**TARGET AUDIENCE:** All Canadian health care professionals.

**OBJECTIVE:**

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

**ABBREVIATIONS:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>aPTT</td>
<td>activated partial thromboplastin time</td>
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<td>DVT</td>
<td>deep vein thrombosis</td>
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<td>HIT</td>
<td>heparin induced thrombocytopenia</td>
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<td>INR</td>
<td>international normalized ratio</td>
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<tr>
<td>LMWH</td>
<td>low-molecular-weight heparin</td>
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<td>PE</td>
<td>pulmonary embolism</td>
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<tr>
<td>UFH</td>
<td>unfractionated heparin</td>
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<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
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**BACKGROUND:**

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), complicates 0.5-1.7 per 1,000 deliveries. The daily risk of VTE is increased 5- to 10-fold during pregnancy and 15- to 35-fold early after delivery. The elevated risk of VTE returns to baseline by the end of the 6th postpartum week. 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.

**AGENTS AND DOSING:**

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 have the potential to cause teratogenicity (e.g. warfarin embryopathy and central nervous system anomalies), as well as pregnancy loss and fetal bleeding. Pregnant women were excluded from clinical trials evaluating the new oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban) and the human reproductive risks of these medications are unknown. Fondaparinux appears to
cross the placenta in small quantities. Although a small number of reports of the successful use of this agent in pregnant woman have been published, most of these involve second trimester or later exposure.

Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and danaparoid do not cross the placenta and, therefore, are safe for the fetus. LMWH has a better maternal safety profile than UFH. Observational 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 significant renal dysfunction. Fondaparinux should be restricted to those patients in which there is no safe alternative.

The same weight-based dosing regimen as in the nonpregnant population is recommended when LMWH is used for the initial 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 any 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 those with large PE) can use either initial intravenous therapy followed by adjusted-dose subcutaneous UFH given every 12 hours or twice-daily adjusted-dose subcutaneous UFH. With subcutaneous therapy, UFH doses should be adjusted to prolong a mid-interval (6 hours post-injection) activated partial thromboplastin time (aPTT) into therapeutic range.

No studies have assessed 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 6 weeks postpartum (and for a minimum total duration of 3 months).

UFH, LMWH and warfarin are safe for the breast-fed infant when administered to the nursing mother. The manufacturer recommends that caution be used when administering fondaparinux to breastfeeding women, while the manufacturers of dabigatran, apixaban and rivaroxaban all recommend against using these medications while breastfeeding.

**MONITORING:**

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 are equally reasonable, including:
(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 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:**

The indications for the use of inferior vena caval filters during pregnancy are the same as in nonpregnant patients and include contraindications to anticoagulant therapy in the setting of acute VTE or failure of appropriate anticoagulation. Experience with the use of inferior vena caval filters during pregnancy is limited.

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 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 levels, then 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. Alternatively or in addition, a temporary inferior vena caval filter can be inserted and removed postpartum.

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 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 is continued until an INR ≥2.0 is reached and maintained for 24 hours.
**PEDIATRICS:**

In adolescents who are pregnant, adult recommendations for VTE treatment should be followed.

**REFERENCES:**


*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.*