# PREGNANCY: THROMBOPROPHYLAXIS

Thrombosis Canada
Thrombose Canada

## OBJECTIVE:

To provide recommendations for the prevention of venous thromboembolism (VTE) during pregnancy (antepartum) and the postpartum period.

## BACKGROUND:

VTE complicates 1-2 per 1,000 deliveries. The daily risk of VTE is increased 5- to 10-fold during pregnancy and 15- to 35-fold in the early postpartum period compared to the non-pregnant, age-matched population. Although most studies have reported that the elevated risk of VTE returns to baseline by the end of the sixth postpartum week, a small increase in risk may persist for 12 weeks after delivery.

The absolute risk of pregnancy-related VTE in most women with thrombophilia without a prior thrombotic event or family history remains low (1% or less). However, women who have factor V Leiden homozygosity, prothrombin gene mutation homozygosity, a deficiency of protein C, S or antithrombin (with a positive family history) or who have combined thrombophilia have a higher risk of VTE. The risk of pregnancy-related VTE in thrombophilic women with a positive family history appears to be 2-4 times greater than that in thrombophilic women without a positive family history of VTE.

Previous VTE increases the risk of pregnancy-related deep vein thrombosis (DVT) and pulmonary embolism (PE). Women with one prior episode of VTE associated with a transient risk factor not related to pregnancy or hormone use appear to be at low risk of antepartum recurrence (≤5%) compared with those with an unprovoked, pregnancy-related or estrogen-related VTE (5-10%). The impact of thrombophilia on the risk of recurrent VTE in pregnancy is unclear.

In recent studies, uncomplicated nonemergent caesarean section has not been associated with an increased risk of VTE, compared with vaginal delivery.

Additional clinical risk factors that also appear to increase the risk of pregnancy-associated VTE include: obesity or increased body mass index (BMI), age ≥ 40 years, pre-eclampsia with intrauterine growth restriction, strict antepartum bed rest for at least 7 days, smoking >5 cigarettes/day prior to pregnancy, systemic lupus erythematosus (SLE), sickle cell disease, cancer, cardiac disease, severe ovarian hyperstimulation syndrome post assisted reproduction, serious postpartum infection, major postpartum hemorrhage requiring surgery, and emergency caesarean section. The magnitude of the risk increases with these factors and how they interact remain uncertain. However, predictive models for assessing individual patient risk of thrombosis are currently under evaluation and may prove helpful in the near future.

**AGENTS AND DOSING:**

During pregnancy, the risks of anticoagulant therapy to the fetus must be considered, in addition to maternal safety and the efficacy of the anticoagulant. Evidence extrapolated from observational studies suggest that pharmacologic VTE thromboprophylaxis is associated with about a 75% relative risk reduction in pregnancy-related VTE. Thus, women with a higher baseline risk of VTE will derive more benefit than those with a lower baseline risk of VTE.

**Low molecular weight heparin (LMWH**) and **unfractionated heparin (UFH)** do not cross the placenta and, therefore, are safe for the fetus. The potential for bleeding in pregnant women receiving LMWH or UFH prophylaxis is low and does not appear to be different from that reported in non-pregnant patients. LMWH has a better safety profile than UFH; therefore, **LMWH is the drug of choice for prevention of VTE during pregnancy**.

- The optimal dose of LMWH for antepartum and postpartum prophylaxis to prevent pregnancy-related VTE is unknown. In general, either standard once daily prophylaxis or intermediate dosing (either twice daily prophylaxis dosing or once daily intermediate dose) is recommended; in women ≥100-120 kg, use of intermediate dosing is suggested. Specific recommendations for VTE prophylaxis are contained in **Table 1** below.
- Maternal weight gain and increased renal clearance of LMWH during pregnancy has led to a suggestion that the anticoagulant effect of LMWH prophylaxis be monitored using anti-Xa levels. However, there are no high quality studies showing that dose adjustment to attain specific anti-Xa levels increases the safety or efficacy of prophylaxis. **Anti-Xa monitoring for prophylactic anticoagulation with LMWH is not routinely recommended.**
- LMWH is safe for the breast-fed infant when administered to the nursing mother.

**Vitamin K antagonists** (such as **warfarin**) cross the placenta and can lead to teratogenicity (warfarin embryopathy and central nervous system anomalies), as well as pregnancy loss and fetal bleeding. However, warfarin is safe for the breast-fed infant when administered to the nursing mother.

**Direct oral anticoagulants should NOT be used in pregnant or breastfeeding women.** Pregnant women were excluded from clinical trials evaluating the oral direct thrombin inhibitors (**dabigatran**) and anti-Xa inhibitors (**rivaroxaban, apixaban, edoxaban**), so the human reproductive risks of these medications are unknown. However, these small molecules are known to cross the placenta. Therefore, at present, the direct oral anticoagulants should not be used during pregnancy. We also recommend against using these agents while breastfeeding. Rivaroxaban and dabigatran have been demonstrated in breast milk samples; other drugs in this group may also be excreted into breast milk.

**TABLE 1: RECOMMENDATIONS FOR ANTEPARTUM AND POSTPARTUM THROMBOPROPHYLAXIS**

| CLINICAL SCENARIO | MANAGEMENT |
|---|---|
| **Prior VTE** (not receiving long-term anticoagulation):<br>• Unprovoked VTE<br>• Hormonal-related VTE (oral | **Antepartum**: prophylactic[1] or intermediate-dose[2] LMWH[3]<br>**Postpartum**: prophylactic[1] or intermediate-dose[2] LMWH or warfarin (target INR 2.0 to 3.0) for 6 weeks |

| | |
|---|---|
| contraceptive pill, pregnancy) | |
| **Prior VTE** (not receiving long-term anticoagulation):<br>• VTE associated with a transient major provoking risk factor | **Antepartum**: clinical vigilance (no prophylaxis)<br>**Postpartum**: prophylactic[1] or intermediate-dose[2] LMWH or warfarin (target INR 2.0-3.0) for 6 weeks |
| **Assisted Reproductive Technology**<br>• Without ovarian hyperstimulation syndrome (OHSS) | **Antepartum:** No prophylaxis |
| **Assisted Reproductive Technology**<br>• With severe OHSS | **Antepartum**: prophylactic[1] or intermediate-dose[2] LMWH[3] until 12 weeks post resolution of syndrome |
| **Strict antepartum bedrest and BMI >30 kg/m$^2$ at first antenatal visit or prior VTE (regardless of BMI)** | **Antepartum**: prophylactic[1] or intermediate-dose[2] LMWH while immobilized |
| **Postpartum immobilization with at least one of: (1) thrombophilia or (2) significant medical comorbidity or (3) history of strict antepartum bedrest for ≥7 days and BMI>30 kg/m$^2$ at first antenatal visit** | **Postpartum**: prophylactic[1] or intermediate-dose[2] LMWH while in hospital |
| **Caesarean Section**:<br>• With no additional thrombosis risk factors | **Postpartum:** Early mobilization |
| **Caesarean Section**:<br>• With one **major** or two **minor** risk factors<br>– ***Major risk factors:*** pre-eclampsia with IUGR, previous VTE, antepartum bedrest ≥7 days, higher risk thrombophilia (homozygosity for the factor V Leiden mutation or prothrombin gene mutation, antithrombin deficiency), serious postpartum infection, major postpartum hemorrhage > 1 L requiring surgery, medical conditions (heart disease, SLE, sickle cell disease, cancer, inflammatory bowel disease), transfusion<br>– ***Minor risk factors:*** BMI >30 kg/m$^2$, multiple pregnancy, postpartum hemorrhage > 1 L, smoking, fetal growth restriction, lower risk thrombophilia (protein S, protein C deficiency), preeclampsia, emergency caesarean section | **Postpartum:** Prophylactic or intermediate-dose LMWH[1,2] (or mechanical prophylaxis with intermittent pneumatic compression, with or without TED© stockings, if anticoagulants contraindicated) while in hospital. Consider combined prophylaxis if very high risk due to multiple risk factors.<br>If significant risk factors persist post-delivery, extended prophylaxis for up to 6 weeks postpartum should be considered.[5] |

1. Prophylactic doses of the LMWHs are: dalteparin 5,000 U SC once daily, enoxaparin 40 mg SC once daily, tinzaparin 4,500 U SC once daily, nadroparin 2850 U SC daily.
2. Intermediate doses of the LMWHs are: dalteparin 5,000 U SC twice daily or 10,000 U SC once daily, enoxaparin 40 mg SC twice daily or 80 mg SC once daily, tinzaparin 10,000 U SC once daily, nadroparin 2850 U SC twice daily or 5700 U SC once daily or any LMWH adjusted to peak anti-Xa levels of 0.2 to 0.6 U/mL (anti-Xa levels are not routinely recommended).
3. Antepartum clinical vigilance is also acceptable for patients who accept the risk of recurrence quoted above and for whom the burden of LMWH prophylaxis outweighs potential benefits.
4. Women who are protein C or protein S deficient should receive LMWH in preference to warfarin [see Thrombophilia: Deficiencies of Protein C, Protein S and Antithrombin guide]
5. Clinical vigilance is also acceptable for patients who accept the risk of VTE and for whom the burden of prophylaxis outweighs potential benefits.

## TABLE 2: RECOMMENDATIONS FOR THROMBOPROPHYLAXIS IN WOMEN WITH THROMBOPHILIA

In women who do NOT have a personal history of VTE (recommendations based on VTE risk thresholds of 2% antepartum and 1% postpartum for recommending LMWH prophylaxis):

| Hereditary thrombophilia | Family history of VTE | Antepartum Prophylaxis | Postpartum Prophylaxis |
|---|---|---|---|
| Heterozygous PGM or Heterozygous FVL | Yes | No | No |
| | No | No | No |
| Protein S or Protein C Deficiency | Yes | No | Yes |
| | No | No | No |
| Antithrombin Deficiency | Yes | Yes | Yes |
| | No | No | No |
| Homozygous PGM | Yes | Yes* | Yes |
| | No | No | Yes |
| Homozygous FVL | Yes | Yes | Yes |
| | No | Yes | Yes |
| Combined Thrombophilia | Yes | Yes | Yes |
| | No | Yes | Yes |

PGM: Prothrombin Gene Mutation, FVL: Factor V Leiden
*There are no family studies available to inform this recommendation, but antepartum prophylaxis is recommended given overall VTE risk estimate

## SPECIAL CONSIDERATIONS:

**Starting thromboprophylaxis:**
If the decision to use antepartum prophylaxis is taken, it should be initiated early in pregnancy.

**Labour and delivery:**
The risk of maternal hemorrhage and epidural hematoma at the time of delivery can be minimized with careful planning. Delivery options include both planned delivery and spontaneous labor with discontinuation of prophylaxis when labor commences, in consultation with obstetrics and anesthesiology.

The choice of delivery mode may be influenced by the desire for epidural anesthesia. Epidural placement should occur no sooner than 12 hours after standard prophylactic LMWH and 24 hours after higher doses of LMWH. If prophylactic UFH is substituted for LMWH close to term, practice guidelines suggest that neuraxial block occur 4 to 6 hours after heparin administration (in patients receiving UFH 5,000 units BID or TID), although individual anesthesiologists may differ in their practice. Typically, resumption of prophylaxis should be delayed until adequate hemostasis is assured and generally at least 12 hours post-delivery or epidural removal.

**Duration of postpartum thromboprophylaxis:**
For most women receiving pregnancy thromboprophylaxis, the prophylaxis should continue for 6 weeks postpartum since this is the highest risk period for VTE. Extending postpartum prophylaxis from 6 weeks to 12 weeks is likely only to benefit those women at highest risk of delayed VTE (e.g.

those with a prior late postpartum event or those with multiple VTE risk factors persisting beyond 6 weeks).

**Suspected VTE during pregnancy:**
**[See Clinical Guide Pregnancy: Diagnosis of DVT and PE]**
Women at risk of VTE should be educated about the need to seek urgent medical attention should they develop symptoms or signs suggestive of DVT or PE. Objective testing is mandatory if symptoms suspicious of DVT or PE occur as there is limited validation of standard clinical diagnostic algorithms in the setting of pregnancy.

**Pediatrics:**
In adolescents who are pregnant, the above adult recommendations for thromboprophylaxis should be followed.

## OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

- Deep Vein Thrombosis: Diagnosis
- Deep Vein Thrombosis: Treatment
- Pregnancy: Diagnosis of DVT and PE
- Pregnancy: Venous Thromboembolism Treatment
- Pulmonary Embolism: Diagnosis
- Pulmonary Embolism: Treatment
- Thrombophilia: Deficiencies of Protein C, Protein S and Antithrombin
- Unfractionated Heparin, Low-molecular-weight Heparin, and Fondaparinux

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*Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.*