Deep vein thrombosis and pulmonary embolism in pregnancy: Treatment

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INTRODUCTION

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). Treatment of VTE in pregnant patients is unique in several ways. (See "Use of anticoagulants during pregnancy and postpartum".)

- 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.

Treatment of VTE during pregnancy and the puerperium will be reviewed here [1-6]. The epidemiology, pathogenesis, diagnosis, and prevention of VTE during pregnancy and the puerperium are discussed separately. (See "Deep vein thrombosis in pregnancy: Epidemiology, pathogenesis, and diagnosis" and "Deep vein thrombosis and pulmonary embolism in pregnancy: Prevention".)

GENERAL APPROACH

Initial management of suspected venous thromboembolism (VTE) depends upon the degree of clinical suspicion for acute pulmonary embolism (PE), whether there are contraindications to anticoagulation, and whether PE, deep vein thrombosis (DVT), or both are suspected:

- When there is a high clinical suspicion for acute PE, empiric anticoagulant therapy is indicated prior to the diagnostic evaluation. Anticoagulant therapy is discontinued if VTE is excluded.
- When there is low or moderate clinical suspicion for PE, empiric anticoagulant therapy prior to diagnostic evaluation is determined on a case-by-case basis.
- For those patients in whom PE is suspected but anticoagulant therapy is contraindicated, diagnostic evaluation should be expedited. Anticoagulation-independent therapy (eg, inferior vena cava filter) is indicated if VTE is confirmed.
- When there is suspicion for DVT alone (no clinical evidence or suspicion of acute PE), anticoagulant therapy is generally withheld until VTE is confirmed, assuming that diagnostic evaluation can be performed in a timely fashion.

ANTICOAGULATION

The following approach is generally consistent with the 2012 American College of Chest Physicians (ACCP) guidelines on VTE and pregnancy, the 2018 American College of Obstetricians and Gynecologists (ACOG) practice statement on thromboembolism and pregnancy, the European Society of Cardiologists, and the American Society of Hematology [1,7-9]. 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]. (See "Venous thromboembolism: Initiation of anticoagulation (first 10 days)".)

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) [10]. 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).

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. (See 'Dosing' below.)

Direct oral anticoagulants are avoided since little is known about their safety in pregnancy. One review reported among 137 pregnancies in women exposed to DOACs, a miscarriage rate of 23 percent and possible embryopathy in 2.2 percent of cases was reported; most were on rivaroxaban [11].

Dosing — Little information exists about the appropriate dosing of anticoagulants during pregnancy [12]. Thus, additional caution seems prudent, including weight-adjusted dosing and more vigilant monitoring of anticoagulant activity. The following regimens are reasonable for the initial treatment of VTE during pregnancy or the puerperium. Regardless of the regimen, anticoagulant therapy should continue through the pregnancy.

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 [1]. 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 [1,7].

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 [1].

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 [13]. 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 [1].

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 [1]. 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 [14]. 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. During the last 10 weeks of the pregnancy, more frequent monitoring is warranted.

Labor and delivery — Treatment with subcutaneous LMWH should be discontinued at least 24 hours prior to delivery if the delivery time is predictable (eg, induction of labor, planned cesarean section). This allows the effect of heparin to resolve, which is particularly important for patients who desire neuraxial anesthesia because anticoagulation during insertion (or removal) of a neuraxial anesthesia catheter increases the risk for spinal hematoma. (See "Adverse effects of neuraxial analgesia and anesthesia for obstetrics", section on 'Neuraxial analgesia and the anticoagulated patient'.)

A period of 24 to 36 hours without anticoagulant therapy may be undesirable in pregnant women who are at high risk for recurrent VTE (eg, those with an acute PE or proximal DVT that developed within the past month). Such patients may benefit from having their subcutaneous LMWH or subcutaneous UFH switched to IV UFH, which can be discontinued 4 to 6 hours prior to delivery [1]. A neuraxial catheter may be placed when the aPTT has returned to normal [15].

The clinician may be unwilling to tolerate even a short interval without anticoagulant therapy in rare circumstances, such as a patient with reduced cardiopulmonary reserve and a recent PE. A temporary inferior vena cava (IVC) filter can be inserted in this situation, or delivery can proceed despite full anticoagulation [16].

Delivery despite full anticoagulation may also occur if labor begins unexpectedly. Many patients who deliver while anticoagulated will not have excessive intrapartum bleeding [16]. However, anticoagulated patients are at increased risk for a spinal hematoma if a neuraxial anesthesia catheter is inserted [17,18]. Neuraxial anesthesia should not be administered to an anticoagulated patient.

In cases in which preterm delivery is anticipated (eg, triplets, preterm rupture of membranes, significant cervical dilation, preeclampsia, growth restriction), it is common to discontinue

subcutaneous LMWH or subcutaneous UFH at 36 weeks of gestation. IV UFH is then used instead.

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 [19].

Length of therapy — The optimal duration of anticoagulation is unknown and should be individualized on a case-by-case basis. However, based upon extrapolated data from the general population as well as clinical experience, the total duration of anticoagulant therapy (pregnancy plus the postpartum period) should be at least three to six months for women whose only risk factors for VTE were transient (eg, pregnancy, cesarean section) [1,20-22]. Anticoagulant therapy generally continues for at least six weeks postpartum [1,23]. Patients with persistent risk factors for VTE may require a longer duration of therapy. (See "Venous thromboembolism: Initiation of anticoagulation (first 10 days)".)

INFERIOR VENA CAVA FILTERS

Inferior vena cava (IVC) filters have been used during pregnancy [24,25]. Indications for insertion of an IVC filter are the same in pregnant and non-pregnant patients [24,25] :

- Conventional anticoagulation is contraindicated, such as during active bleeding, following recent surgery, or following a hemorrhagic stroke.
- Conventional anticoagulation has proven ineffective, such as in patients who develop new venous thromboembolism (VTE) despite being anticoagulated.
- A complication of anticoagulation develops (eg, significant bleeding), which prohibits continuation of anticoagulant therapy.
- The pulmonary vascular bed is already significantly compromised (eg, massive pulmonary embolism, chronic thromboembolic pulmonary hypertension) and unlikely to tolerate another insult.

Temporary, retrievable IVC filters may prove well-suited to use in patients who develop VTE during pregnancy or the puerperium, since the patient population tends to be quite young and have temporary risk factors for VTE (ie, pregnancy) [26,27]. However, inability to later retrieve a filter placed during the third trimester of pregnancy has been reported due to filter tilt [28].

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) [29]. (See "Thrombolytic (fibrinolytic) therapy in acute pulmonary embolism and lower extremity deep vein thrombosis".)

Observational studies provide the only data about the efficacy and safety of thrombolytic therapy and/or thrombectomy during pregnancy (ie, there are no controlled trials) [30-38]. 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 [30]. 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 [31-36]. Case reports of thrombectomy suggest that it can be used successfully as a life saving measure when other measures have failed [36,37].

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. The diagnosis and management of HIT are discussed in detail separately. (See "Management of heparin-induced thrombocytopenia".)

- **Skin necrosis** – Heparin-induced skin necrosis is a manifestation of HIT and may occur in the absence of thrombocytopenia. The diagnosis and management of HIT are discussed in detail separately. (See "Management of heparin-induced 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. This issue is discussed in detail separately. (See "Drugs that affect bone metabolism", section on 'Anticoagulants'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Superficial vein thrombosis, deep vein thrombosis, and pulmonary embolism" and "Society guideline links: Anticoagulation in pregnancy".)

SUMMARY AND RECOMMENDATIONS

- 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). (See 'Introduction' above.)
- Initial management of suspected VTE during pregnancy depends on the degree of clinical suspicion, whether anticoagulation is contraindicated, and whether PE, DVT, or both are suspected. (See 'General approach' above.)
- For pregnant women, we recommend adjusted dose subcutaneous low molecular weight heparin (LMWH), rather than adjusted dose intravenous unfractionated heparin (IV UFH) (**Grade 1B**) or vitamin K antagonists (**Grade 1A**). We recommend against the use of oral direct thrombin inhibitors (eg, dabigatran) or anti-Xa inhibitors (eg, rivaroxaban, apixaban) in pregnant women (**Grade 1C**).
- We suggest that anticoagulant therapy continue at least six weeks postpartum (**Grade 2C**). We suggest a total duration of anticoagulant therapy of at least three to six months for women whose only risk factors for VTE were transient (eg, pregnancy) (**Grade 2C**). Patients with persistent risk factors for VTE may require longer therapy (see 'Length of therapy' above).
- Thrombolytic therapy should be reserved for pregnant or postpartum patients with life-threatening acute PE (ie, persistent and severe hypotension due to the PE). (See 'Thrombolysis/thrombectomy' above.)

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