk factors such as increased body mass index (BMI), age >35 years and parity ≥3.
- High-risk patients should be managed in conjunction with a haematologist. Further, women with APS should be managed in conjunction with a haematologist and rheumatologist.
- Antepartum and postpartum thromboprophylaxis with LMWH and low-dose aspirin is recommended in women with APS and previous VTE. Higher doses of LMWH may be required.[18]

Caesarean delivery and VTE risk

Caesarean delivery (CD) is an important independent risk factor for VTE in the postpartum period.[20] The risk of VTE after an emergency CD is twice greater than after an elective CD.

- In hospital, thromboprophylaxis should be considered in all women who have undergone an elective CD.[21]
- Additional risk factors for VTE post CD include: multiple pregnancy, BMI ≥30 kg/m^2, severe pre-eclampsia, re-operation, prolonged immobilisation and placenta praevia.[1]

Antepartum and postpartum thromboprophylaxis

The ideal anticoagulant in pregnancy should be one that does not cross the placenta and can be easily reversed.

- The oral direct thrombin and factor Xa inhibitors should not be used in pregnancy as the molecules are small and cross the placenta.
- Warfarin is associated with a teratogenic effect, especially between 6 and 12 weeks' gestation. In addition, there is an increased risk of miscarriage, prematurity and fetal bleeding (including intracranial haemorrhage resulting in brain damage) at any time during pregnancy.
- The preferred anticoagulant is LMWH.
- Allergic skin reactions can occur with LMWH but are uncommon. In pregnant women with severe allergic skin reactions, an alternative LMWH should be used.
- It is recommended that the platelet count be monitored one week after initiation of LMWH and at regular follow-ups thereafter.

Table 2. Obstetric antepartum thromboprophylaxis risk assessment[4-8]

Risk Category	Recommendation
High Risk	
Previous unprovoked or pregnancy or oestrogen-related VTE	Antepartum Thromboprophylaxis indicated
High-risk hereditary thrombophilia (compound heterozygous or homozygous for Factor V Leiden or prothrombin gene mutation and some deficiencies of antithrombin)[19] and a positive family history of VTE*	
Anti-phospholipid syndrome and previous VTE	
Intermediate Risk	
Single VTE related to a transient risk factor (not related to pregnancy or oestrogen use)	Clinical monitoring indicated
Low and intermediate risk hereditary thrombophilia (some antithrombin deficiencies, Protein S deficiency, Protein C deficiency; heterozygous for Factor V Leiden or prothrombin gene mutation) [19] and a positive family history of VTE*	
High risk hereditary thrombophilia and no positive family history of VTE	Consider thromboprophylaxis
Antiphospholipid syndrome	
Non-obstetric surgery during pregnancy	
Medical co-morbidities, e.g. cancer, heart failure, peripartum cardiomyopathy, active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease; nephrotic syndrome; type 1 diabetes mellitus with nephropathy, sickle cell disease, current intravenous drug user	
Ovarian hyperstimulation syndrome (3 months after resolution)	
Low Risk	
Age >35 years	Early mobilisation and avoid dehydration
BMI ≥30 kg/m²†	
Parity ≥3	
Smoker (at least 10 cigarettes per day)	Thromboprophylaxis if multiple (≥4) risk factors are present
Family history of unprovoked or oestrogen-related VTE in first-degree relative	
Low-risk thrombophilia	
Gross varicose veins‡	
Current systemic infection or peri-operative infection	
Immobility, e.g. paraplegia, long-distance travel (>8 hours), strict bedrest ≥7 days	
Pre-eclampsia with intrauterine growth restriction	
Multiple pregnancy	
In vitro fertilisation	
Dehydration/hyperemesis	

*A positive family history of VTE is associated with a two- to fourfold increase in the risk of VTE.
†The patient's BMI is based on the booking weight.
‡Gross varicose veins are by definition symptomatic, above the knee or associated with phlebitis or oedema or skin changes.

- Fondaparinux may be considered in consultation with a haematologist.[22]
- Antepartum prophylaxis should be initiated early in pregnancy.
- Postpartum thromboprophylaxis should be continued for 6 weeks in high-risk women, for 10 days in intermediate-risk women and at least until discharge from hospital in low-risk women.
- In the presence of ongoing risk factors, e.g. prolonged hospital admission, wound infection, surgery extended thromboprophylaxis until the risk factor is no longer present should be considered.
- The use of mechanical prophylaxis, such as IPC, can be considered in patients at high risk of bleeding.

LMWH dose

- Fixed doses of LMWH, e.g. dalteparin 5 000 units daily or nadroparin 2 850 units daily or enoxaparin 40 mg daily are recommended. This is practical and covers most of the obstetric population.
- There is an increased dose requirement of LMWH during pregnancy because of increased volume of distribution and renal clearance. Therefore, regular anti-Xa monitoring is suggested.
- Dose adjustments (increase or decrease by 10 mg) to achieve a target anti-Xa level of 0.3 - 0.5 units/mL in conjunction with a haematologist is suggested.
- It is recommended to use weight-adjusted LMWH dosing with anti-Xa monitoring in patients at extremes of weight (Table 4).[4,5]
- Anti-Xa monitoring is also indicated in renal disease and severe pre-eclampsia.[23]

Delivery

- It is recommended that all pregnant women receiving antepartum thromboprophylaxis have a delivery plan.
- The mode of delivery is determined by the obstetric indication. A planned CD is often indicated.
- Prophylactic LMWH should be discontinued at least 12 hours prior to the expected time of epidural analgesia or delivery.
- Patients should be advised to discontinue thromboprophylaxis upon the onset of spontaneous labour.

Spinal and epidural anaesthesia

- The catheter should not be placed within 12 hours of the last dose of LMWH.
- LMWH should be started at least 6 hours after removal of the catheter.[9]
- LMWH should be delayed at least 24 hours if there is blood in the needle or neuraxial catheter during needle insertion.
- Neurological monitoring is mandatory for a minimum of 12 hours and ideally for 72 hours after neuraxial blockade.
- Extreme caution should be exercised in patients on other agents such as aspirin, clopidogrel and non-steroidal anti-inflammatories that may interfere with normal haemostasis.

Postpartum

- Assess for major bleeding postpartum (resulting in a drop in the haemoglobin concentration ≥2 g/dL or bleeding requiring transfusion of at least 2 units of packed red blood cells).

Table 3. Obstetric postpartum thromboprophylaxis risk assessment[4-8]

Risk Category	Recommendation
High Risk	
Anyone requiring antenatal LMWH Previous VTE High-risk hereditary thrombophilia (compound heterozygous or homozygous for Factor V Leiden or prothrombin gene mutation or some deficiencies of antithrombin) Low- and intermediate-risk (some antithrombin deficiencies, Protein S deficiency, Protein C deficiency, heterozygous for Factor V Leiden or prothrombin gene mutation) hereditary thrombophilia and positive family history of VTE* Antiphospholipid syndrome	Postpartum thromboprophylaxis indicated for at least 6 weeks
Intermediate Risk	
Caesarean delivery in labour Readmission or prolonged admission (≥ 3 days) postpartum Surgery in the puerperium (except immediate repair of the perineum)	Postpartum thromboprophylaxis indicated for at least 7 - 10 days
Medical co-morbidities e.g. cancer, heart failure, peripartum cardiomyopathy, active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease, nephrotic syndrome, type 1 diabetes mellitus with nephropathy, sickle cell disease, current intravenous drug user BMI ≥40 kg/m^{2}†	If risk factors persist or multiple (≥2) risk factors are present, consider extending thromboprophylaxis
Low Risk	
Age >35 years BMI ≥30 kg/m^{2} Parity ≥3 Smoker Elective caesarean delivery Family history of VTE Low-risk thrombophilia Gross varicose veins‡ Current systemic infection Immobility, e.g. paraplegia, long-distance travel (>8 hours) Multiple pregnancy Preterm delivery in this pregnancy (<37 weeks) Stillbirth in this pregnancy Mid-cavity or rotational operative delivery Prolonged labour (>24 hours) Postpartum haemorrhage (> 1 L or blood transfusion requiring re-operation)	Early mobilisation, mechanical prophylaxis§ and avoid dehydration Postpartum thromboprophylaxis at least until discharge from hospital if multiple (≥ 2) risk factors

*A positive family history of VTE is associated with a two- to fourfold increase in the risk of VTE.
†The patient's BMI is based on the booking weight.
‡Gross varicose veins are by definition symptomatic, above the knee or associated with phlebitis or oedema or skin changes.
§Mechanical prophylaxis includes intermittent pneumatic compression which is preferable to graduated compression stockings.

Table 4. Recommended dosages of LMWH thromboprophylaxis[5]

Weight (kg)	Dosage
<50	Enoxaparin 20 mg once daily Dalteparin 2 500 units daily
50 - 90	Enoxaparin 40 mg once daily Dalteparin 5 000 units daily Nadroparin 2 850 units daily
91 - 130	Enoxaparin 60 mg once daily Dalteparin 7500 units daily
131 - 170	Enoxaparin 80 mg once daily Dalteparin 10 000 units daily
>170	Enoxaparin 0.6 mg/kg once daily Dalteparin 75 units/kg once daily

LMWH = low-molecular-weight heparin.

Table 5. Interpretation of anti-Xa levels in patients on LMWH

Target anti-Xa levels	0.3 - 0.5 anti-Xa units/mL
Low anti-Xa level	Inadequate dosing Delayed specimen draw Dose of LMWH omitted Weight gain Gestation (volume of distribution of LMWH changes)
High anti-Xa level	Excessive dosing Weight loss Renal dysfunction Reduced creatinine clearance (end of the third trimester)

Anti-Xa = anti-factor Xa ; LMWH = low-molecular-weight heparin.

- Every woman should have a repeat VTE risk assessment after delivery.
- Prophylactic LMWH may be started/restarted 6 - 12 hours post delivery or should be delayed if there is any evidence of bleeding from the surgical site.
- Warfarin, LMWH, fondaparinux and UFH are safe to use in breastfeeding mothers. The oral direct thrombin and factor Xa inhibitors should be avoided.

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