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Treatment of Deep Vein Thrombosis and Pulmonary Embolism in Pregnancy

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Abstract:
Pregnancy and the puerperium are well-established risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE), which are collectively referred to as venous thromboembolic disease (VTE). The venous thromboembolic disease can manifest during pregnancy as an isolated lower extremity deep vein thrombosis (DVT) or clot can break off from the lower extremities and travel to the lung to present as a pulmonary embolus (PE). PE is the seventh leading cause of maternal mortality, responsible for 9 percent of maternal deaths. Thus, the detection of DVT during pregnancy is critical to preventing deaths from PE. Although most reports suggest that VTE can occur at any trimester in pregnancy, studies suggest that VTE is more common during the first half of pregnancy. The Treatment of VTE during pregnancy and the puerperium will be reviewed here.

Introduction:

Venous thromboembolism (VTE) is a blood clot that starts in a vein. It is the third leading vascular diagnosis after heart attack and stroke, affecting about 300,000–600,000 Americans each year. There are two types: Deep vein thrombosis (DVT) is a clot in a deep vein, usually in the leg, but sometimes in the arm or other veins. Pulmonary embolism (PE) occurs when a DVT clot breaks free from a vein wall, travels to the lungs and blocks some or all of the blood supply. Blood clots in the thigh are more likely to break off and travel to the lungs than blood clots in the lower leg or other parts of the body. Pregnancy is a risk factor for the development of VTE with a reported incidence that is 4 to 50 times higher in pregnant women compared to nonpregnant women. Increased risk for lower extremity DVT is highest in the first six weeks of the postpartum period, with a higher than usual incidence of left-sided DVT and pelvic vein clot [1-2]. Treatment of VTE in pregnant patients is unique in several ways. Warfarin should be avoided, particularly in the first trimester, because it may be teratogenic. Fondaparinux, a synthetic heparin pentasaccharide, is generally avoided due to a paucity of safety data during pregnancy, with the only potential indication in the setting of heparin-induced thrombocytopenia (HIT).

The direct oral anticoagulants, which include the oral direct thrombin inhibitors and the factor Xa inhibitors, should be avoided due to insufficient information about their safety when used during pregnancy. Monitoring of anticoagulant activity tends to be more vigilant because less is known about the appropriate dosing of anticoagulants during pregnancy [3]. ANTICOAGULATION — The following approach is generally consistent with the 2012 American College of Chest Physicians (ACCP) guidelines on VTE and pregnancy [3]. Once it is determined that anticoagulation is indicated, it should be initiated using subcutaneous low molecular weight heparin (LMWH), intravenous unfractionated heparin (IV UFH), or subcutaneous UFH [1,4]. Subcutaneous LMWH is preferred over IV UFH or subcutaneous UFH in most patients because it is easier to use and it appears to be more efficacious with a better safety profile. These findings are extrapolated from clinical trials in non-pregnant patients. In a meta-analysis of 22 randomized trials (8867 patients), subcutaneous LMWH decreased mortality (odds ratio 0.76, 95% CI 0.62-0.92) and recurrent thrombosis (odds ratio 0.68, 95% CI 0.55-0.84). It was also more likely to reduce thrombus size (odds ratio 0.69, 95% CI 0.59-0.81) and less likely to cause major hemorrhage (odds ratio 0.57, 95% CI 0.39-0.83) [5].

In contrast, IV UFH is preferred in patients who have a markedly elevated risk of bleeding or persistent hypotension due to pulmonary embolism (PE). This preference is based on clinical experience. The rationale is that its short half-life and near complete reversal with protamine are desirable if the anticoagulant effect needs to be stopped due to bleeding or to perform a procedure.

UFH (either IV or subcutaneous) is preferred over subcutaneous LMWH in patients who have severe renal failure. Direct oral anticoagulants are avoided since little is known about their safety in pregnancy.

Discussion:

The overall prevalence of venous thromboembolism (VTE) in pregnancy is low. In the United States, VTE is diagnosed during 1 in 500 to 2000 pregnancies (absolute incidence; 0.025 to 0.1 percent) [6,7]. In a retrospective case-control study of 395,335 pregnant women at 24 weeks of gestation, the incidence of VTE was 85 per 100,000 pregnancies [8]. A population-based inception cohort study over a 30 year period detected an overall incidence of VTE of 200 per 100,000 woman-years [9]. DVT was three times more common than PE [9]. Similar rates are observed in Europe [9]. In one retrospective study of over 72,000 deliveries, the incidence of DVT was 0.71 per 1000 deliveries (95% CI 0.5-0.9) with 0.5 (95% CI 0.34-0.66) and 0.21 (95% CI 0.11-0.31) occurring antenatally and postnatally, respectively [10].The incidence of PE was 0.15 per 1000 deliveries (95% CI 0.06-0.24) with 0.07 (95% CI 0.01-0.13) and 0.08 (95% CI 0.02-0.14) occurring antenatally and postnatally, respectively [10]. PE is the seventh leading cause of maternal mortality and accounts for 9 percent of maternal deaths. The drugs that used in treatment of VTE are low molecular weight heparin (LMWH) and unfractionated heparin, LMWH — Reasonable initial doses of subcutaneous LMWH include dalteparin 200 units/kg once daily, tinzaparin 175 units/kg once daily, dalteparin 100 units/kg every 12 hours, or enoxaparin 1 mg/kg every 12 hours [3] .The dose is then titrated to an anti-Xa level of 0.6 to 1.0 IU/mL for twice daily administration, or 1 to 2 IU/mL for once daily administration [3].The first anti-Xa level is generally measured four hours after the third or fourth dose if the dosing is every 12 hours, or four hours after the second or third dose if the dosing is once daily. Most adjustments should be an increase or decrease of 10 to 25 percent. The anti-Xa level may be measured four hours after the third injection that follows a dose adjustment. Once a satisfactory anti-Xa level is reached, some clinicians recheck the level every one to three months, although this is controversial because few women require dose adjustments [3].

IV UFH — Initial dosing of IV UFH consists of an IV UFH bolus of 80 units/kg, followed by a continuous infusion of 18 units/kg per hour [4]. The infusion is titrated every six hours to achieve a therapeutic activated partial thromboplastin time (aPTT), defined as the aPTT that corresponds to an anti-Xa level of 0.3 to 0.7 U. The target aPTT range will be laboratory-specific. Once the target aPTT level is achieved, it should be rechecked once or twice daily. IV UFH can be transitioned to subcutaneous UFH or subcutaneous LMWH if long-term or outpatient anticoagulant therapy is planned [3]. Subcutaneous UFH — A reasonable initial dose of subcutaneous UFH is 17,500 units every 12 hours. The dose is then titrated to achieve a therapeutic aPTT, defined as the aPTT that corresponds to an anti-Xa level of 0.3 to 0.7 U [3]. The target aPTT range will be laboratory-specific.

The first aPTT is generally measured six hours after the second dose. Most adjustments should be an increase or decrease of 10 to 30 percent. The aPTT may be measured six hours after the second injection that follows each dose adjustment. Once a stable dose is achieved, the aPTT may be measured after three to four days of treatment and then every few weeks. During the last 10 weeks of the pregnancy, more frequent monitoring is warranted. Many clinicians prefer to begin with IV UFH and then transition to subcutaneous UFH in order to achieve a rapid therapeutic effect for treatment. The transition is traditionally done after the patient has received IV UFH for 5 to 10 days. In this situation, the first aPTT can be checked six hours after the first subcutaneous UFH dose and then six hours after every dose adjustment until a stable dose that produces the desired therapeutic level is achieved. Once a stable dose of subcutaneous UFH is achieved, the aPTT may be initially checked once or twice daily for three to four days and then every few weeks. After delivery — A heparin regimen (subcutaneous LMWH, IV UFH, or subcutaneous UFH) should be restarted 12 hours after a cesarean delivery or six hours after a vaginal birth, assuming that significant bleeding has not occurred. Options for long-term anticoagulant therapy include subcutaneous LMWH, subcutaneous UFH, or an oral vitamin K antagonist (eg, warfarin). If warfarin therapy is chosen, the patient should receive both warfarin and heparin for at least five days. The heparin should not be stopped until the international normalized ratio (INR) has been within therapeutic range (usually 2 to 3) for two consecutive days. Warfarin is considered safe during lactation because it does not accumulate in breast milk to a substantial degree. THROMBOLYSIS/THROMBECTOMY — Teratogenicity due to thrombolytic agents has not been reported, but the risk of maternal hemorrhage is high. As a result, thrombolytic therapy should be reserved for pregnant patients with life-threatening acute pulmonary embolism (PE; ie, persistent and severe hypotension due to the PE). In a systematic review of case series and case reports (172 pregnant women treated with thrombolytic agents), the maternal mortality rate was 1 percent, the incidence of fetal loss was 6 percent, and incidence of maternal hemorrhagic complications was 8 percent .The risk of postpartum hemorrhage appears to be greatest among women treated within eight hours of delivery, although only a few cases have been described .Case reports of thrombectomy suggest that it can be used successfully as a life saving measure when other measures have failed [11]. COMPLICATIONS — Heparin has several side effects, including bleeding, thrombocytopenia, skin necrosis, and osteoporosis. These adverse effects can occur even at prophylactic doses and are more likely with long-term use. Bleeding – The management of bleeding during heparin therapy depends upon the location and severity of the bleeding, the degree of anticoagulation (ie, the anti-Xa level or activated partial thromboplastin time [aPTT]), and the risk of discontinuing the anticoagulant. In many cases, the heparin can be stopped and restarted after the bleeding is controlled. However, insertion of an inferior vena caval (IVC) filter should be considered if the bleeding is sufficiently severe to prohibit resumption of anticoagulant therapy. Clinicians should NOT resume anticoagulant therapy if the bleeding is related to a placenta previa or abruption, although this recommendation is based on low quality evidence. Thrombocytopenia – Heparin-induced thrombocytopenia (HIT) is a potentially fatal complication of heparin therapy. Skin necrosis – Heparin-induced skin necrosis is a manifestation of HIT and

may occur in the absence of thrombocytopenia. Osteoporosis – Long-term heparin therapy (longer than seven weeks) can reduce bone mineral density by reducing bone formation. This effect appears to be more common with unfractionated heparin than low molecular weight heparin.

Conclusion:

- Pregnancy and the puerperium are well-established risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE), which are collectively referred to as venous thromboembolic disease (VTE).
- For pregnant women, we recommend adjusted dose subcutaneous low molecular weight heparin (LMWH), rather than adjusted dose intravenous unfractionated heparin (IV UFH).
- Thrombolytic therapy should be reserved for pregnant or postpartum patients with life-threatening acute PE (ie, persistent and severe hypotension due to the PE).

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