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Venous thromboembolism in pregnant woman – a challenge for the clinician

Mini-Review

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Abstract: Deep vein thrombosis and pulmonary embolism are two clinical entities of a single disease called venous thromboembolism. Venous thromboembolism is an important cause of maternal morbidity and mortality. Diagnosis and treatment of venous thromboembolism in pregnant women are much more difficult than in non-pregnant women. Pregnant patients were excluded from all major clinical trials investigating therapeutic combinations for acute thromboembolism. Although, for many years, the standard anticoagulant during pregnancy and postpartum was unfractionated heparin, current guidelines recommend low molecular weight heparin. The advantages of low molecular weight heparin are lower risk of bleeding, predictable pharmacokinetics, lower risk of fracture because of thrombocytopenia and heparin-induced osteoporosis.

Keywords: *Thromboembolism • Pregnancy • Anticoagulation*

1. Introduction

Venous thromboembolism (VTE) is a term that includes deep vein thrombosis and pulmonary embolism. Thromboembolism was the leading cause of death in pregnant women in United Kingdom since 1985; now it has dropped into third place, after deaths by sepsis and pre-eclampsia/eclampsia [1]. Maternal mortality from pulmonary embolism seems to be on a downward trend in the developed world [2]. However, data from non-European countries still mention this disease as a leading cause of mortality [3].

Virchow triad, represented by hypercoagulability, venous stasis and vascular damage, all present in pregnancy, confers an increased risk for pregnant or postpartum women.

Compared with non-pregnant women, pregnant women have a 3-4 times higher risk for arterial thromboembolism and 4-5 times higher risk for venous thromboembolism [4-6]. Postpartum, the risk is even higher (20 times) [6]. The prevalence of thromboembolic events in pregnancy is approximately 2 to 1000 births [4,5]. Of these, 20% are arterial and 80% are venous [4,5].

2. Risk factors

Risk factors for VTE are age older than 35 years, obesity (body mass index greater than 30), multiparity, personal or family history of VTE or thrombophilia [7] (Table 1). Between 15 and 25% of thromboembolic events in pregnancy are actually recurrences. In recent studies, the incidence of VTE recurrence in women who were not anticoagulated was 2.4-12.2% [8-10]; in those receiving anticoagulant therapy, recurrence rates ranged between 0 and 2, 4% [7,11,12]. Other important risk factors are prolonged bed rest, over four days, dehydration,

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Table 1. Risk factors for thromboembolism in pregnancy.

Low risk	Age < 35 yo, no risk factors
Moderate risk	Age > 35 yo Obesity Cesarean section
High risk	Personal history of VTE/PE Thrombophilias

smoking, certain conditions such as congestive heart failure, severe infection, nephrotic syndrome, surgery, preeclampsia, diabetes mellitus [13]. Caesarean birth is associated with greater risk than vaginal birth.

Studies have shown that about half of pregnant women with VTE had thrombophilia compared to 10% in the general population [7]. Data available to date does not recommend general screening for thrombophilia, which is not cost-effective. However, some experts recommend testing women with personal or family history of thrombophilia or thrombosis [14]. During pregnancy, the results should be interpreted with caution because the protein S is normally lower in the second trimester of pregnancy. Nephrotic syndrome is associated with decreased levels of antithrombin and liver diseases with decreased levels of protein C and S.

Antiphospholipid antibody syndrome, the most common form of thrombophilia in pregnancy, is defined by the presence of antiphospholipid antibodies with one or more clinical manifestations, most commonly thrombosis or recurrent abortions. A positive test for lupus anticoagulant or moderate or high titers of IgG or IgM anticardiolipin antibodies provide laboratory confirmation of antiphospholipid antibody syndrome, if the result is positive twice after being repeated at 6 weeks. Thrombophilic pregnant women have a higher risk of complications in pregnancy, pregnancy loss, intrauterine growth delay, and placental rupture.

Deep vein thrombosis occurs with equal frequency in any trimester of pregnancy and in postpartum [15]. During pregnancy, 78-90% of VTE occur in the left leg, 72% in the ilio-femoral vein, with high risk of embolization [7]. In non-pregnant women, 55% of VTE occur in the left leg and 9% in the ilio-femoral vein [7]. Pulmonary embolism is more common in the postpartum period than during pregnancy, especially after caesarean section.

3. Diagnosis

Clinical suspicion is essential for the diagnosis of VTE, because many of the classic signs and symptoms of VTE, including lower limb edema, tachycardia, dyspnea, tachypnea, are normally found in pregnancy. However, women with clinical laboratory findings suggestive of VTE should be further investigated to rule out VTE.

Table 2. Paraclinic investigations for diagnosis of deep vein thrombosis in non-pregnant and pregnant women.

Non-pregnant women	Pregnant women
Contrast venography	Repeated compression ultrasound
Compression ultrasound	Venography
Plethysmography	Nuclear magnetic resonance
D-dimer	
Nuclear magnetic resonance venography	

The methods of diagnosis of deep venous thrombosis in pregnancy are similar to those used in non-pregnant patients. In non-pregnant women, a negative D-dimer test in combination with a low probability score have a negative predictive value of nearly 100%, when using a highly sensitive detection method (ELISA) [16,17]. However, D-dimer increase progressively during normal pregnancy, and the values considered normal according to gestational weeks are not yet universal set [18,19]. Current recommendations suggest that D-dimer should be used in combination with other tests. A negative D-dimer test may be useful if vascular compression ultrasound result is normal, while a positive D-dimer test requires additional diagnostic tests [17].

Laboratory investigations used for diagnosis of deep vein thrombosis in non-pregnant women are contrast venography, compression ultrasound, plethysmography, D-dimer and nuclear magnetic resonance venography (Table 2). When there is a suspicion of deep vein thrombosis in a pregnant woman, the first imaging diagnostic test should be vascular ultrasound with compression of the entire leg [17]. A normal ultrasound result does not exclude deep vein thrombosis, the investigation should be repeated every 1-2 days and then after a week. If compression ultrasound raises the suspicion of iliac thrombosis, venography or magnetic resonance can be recommended.

Patients in whom pulmonary embolism is suspected, but with normal compression ultrasound, require further laboratory investigation. For a diagnosis of pulmonary embolism in non-pregnant women the methods are pulmonary angiography, ventilation-perfusion studies, spiral CT, plus D-dimer testing. Spiral CT is increasingly used to diagnose pulmonary embolism; it has a very good sensitivity for large, central, pulmonary emboli, and less good for small peripheral emboli.

Computer tomographic pulmonary angiography is necessary to elucidate the diagnosis of pulmonary embolism in pregnant women. Recommendation of these investigations can be difficult due to concerns about the risks of fetal exposure to ionizing radiation,

especially oncogenicity and teratogenicity. Most of the large studies that examined the link between cancer in children and exposure to radiation in utero reported a small increase in relative risk (between 1.2 to 2.4) [20]. Studies that have investigated the teratogenic potential of exposure to radiation in utero reported no increased risk of miscarriage, intrauterine growth delay or mental retardation, but only a slight increase in congenital eye anomalies [21].

4. Treatment of VTE in pregnant women

Diagnosis of deep vein thrombosis or pulmonary embolism requires the initiation of anticoagulant treatment. The main therapeutic options are low molecular weight heparins (LMWH), unfractionated heparin and oral anticoagulants.

Pregnant patients were excluded from all major clinical trials investigating various therapeutic combinations for acute VTE. Although, for many years, the standard anticoagulant used in pregnancy and postpartum was unfractionated heparin, current guidelines recommend LMWH [22]. The advantages of LMWH are lower risk of bleeding, predictable pharmacokinetics, lower risk of fracture because of thrombocytopenia and heparin-induced osteoporosis. In non-pregnant women, treatment regimens with LMWH for acute VTE are clearly defined, and doses are dependent on body weight. Moreover, it appeared that long-term treatment with LMWH is at least as effective as vitamin K antagonists for prevention of recurrent VTE. However, in pregnant women, treatment with LMWH is more difficult. First, it is unclear whether LMWH dosing regimens can be made taking into account body weight before pregnancy or permanent dose adjustment is necessary based on body weight change during pregnancy. Second, because the volume of distribution of LMWH and glomerular filtration rate change in the second trimester of pregnancy, we do not know whether the administration twice a day is preferable to a single intake.

Choosing the optimal anticoagulant treatment of VTE in pregnant women should consider the safety profile of both the mother and the fetus, but also its efficiency. Unfractionated heparin and LMWH does not cross the placenta and are considered safe in pregnancy, based on several observational studies. Vitamin K antagonists cross the placenta and vitamin K deficiency that is induced in the fetus may cause coumadinic embryopathy, a disorder characterized by nasal hypoplasia. The teratogenic effect occurs only if vitamin K antagonists are administered during weeks 6-12 of gestation [23]. In the last trimester of pregnancy because of risk of bleeding in the fetus, especially during childbirth, it is recommended to avoid vitamin K antagonists.

Fondaparinux is a new selective inhibitor of factor Xa used in thromboprophylaxia. Data about its administration in pregnancy is insufficient.

Regarding the duration of treatment, data derived from studies on non-pregnant women suggests that anticoagulation therapy after a first episode of VTE should continue for at least 6 months. In pregnancy, current recommendations support a treatment period between 3-6 months, including 6 weeks postpartum [24]. Treatment longer than 12 months is recommended for women with VTE and antiphospholipid syndrome and those with thrombophilia and recurrent thrombotic events.

Therapeutic doses of heparin in pregnancy are:

- LMWH (enoxaparin) 1 mg/kgc subcutaneously every 12 hours.
- Unfractionated heparin 5000 IU iv loading dose, then continuous iv infusion to a dose of 30 000 IU/24 h OR 10 000 IU subcutaneously every 8 hours OR 20 000 IU subcutaneously every 12 hours; APTT should be monitored and the dose should be adjusted to maintain APTT 1.5-2 times higher than the control. Unfractionated heparin therapy is followed by treatment with subcutaneous LMWH.

In the last month of pregnancy, women can be converted from LMWH to UFH because it has a shorter duration of action and lower risk of bleeding during childbirth. Caesarean birth doubles the risk of VTE, patients with at least one risk factor may be candidates for thromboprophylaxis with intermittent pneumatic compression, unfractionated heparin or low molecular weight heparin. Patients with multiple risk factors for VTE should receive thromboprophylaxis with intermittent pneumatic compression and unfractionated heparin or LMWH. To decrease the risk of bleeding complications, resumption of anticoagulant therapy should be delayed at least 12 hours after vaginal delivery or 24 hours after caesarean birth.

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Conflicts of interest

None.

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