

## PREGNANCY: VENOUS THROMBOEMBOLISM TREATMENT



Thrombosis Canada  
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### OBJECTIVE:

To provide an evidence-based approach to treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) during pregnancy and the postpartum period.

### BACKGROUND:

Venous thromboembolism (VTE), which comprises DVT and PE, complicates 1-2 per 1,000 deliveries. Although the absolute risk of pregnancy-associated VTE is low, PE remains a leading cause of maternal mortality in the Western world and VTE in pregnancy is an important cause of maternal morbidity. The cornerstone of VTE treatment in pregnancy is anticoagulant therapy. Recommendations are largely based on observational data and expert opinion given the lack of high-level evidence on optimal management.

### ANTICOAGULANTS IN PREGNANCY:

During pregnancy, the risks posed to the fetus by anticoagulant therapy must be considered, in addition to maternal safety and efficacy. Vitamin K antagonists such as **warfarin** cross the placenta and may cause teratogenicity (e.g. warfarin embryopathy and central nervous system anomalies), as well as pregnancy loss and fetal bleeding. Therefore, warfarin is contraindicated for the treatment of VTE in pregnancy.

Pregnant women were excluded from clinical trials evaluating the direct oral anticoagulants (including **apixaban, dabigatran, edoxaban, and rivaroxaban**) which are likely to cross the placenta and the human reproductive risks of these medications are unknown. They should also be avoided in pregnancy.

**Unfractionated heparin (UFH)** and **low molecular weight heparin (LMWH)** do not cross the placenta and, therefore, are safe for the fetus. Studies have confirmed the safety and efficacy of LMWH in the pregnant population when used for treatment of VTE. Therefore, LMWH is the drug of choice for treatment of VTE during pregnancy, except in patients with heparin-induced thrombocytopenia (HIT), a history of HIT or severe renal dysfunction. The same weight-based dosing regimen as in the nonpregnant population is recommended when LMWH is used for treatment of VTE in pregnancy. Some recommend a twice-daily LMWH dosing schedule during pregnancy to compensate for increases in glomerular filtration rate that occur in the second trimester. However, a once-daily regimen simplifies administration and enhances compliance. Observational studies have not demonstrated an increase in the risk of VTE recurrence with the once-daily regimen compared with twice-daily schedules.

Clinicians selecting UFH (e.g. in patients with renal dysfunction or perhaps initially those with very large burden VTE) can use either initial intravenous therapy followed by adjusted-dose subcutaneous

UFH given every 12 hours or twice-daily adjusted-dose subcutaneous UFH without initial IV heparin. With subcutaneous therapy, UFH doses should be adjusted to prolong a mid-interval (4-6 hours post-injection) activated partial thromboplastin time (aPTT) into the therapeutic range.

No studies have assessed the optimal **duration of anticoagulant therapy** for treatment of pregnancy-associated VTE. As in nonpregnant patients, a minimum total duration of 3 months is recommended. However, given the additional increase in risk for VTE during pregnancy and the postpartum period, treatment is generally extended throughout pregnancy and for at least 6 weeks postpartum (with a minimum total duration of 3 months).

UFH, LMWH and warfarin are safe for the **breast-fed infant** when administered to the nursing mother. Rivaroxaban has been shown to pass into breast milk and the manufacturers of apixaban, dabigatran, edoxaban, and rivaroxaban all recommend against using these medications while breastfeeding.

### **MONITORING OF ANTICOAGULANTS IN PREGNANCY:**

Maternal weight gain and increased renal clearance of LMWH during pregnancy has led to the suggestion that the dose of LMWH should be adjusted over the course of pregnancy; however, this remains controversial. In the absence of robust data, 3 options can be considered:

- 1) no further dose adjustment after initial dosing,
- 2) dose adjustment guided by changes in weight, and
- 3) dose adjustment guided by peak anti-factor Xa LMWH levels (samples obtained 2-4 hours after a dose) to maintain anti-factor Xa levels of 0.6-1.0 units/mL if a twice-daily regimen is used and slightly higher levels if a once-daily regimen is chosen.

Expert guidelines suggest that routine platelet count monitoring for detection of HIT is not required in pregnant women treated exclusively with LMWH.

### **SPECIAL CONSIDERATIONS:**

**Labour and delivery:** The risks of anticoagulant-related maternal hemorrhage and epidural hematoma in women using anticoagulants at the time of delivery can be minimized with careful planning. The plan for delivery should take account of obstetric, hematological and anesthetic issues. In order to avoid an unwanted anticoagulant effect during delivery (especially with neuraxial anesthesia), women receiving therapeutic subcutaneous UFH or LMWH should generally have a planned delivery. Twice daily therapeutic doses of subcutaneous UFH or LMWH should be discontinued 24 hours before induction of labor or cesarean section, while patients taking once daily therapeutic doses of LMWH should take only 50% of their dose on the morning of the day prior to delivery.

Pregnant women receiving LMWH or UFH should be instructed to withhold their injection if they believe they have entered labor spontaneously. If spontaneous labor occurs in fully anticoagulated women, neuraxial anesthesia should not be used. Where the level of anticoagulation is uncertain and where laboratory support allows for rapid assessment of heparin activity, testing can be considered to guide anesthetic and surgical management.

Women with a very high risk for recurrent VTE (e.g. proximal DVT or PE within 2-4 weeks) can be switched to therapeutic intravenous UFH, which is then discontinued 4-6 hours prior to the expected time of delivery or epidural insertion.

**Postpartum anticoagulation:** Postpartum LMWH or UFH therapy should be restarted as soon as it is safe to do so – usually within 6-24 hours of delivery, depending on bleeding concerns and local experience. However, resumption of full dose LMWH or UFH following epidural catheter removal should generally be delayed 24 hours (longer if catheter placement was bloody or traumatic). Unless there are bleeding concerns, postpartum warfarin can be started, if desired, at the same time as LMWH or UFH is initiated. Heparin or LMWH is continued after an overlap of at least 5 days and until an INR  $\geq 2.0$  is reached and maintained for at least 24 hours.

**Thrombolytic therapy:** Although thrombolytic therapy has been used successfully in pregnant women, experience with this intervention during pregnancy is limited. Therefore, thrombolysis should be reserved for women with life- or limb-threatening VTE.

**Inferior vena cava filters:** The indication for use of inferior vena caval filters during pregnancy is the same as in nonpregnant patients – an absolute contraindication to anticoagulant therapy in the setting of acute VTE. Experience with the use of inferior vena caval filters during pregnancy is limited.

#### **OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**

- Deep Vein Thrombosis (DVT): Treatment
- Pregnancy: Diagnosis of PE and DVT
- Pregnancy: Thromboprophylaxis
- Pulmonary Embolism (PE): Treatment
- Unfractionated Heparin, Low-Molecular-Weight Heparin, and Fondaparinux

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**Date of Version:** 2018May11

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