Pregnancy: Venous Thromboembolism Treatment

Thrombosis Canada
Thrombose Canada

Objective:

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

Background:

Venous thromboembolism (VTE) complicates approximately 1.2 per 1,000 deliveries. The absolute risk of pregnancy-associated VTE is low, but PE remains a leading cause of maternal morbidity and mortality in the Western world. The cornerstone of VTE treatment in pregnancy is anticoagulant therapy with low-molecular-weight heparin (LMWH). 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.

Anticoagulant	Safe during pregnancy	Safe during breastfeeding	Summary
Heparins (UFH, LMWH)	Yes	Yes	Does not cross the placenta Extensive real-world experience confirms efficacy and safety
Warfarin	No	Yes	Crosses the placenta; may cause warfarin embryopathy (if used between 6th and 12th week of gestation), fetal bleeding, and neurodevelopmental deficit Generally considered compatible with breastfeeding
DOACs	No	Unknown	Cross the placenta and are currently contraindicated for use in pregnancy or during breastfeeding May be an option in the post-partum period if women choose not to breastfeed
Danaparoid	Yes	Yes	Does not cross the placenta Evidence shows that it could be found in breast milk, however, it would not be systemically absorbed when taken orally by the infant
Fondaparinux	Yes	Unknown	Does cross the placenta in small amount Unknown if present in breast milk

UFH, unfractionated heparin; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant
Adapted from Middledorp et al, 2020;136(19):2133–42.

1. **Heparins: Unfractionated heparin (UFH)** and **low molecular weight heparin (LMWH)** do not cross the placenta and are safe for the fetus. Studies have confirmed the efficacy and safety 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 a history of heparin-induced thrombocytopenia (HIT) or severe renal dysfunction. The preference of LMWH over UFH is based on extrapolation of efficacy data from trials in the non-pregnant population where LMWH is more effective, has more predictable pharmacokinetics and a more favorable risk profile than UFH. LMWH dosing is adjusted according to the actual body weight at time of diagnosis and once daily is preferred over twice daily due to patient convenience.

   When UFH treatment is required (in patients with severe renal dysfunction, in patients in whom rapid anticoagulant reversal may be required, or those who may require thrombolytic treatment) dose adjustment is based on activated partial thromboplastin time (aPTT).

2. **Vitamin K antagonists: (warfarin, acenocoumarol):** these agents 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 during pregnancy.

3. **Direct oral anticoagulants (DOACs):** Pregnant women were excluded from clinical trials evaluating the DOACs including **apixaban, dabigatran, edoxaban,** and **rivaroxaban**, which are likely to cross the placenta. The human reproductive risks of these medications are unknown. DOACs should be avoided

during breastfeeding until more is known. Counselling for accidental first trimester exposure to DOACs is currently limited, but observational data is reassuring with a relatively low risk of embryopathy.

Breastfeeding:

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

Duration of anticoagulation:

No studies have assessed the optimal duration of anticoagulant therapy for treatment of pregnancy-associated VTE. 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).

Monitoring of anticoagulants in pregnancy:

Maternal weight gain and increased renal clearance of LMWH during pregnancy have 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 several options can be considered:

1. Dosing based on actual body weight at the time of diagnosis with no further dose adjustment. This is the simplest option and is consistent with the approach favored by the ASH 2018 guidelines for diagnosis and treatment of VTE in pregnancy. Extensive real-world use confirms the efficacy and safety of this approach.
2. Dose adjustment throughout pregnancy guided by changes in weight.
3. Dose adjustment based on peak anti-factor Xa laboratory measurements. Routine use of peak anti-factor Xa levels for monitoring LMWH therapy is not recommended due to lack of benefit and lack of robust data surrounding the optimal reference range, but could be considered for extremes of body weight, patients with breakthrough thrombosis, and select cases with very high risk of thrombosis. Trough anti-Xa levels are used for monitoring drug accumulation in patients with severe renal dysfunction.

The risk of HIT with LMWH is low in pregnant women and routine platelet count monitoring is not suggested.

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. Practices for management of therapeutic anticoagulation at the time of delivery vary widely and familiarizing yourself with institutional protocols and practices is important.

1. In order to avoid an unwanted anticoagulant effect during delivery and allow for neuraxial anesthesia, women receiving therapeutic subcutaneous LMWH should be offered a planned delivery.
2. Patients taking once-daily therapeutic LMWH should take their last dose >24 hours prior to scheduled induction or Caesarean section to allow for neuraxial anesthesia and safe delivery. If Caesarean section is scheduled for early morning, the last dose 24 hours prior should be given as an intermediate dose (typically 50% of the total daily dose).
3. Patients taking twice-daily therapeutic doses of subcutaneous LMWH should take their last dose 24 hours before induction of labor or Cesarean section.
4. Pregnant women receiving therapeutic LMWH should be instructed to withhold their injection if they believe they have entered labor spontaneously.
5. If spontaneous labor occurs in fully anticoagulated women, neuraxial anesthesia should not be used within 24 hours of a therapeutic dose of LMWH.

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. In addition, insertion of an inferior vena cava filter may be considered in women with very recent VTE (within 2 weeks).

Postpartum anticoagulation: Postpartum LMWH or UFH therapy should be restarted as soon as it is safe to do so – usually within 12-24 hours of delivery, depending on bleeding concerns and local experience. Local institutional anesthesia protocols regarding timing of resumption of full-dose LMWH or UFH following epidural removal should be followed. In general, administration of full-dose LMWH or UFH following epidural catheter removal should be delayed 24 hours (longer if catheter placement was bloody or traumatic). For patients with bleeding concerns, prophylactic-dose LMWH may be an option until full-dose anticoagulation can be reinitiated. If desired, postpartum LMWH or UFH may be started simultaneously with warfarin, allowing for an overlap of at least 5 days and until an INR ≥2.0 is maintained for >24 hours. DOACs may be an option in the postpartum period for women who choose not to breastfeed.

Thrombolytic therapy: Although thrombolytic therapy has been used successfully in pregnant women, experience with this intervention during pregnancy is limited. Available reports suggest a low risk of maternal bleeding but highlight concerns about fetal complications including fetal loss. Therefore, thrombolysis should be reserved for women with life- or limb-threatening VTE.

Inferior vena cava filters: Use of inferior vena cava filters during pregnancy should be limited to those an absolute contraindication to anticoagulant therapy in the setting of acute VTE. This typically does not include short-term interruption in anticoagulation for delivery except in those with very recent or untreated DVT. Experience with the use of inferior vena cava filters during pregnancy is limited.

Pregnancy and heparin-induced thrombocytopenia (HIT): In pregnant patients with HIT or a history of HIT, the recommended management involves the use of non-heparin anticoagulants for VTE treatment or prophylaxis. Danaparoid is the suggested first-line treatment for VTE in patients with acute or sub-acute HIT. Experience with use of Fondaparinux during pregnancy is very limited especially during the first trimester.

Other Relevant Thrombosis Canada Clinical Guides:

- Deep Vein Thrombosis: Treatment

- Pregnancy: Diagnosis of PE and DVT
- Pregnancy: Thromboprophylaxis
- Pulmonary Embolism (PE): Treatment
- Unfractionated Heparin and Low-Molecular-Weight Heparin

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Date of Version: 01May2025

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