OBJECTIVE:

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

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 compared to non-pregnant women of similar age. Although most studies have reported that the elevated risk of VTE returns to baseline by the end of the sixth post-partum week, a recent paper suggests that a small residual increase in risk may persist for 12 weeks after delivery. 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.

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 in pregnancy.

Pregnant women were excluded from clinical trials evaluating the novel oral anticoagulants (e.g. dabigatran, rivaroxaban, apixaban) 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 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 very 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 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 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. The manufacturers of dabigatran, rivaroxaban and apixaban 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 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 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, 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.

**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 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 are continued 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. Therefore, thrombolysis should be reserved for women with life-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: Diagnosis
- Deep Vein Thrombosis: Treatment
- Pregnancy: Thromboprophylaxis
- Unfractionated Heparin and Low-Molecular-Weight Heparin

**References:**


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