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.

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Safe during pregnancy</th>
<th>Safe during breastfeeding</th>
<th>Summary</th>
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</table>
| 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 coumadin embryopathy (if used between 6th and 12th week), fetal bleeding, and neurodevelopmental deficit |
| DOACs | No | No | Cross the placenta and are currently contraindicated for use in pregnancy or during breastfeeding  
May be preferred post-partum if women choose not to breastfeed |

UFH, unfractionated heparin; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant

Adapted from Middeldorp 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. LMWH dosing is adjusted according to the actual body weight at time of diagnosis and once daily is preferred than 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). If patients require longer-term UFH treatments due to an ongoing contraindication to LMWH then weight based UFH can be given subcutaneously every 12 hours. 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.

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 breast-fed 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 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 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, but could be considered for extremes of body weight, patients with breakthrough thrombosis, select cases with very high risk of thrombosis, or monitoring for accumulation in patients with 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 UFH or LMWH may choose a planned delivery.

2. Patients taking once daily therapeutic LMWH should take their last dose >24 hours prior to scheduled induction or Cesarean section to allow for neuraxial anesthesia and safe delivery. If Cesarean section is scheduled for early morning the last dose 24 hours prior may be given as an intermediate dose (typically 50% of the total daily dose).

3. Patients taking twice daily therapeutic doses of subcutaneous UFH or LMWH should take their last dose 24 hours before induction of labor or Cesarean section.

4. Pregnant women receiving therapeutic LMWH or UFH 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). 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 ≥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. 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 with 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.

**YEARS algorithm:** The YEARS algorithm is a simplified diagnostic strategy in which 3 clinical items of the Wells score (clinical signs of DVT, hemoptysis, and PE most likely diagnosis) along with differential D-dimer cutoff values was developed to reduce CTPA in patients with suspected PE. The algorithm was recently assessed for its external validity in three prospective cohorts. Overall, the YEARS algorithm safely ruled out PE with a low 3-month thromboembolism risk. However, a higher failure rate of the YEARS algorithm was observed for patients with no YEARS items and a D-dimer < 1000 ng/ml but above their respective age-adjusted D-dimer cutoff. As a result, further external validation is required before the YEARS algorithm can be recommended for non-pregnant patients with suspected PE.

**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
REFERENCES:


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