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Venous Thromboembolism in Pregnancy

ABSTRACT

KEY WORDS: venous thromboembolism, pregnancy

Hormonal-induced changes in haemostasis, fibrinolysis, blood flow, and the vessel wall are the reasons why venous thromboembolisms are more common in pregnancy than in non-pregnant women of the same age. The clinical presentation of venous thromboembolisms is more unreliable than in non-pregnant women; an objective diagnosis should be performed in suspected cases, and some peculiarities related to pregnancy should be considered. Venous thromboembolism treatment in pregnancy is based on heparins, preferably low-molecular-weight, while oral drugs (vitamin K antagonists and direct oral inhibitors of coagulation) are contraindicated. Venous thromboembolism treatment should last at least throughout the whole pregnancy and six weeks postpartum.

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VENOUS THROMBOEMBOLISM IN PREGNANCY

In pregnancy, a changed hormonal status results in increased venous capacity, and changes in coagulation and fibrinolytic processes result in a procoagulant state. Therefore, a venous thromboembolism (VTE) is more common in pregnant women. The additional reasons for increased risk for VTE in pregnant women are slower blood flow through the affected veins and possible endothelial trauma during delivery. All three factors of Virchow's triad (hypercoagulability, hemodynamic changes, endothelial injury) are involved, but changes in the coagulation system are probably the most important.

Hemostasis Changes in Pregnancy and Postpartum

In normal pregnancy, marked procoagulant activity is observed. It is evolutionarily reasonable, because it protects the mother against bleeding, which has historically been the leading cause of maternal mortality and still is in developing countries *(1)*. Increased levels of coagulation factors V, VII, VIII, IX, X, XI, and XII, von Willebrand's factor and fibrinogen are detected. Changes in antithrombin and protein C concentrations are minor. The protein C-dependent pathway is less effective due to thrombomodulin and protein C receptor changes. This can be described as acquired activated protein C resistance, which could also be congenital in patients with factor V Leiden mutation. Protein S concentration is lowered in pregnancy. All described changes result in procoagulant activity. Fibrinolysis, the opposite physiological process of coagulation, is less active in pregnancy due to increased concentrations of plasminogen activator inhibitors 1 (PAI 1) and 2 (PAI 2). An elevated D-dimer concentration is detected because of accelerated clot generation and fibrinolysis. However, most of the described changes are normalized by the end of the sixth week postpartum, when the maternal procoagulant hemostatic system gradually returns to a state close to that of non-pregnancy. This process is finished after the twelfth week postpartum *(1)*.

Epidemiology

The incidence of VTE in pregnancy is around 199 per 100,000 pregnancies. It is around four times more common than in non-pregnant women of the same age *(2)*. VTE is slightly more common in the last than in the first two trimesters. About half of VTE events are detected postpartum – the majority in the first six weeks postpartum *(2)*. This period lasts until the end of the tenth week postpartum, but after the sixth week, the incidence is remarkably lower *(2)*. Pulmonary embolism (PE) remains a leading cause of maternal death in the developed world, causing 0.8–1.49 deaths per 100,000 pregnancies *(2)*. Death from PE represents about one-tenth of all maternal deaths. The post-thrombotic syndrome is also important – these are chronic changes after acute deep vein thrombosis (DVT), which can worsen during the following years and may represent serious problems due to functional and aesthetic disability.

In addition to changes in coagulation and fibrinolysis, there are some other risk factors related only to pregnancy: over 35 years of age, caesarean section (urgent cases represent a higher risk), multiparity, infection, bleeding, preeclampsia, eclampsia, assisted reproduction, placenta praevia, obesity, and prolonged bed rest *(3)*. The precise risk is sometimes difficult to assess because of the combination of different risk factors.

Clinical Picture

Symptoms and signs of VTE are the same as in non-pregnant women. However, leg swelling, often bilateral, is a frequent complaint or finding in normal pregnant women. Dyspnea is also quite common in healthy

pregnant women, and therefore PE is sometimes suspected. This explains why VTE is confirmed in only 10% of suspected pregnant women *(1)*. Diagnostic procedures already established in non-pregnant populations have some differences related to pregnancy.

Diagnosis of Deep-Vein Thrombosis

The diagnostic procedure is the same as in non-pregnant women. It starts with a clinical assessment, followed by D-dimer testing and ultrasound (US) investigation. Rarely some other examinations are used.

Clinical Assessment

While clinical decision rules have been demonstrated to be very useful in assigning pretest probability outside pregnancy, studies deriving and validating these models did not include pregnant patients. Nevertheless, the diagnostic procedure begins with a clinical prediction rule, which should be confirmed by objective testing.

D-dimer

In VTE, the D-dimer is usually elevated. However, the usefulness of D-dimer testing in pregnancy is potentially limited by normal physiological increases in D-dimer levels, although it is still used in diagnostic procedures.

Ultrasound Investigation

A pregnancy US is the most important investigation. Two strategies are used; the serial US – proximal veins twice in one week, when the first investigation is negative, or the whole leg US in one – the first session. We propose to investigate the whole leg at first visit; if negative and DVT is still suspected, the US should be repeated in one week. A US could be nondiagnostic in the investigation of iliac veins when iliac vein thrombosis is suspected. Then, indirect measures, such as the absence of flow or visible thrombus on B-mode imaging of the vessels, can be useful *(4)*. The accuracy of these indirect US assessments of iliac veins is uncertain. If there is strong clinical suspicion of iliac vein thrombosis and the US is negative, MRI without contrast or classic phlebography is proposed *(5)*.

Treatment of Deep-Vein Thrombosis

VTE treatment in pregnancy is generally the same as in non-pregnant women with some modifications. Nevertheless, some pregnancy-related characteristics must be considered.

Anticoagulant Treatment

Vitamin K antagonists are probably acceptable until the sixth week of pregnancy but are later contraindicated due to teratogenicity and increased risk for fetal bleeding. They can be used postpartum in breastfeeding mothers. Direct anticoagulant drugs (DOACs: rivaroxaban, dabigatran, apixaban, and edoxaban) are contraindicated in pregnancy and during breastfeeding. Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH) are allowed in pregnancy. The anticoagulation effects of LMWHs are more predictable, therefore, these are the drugs of choice during pregnancy. Because of its shorter half-life and the ability to fully reverse its anticoagulant activity, if necessary, UFH could be used, especially at the time of delivery or in some other procedures with a high risk of bleeding *(3, 5)*. During treatment with LMWH, clinical bleeding could be expected in around 2% of treated patients: 0.4% before delivery, 1% after delivery, and 0.6% from post-operative wounds. Allergic reactions are described in 1.8% of patients, and heparin-induced thrombocytopenia can occur very rarely (0.025%) *(3, 4)*. Reduced bone density, which is to some degree physiological in pregnancy, is detected in

less than 0.04% of treated patients. LMWH should be given subcutaneously once or twice daily and adjusted to body weight. We suggest using the twice-daily regimen in the last month of pregnancy and the once-daily regimen outside of this period and postpartum. The exceptions are patients with a body weight of over 100 kg, in whom a twice-daily regimen is prescribed by the drug producers as in non-pregnant population. The treatment should last the whole pregnancy and six weeks postpartum but at least three months if VTE is detected late during pregnancy. That is important in patients who develop VTE late. In patients with late VTE, occurring in the last weeks of pregnancy, the treatment should be prolonged until the end of the third month after VTE was detected *(4, 6)*. Monitoring anti-Xa levels in women on LMWH is rarely needed. The current recommended anti-Xa range in pregnancy with LMWH twice-daily is 0.5–1.0 IU/ml (blood drawn 4 hours after the dose). In patients treated with LMWH once-daily, the target range at 4–6 hours after the dose is less clear, but 1.0–2.0 IU/mL is considered reasonable. UFH should be monitored, and the dose adjusted according to activated partial thromboplastin time (aPTT) as in the non-pregnant population *(6)*. In the management of pregnant women with acute VTE close to the term of delivery, the risk of stopping anticoagulation must be balanced with the risk of recurrent VTE. There are no general precise recommendations on how to handle anticoagulation treatment. We suggest a twice-daily regimen in the last month of pregnancy. The last half dose is administered the day before the delivery, and we suggest starting anticoagulation treatment 12 hours postpartum. If VTE is diagnosed near the term (over 37 weeks), then consideration should be given to the placement of an inferior vena cava (IVC) retrievable filter. This is followed by anticoagulation reversal with a planned induction performed after the anticoagulation reversal. Anticoagulation reversal without IVC filter protection is strongly discouraged in the two weeks after the diagnosis of the VTE, given the mortality of untreated VTE in this period in non-pregnant patients. In these cases, UFH is suggested close to term *(3)*. Lacking proper studies, the time window for the first dose of anticoagulation postpartum is 6–24 hours. Usually, the prophylactic dose is suggested. Twelve hours later, we proceed with the prelabour regimen, which lasts at least six weeks postpartum. In case of cesarean delivery, the risk of bleeding is increased. However, the risk of thrombosis is higher than in vaginal delivery. Therefore, the administration of the first dose of LMWH is also 6–12 hours postpartum. When neuraxial anesthesia is administered, the time of placement of the catheter should be at least 24 hours after the half-therapeutic dose of LMWH. When the prophylactic dose is used, the first dose after catheter removal should be administered at least 2 hours later, and at least 12 hours later when the half therapeutic dose is used *(3, 6)*. The filter could be considered also when therapeutic anticoagulation is contraindicated because of a high risk of bleeding, or in patients who have objectively confirmed recurrent VTE despite proper therapeutic anticoagulation *(7)*.

Pulmonary Embolism

The clinical assessment of PE in pregnancy is less reliable than in non-pregnant women. The Geneva pregnancy adapted risk assessment score (age > 40 years, surgery or limb fracture, previous VTE, unilateral limb pain, hemo-ptysis, pain on lower limb palpation and unilateral edema, heart rate > 110 per minute) or the YEARS algorithm (clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis) both with D-dimer testing could be used to diminish the need for a CT pulmonary angiography (CTPA). However, CTPA is still needed in

about 10% of suspected pregnant women. Sometimes, the ventilation perfusion scintigraphy could be used as well. Radiation is a concern, but the radiation is very low, and not harmful for the fetus. Postpartum MRI angiography is probably the safest option. However, breastfeeding should be omitted for 12 hours after MR investigation *(3, 5, 6)*.

Recanalization Procedures in Patients with Pulmonary Embolism

Pregnant women with a high-risk PE have an approximately 37% risk of PE case fatality *(5)*. Therefore, in pregnant women with high-risk PE, which is associated with hypotension circulatory collapse at presentation, thrombolysis or some other recanalization procedures, for example the aspiration of the pulmonary artery thrombus with some dedicated devices with or without extracorporeal membrane oxygenation, should be considered. Surgical removal of the thrombus is also possible *(5)*.

CONCLUSION

Cases of VTE – namely DVT and PE are common during the whole pregnancy and postpartum due to pregnancy-related changes. They are serious adverse events and should be properly treated in an experienced specialized centre.

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