Venous Thromboembolism in Pregnancy

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Summary

During pregnancy, the risk of venous thromboembolism (VTE) can increase 4- to 5-folds as compared to non-pregnant women. This predisposition to thrombosis is the result of the hypercoagulable state of pregnancy related to the increase of procoagulant factors and the decrease of physiological anticoagulants. Several factors account for the development of VTE in pregnancy. Virchow's classic triad associated with the pathogenesis of thrombosis, including stasis, hypercoagulability, and vascular injury, is present during the whole pregnancy. In addition, pregnant patients with acquired or inherited thrombophilic defects are at particularly higher risk for VTE. Clinical symptoms of deep venous thrombosis (DVT) may be elusive and often difficult to be distinguished from gestational edema. Venous compression ultrasonography (CUS) is the diagnostic test of choice meanwhile the tests of choice for the diagnosis of pulmonary embolism (PE) are the ventilation/perfusion lung scinti-scan or computed tomographic pulmonary angiography (CTPA). Therapy of established VTE during pregnancy consists of therapeutic doses of unfractionated heparin or low-molecular-weight heparin (LMWH), generally administered throughout pregnancy and post-partum for an overall period of at least six months after the thrombotic event. An unresolved issue includes the optimal dose of LMWH therapy during pregnancy complicated by VTE. Prevention of VTE remains the goal for the clinician and is related to a careful evaluation of the true risk of VTE in pregnant patients especially those with previous VTE and/or thrombophilia. This article provides a brief overview of the pathophysiology, diagnosis, treatment and prevention of VTE in pregnancy and refers the reader to recent evidence based guidelines.

Key-words: **venous thromboembolism, pregnancy, thrombophilia, anticoagulation.**

Riassunto

Il tromboembolismo in gravidanza

Durante la gravidanza, il rischio di tromboembolismo venoso (TEV) può aumentare di circa 4-5 volte rispetto ad una donna di pari età non in gravidanza. Questa predisposizione alla trombosi è conseguente allo stato di ipercoagulabilità che si verifica in gravidanza per l'incremento di fattori procoagulanti e la riduzione dei livelli degli anticoagulanti fisiologici. I fattori che contribuiscono allo sviluppo del TEV in gravidanza sono svariati. La classica triade di Virchow associata alla patogenesi della trombosi, che comprende la stasi, l'ipercoagulabilità ed il danno vascolare, è riconoscibile durante tutta la gravidanza. Inoltre, donne portatrici di difetti trombofilici ereditari o alterazioni acquisite sono a rischio ancor più elevato di sviluppare eventi trombotici. I sintomi della trombosi venosa profonda in gravidanza possono essere sfumati e spesso non distinguibili dall'edema gestazionale. L'ecografia venosa con compressione (CUS) è il test diagnostico di scelta per la diagnosi di trombosi venosa profonda mentre per la diagnosi di embolia polmonare è necessaria l'esecuzione di una scintigrafia polmonare ventilo/perfusoria o di una angio-TC polmonare. La terapia del tromboembolismo venoso in gravidanza si basa sull'utilizzo di dosi terapeutiche di eparina non frazionata (ENF) o a basso peso molecolare (EBPM). Generalmente tale trattamento viene somministrato per tutta la durata della gravidanza e nel post-partum, per un periodo complessivo non inferiore ai 6 mesi dall'evento trombotico. Quale sia il dosaggio ottimale della terapia con EBPM durante la gravidanza è ancora oggetto di discussione. Uno degli obiettivi principali resta la prevenzione del TEV in gravidanza ed è strettamente correlato alla corretta definizione del rischio trombotico specialmente in presenza di precedenti episodi tromboembolici o di trombofilia. In questo articolo verranno sinteticamente affrontati i temi della fisiopatologia, diagnosi, cura e prevenzione della TEV in gravidanza e si farà breve cenno alle linee guida recentemente pubblicate.

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Introduction

It has been established that venous thromboembolism (VTE) occurs in one case per 1000 individuals per year. This incidence is much lower in the young, being one per 10,000 people per year at an age of less than 45. VTE can be considered a multifactorial disease resulting from the interaction of different risk factors both genetic (inherited thrombophilic conditions) and acquired (age, cancer, myeloproliferative diseases, autoimmune diseases, vasculitis, antiphospholipid antibodies, nephrotic syndrome and others). There are also transient triggering conditions (surgery, fractures, trauma and injury, prolonged immobilization) which can be concomitantly present in patients with the above mentioned risk factors and can account for the development of VTE. These risk factors and triggering conditions are in general distributed equally in both sexes. However, there are transient risk factors for VTE that can be present only in women and make women more exposed than men to the risk of VTE during a particular period of their life. These factors include the use of oral contraceptives (first, second and third generation OCT), hormone replacement therapy, pregnancy and puerperium. In addition, the pathogenesis of several obstetric complications such as fetal loss, intrauterine growth retardation, preeclampsia, was at least partly attributed to impaired placental circulation as well as to the presence of hypercoagulable states.

Epidemiology

The risk of VTE increases by at least 4- to 5-fold during pregnancy and VTE is one of the leading cause of maternal mortality[1,2]. The reported incidence of VTE, in the last decade, ranges from 0.49 to 1.72 per 1000 deliveries[3] and VTE accounts for 1.1 deaths per 100.000 deliveries[3], or 10% of all maternal death. The risk of VTE is even higher in the postpartum period (20-fold)[4], the highest being in the first week after delivery. It has been shown that about 50% of events occur during pregnancy and the remaining during puerperium[5]. Since the duration of pregnancy is about 6-7 times higher than that of puerperium (40 weeks and 6 weeks, respectively), the daily distribution of VTE is much higher during this last time. Approximately 80% of VTE during pregnancy are deep vein thrombosis (DVT) and about 20% are pulmonary emboli (PE)[3]. DVT which occurs during pregnancy is more likely to affect proximal veins[6], to be massive[6], and to develop in the left lower extremity[7].

Risk factors

Pregnancy is classically considered as a hypercoagulable state. The levels of coagulation factors II, VII, X, and fibrinogen are all markedly increased, free protein S levels are decreased, and acquired resistance to activated protein C is common[8]. Other coagulation or fibrinolytic factors levels are also modified during pregnancy. There is a final unbalance towards an acquired hypercoagulability. Moreover, venous stasis may become evident as pregnancy progresses and is frequently attributed to a progesterone-related increase in venous capacitance as well as to the compression of the inferior vena cava by the uterus.

A previous history of thrombosis represents one of the most important risk factor for VTE in pregnancy. Women with previous VTE have an increased risk of recurrent VTE during pregnancy which is about approximately 3.5 folds as compared to non-pregnant periods[9]. The presence of thrombophilic defects is another important determinant of the risk of VTE in pregnancy. In individuals with factor V Leiden mutation, factor II G20210A variant, antithrombin or protein C deficiency, a relative risk of pregnancy associated VTE between 3.4 and 15.2 has been found[10]. Women who are heterozygous for the factor V Leiden or prothrombin gene mutations have a 50-fold (odds ratio [OR] 52; 95% confidence interval [CI], 12.4–219.5) and 30-fold (OR of 31; 95% CI, 4.6–203.6) increased risk of developing VTE associated with pregnancy (including the postpartum period), respectively[2], as compared with non-pregnant controls. Additional risk factors are represented by caesarean delivery (5- to 10-fold)[5,11], age greater than 35 years[5,11], and obesity[12].

Diagnosis

Clinical suspicion is critical for the diagnosis of VTE. D-dimer testing with currently available assays (Elisa, Latex and others) has not been helpful in excluding VTE, as pregnancy is accompanied by a "physiological" increase in D-dimer levels and a high proportion of false positive results. Compression ultrasonography (CUS) is a non-invasive test with a sensitivity of 97% and a specificity of 94% for the diagnosis of symptomatic, proximal deep-vein thrombosis in the general population[13]. CUS is the test of choice in pregnant patients with suspected venous thromboembolism. Patients with suspected pulmonary embolism and normal findings on CUS require additional diagnostic imaging. A chest radiograph should be obtained to rule out alternative diagnoses. Ventilation/perfusion (V/Q) lung scinti-scan or computed tomographic pulmonary angiography (CTPA)[14] should be performed. Both V/Q scanning and CTPA give relatively low radiation exposure to the fetus[15]. There are concerns, however, about maternal radiation exposure because of radiation absorption by maternal breast tissue. The radiation dose delivered to mothers is higher with CTPA than with scinti-scan (2.2 to 6.0 mSv vs 1.4 mSv)[16].

Antitrombotic therapy

Anticoagulant therapy is indicated during pregnancy for the prevention and treatment of venous thromboembolism (VTE). Given the paucity of data regarding the efficacy of anticoagulants during pregnancy, recom-

mendations about their use in pregnant women are largely derived from data from non-pregnant patients, from case reports, and from case series of pregnant patients[17] (Table I).

Treatment. Warfarin, the preferred agent for long-term anticoagulation outside of pregnancy, has harmful fetal effects. The preferred agents for anticoagulation in pregnancy are heparins[17]. Neither unfractionated heparin[18,19] nor low-molecular-weight heparin (LMWH)[19] cross the placenta. Although for many years unfractionated heparin was the standard anticoagulant used during pregnancy and in the puerperium, current guidelines[17] now recommend a twice-daily weight-based LMWH regimen. The management of anticoagulation at the end of pregnancy is challenging. Guidelines suggest discontinuing the heparin at least 24 h prior the elective induction of labor. Anticoagulation therapy with either LMWH or warfarin is recommended for at least 6 weeks post partum and for a total duration of therapy of at least 6 months[17].

Prophylaxis. Antithrombotic prophylaxis with LMWH during pregnancy should be considered in women with personal history of VTE. Women who have had VTE have a much higher risk of a recurrent episode during pregnancy than women without such a history[20]. The risks of venous thromboembolism are even higher in the puerperium. Therefore postpartum pharmacologic thromboprophylaxis for at least 6 weeks (LMWH or warfarin) is recommended for all women who have had a previous thromboembolism[17]. The indications for antepartum pharmacologic prophylaxis are more controversial.

Pregnant women with high-risk thrombophilias (e.g. antithrombin deficiency, the antiphospholipid syndrome, compound heterozygosity for prothrombin G20210A variant and factor V Leiden, or homozygosity for prothrombin G20210A variant or factor V Leiden) should receive antenatal thromboprophylaxis[17]. At present, there is no evidence to support screening for thrombophilia in pregnancy for the prevention of VTE. The natural history of many thrombophilias, expecially in asymptomatic patients, is unknown, appropriate intervention is unclear and cost-effectiveness is unproven.

Fondaparinux is a new selective factor Xa inhibitor used for thromboprophylaxis. Data on its use in pregnancy are limited and, at the present time, there are insufficient evidences to justify the routine use of fondaparinux for prophylaxis of VTE in pregnancy.

Conclusion

Venous thromboembolism in pregnancy is one of the most challenging and, at the same time, debating aspects of the thrombotic disease. To date it remains a major cause of maternal morbidity and mortality. Many

Table I. Key recommendations of ACCP 2008 (8th edition) for antithrombotic therapy in pregnancy[17].

Pregnant women in general (except in women with mechanical heart valves)	Vitamin K antagonists should be substituted with UFH or LMWH	Grade 1A
Pregnant women with acute VTE	LMWH or UFH should be continued throughout pregnancy	Grade 1B
	Anticoagulants should be continued for at least 6 weeks postpartum (for a total minimum duration of therapy of 6 months)	Grade 2C
Pregnant patients with a single prior episode of VTE associated with a transient risk factor that is no longer present and no thrombophilia	Clinical surveillance antepartum and anticoagulant prophylaxis postpartum	Grade 1C Grade 1C
Pregnant women with a history of a single prior episode of VTE who are not receiving long-term anticoagulant therapy	Antepartum prophylactic LMWH/UFH or intermediate-dose LMWH/UFH or clinical surveillance throughout pregnancy plus postpartum anticoagulants	Grade 1C
Pregnant women with multiple episodes of VTE who are not receiving long-term anticoagulants	Antepartum prophylactic with intermediate-dose or adjusted-dose LMWH/UFH followed by postpartum anticoagulants	Grade 2C
Pregnant women with no prior history of VTE but antithrombin deficiency	Antepartum and postpartum prophylaxis	Grade 2C
Pregnant women with thrombophilia but no prior VTE	Antepartum clinical surveillance or prophylactic LMWH or UFH, plus postpartum anticoagulants	Grade 2C

VTE, venous thromboembolism; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

progresses has been made, especially recently, in order to clarify the mechanisms underlying the development of thrombotic complications, the diagnosis and treatment of VTE in pregnancy. Unfortunately, the lack of large prospective studies has always limited the value of the results obtained so far. It is therefore necessary to organize prospective multicenter studies that can definitively clarify the unresolved issues of VTE in pregnancy.

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