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Gaćina, Petar; Čaržavec, Dubravka; Stančić, Vladimir; Pejša, Vlatko

Source / Izvornik: **Acta clinica Croatica, 2006, 45, 31 - 35**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:220:019548

Acta Clin Croat 2006; 45:31-35 Professional Paper

TREATMENT OF VENOUS THROMBOEMBOLISM DURING PREGNANCY AND PUERPERIUM

Petar Gaćina[1], Dubravka Čaržavec[1], Vladimir Stančić[1] and Vlatko Pejša[2]

[1]Department of Hematology, Sestre milosrdnice University Hospital; [2]Department of Hematology, Dubrava University Hospital, Zagreb, Croatia

SUMMARY – Venous thromboembolism (VTE) occurs infrequently but remains the leading cause of pregnancy- and puerperium-related mortality in industrialized countries. In pregnant women, the risk of VTE is about 4- to 5-fold that in non-pregnant women. The pathogenesis of VTE is associated with venous stasis, endothelial damage to pelvic veins at delivery, and procoagulant changes that occur during pregnancy and puerperium. The most common risk factors for VTE during pregnancy and puerperium are previous thrombotic event(s), thrombophilia, age over 35, obesity and operative delivery. Deep venous thrombosis in pregnancy and puerperium is usually left-sided (85% *versus* 55% in non-pregnant patients) and iliofemoral (72% in pregnancy *versus* 9% in non-pregnant patients). Low-molecular weight heparins (LMWHs) are the drugs of choice for the treatment of VTE during pregnancy and puerperium, as they are effective and have substantially fewer side effects such as heparin-induced thrombocytopenia, bleeding and osteoporosis as well as more reliable antithrombotic activity compared with unfractionated heparin.

Key words: *Venous thrombosis – etiology; Pregnancy – complications; Venous thrombosis – therapy; Risk factors*

Introduction

The incidence of pregnancy associated venous thromboembolism (VTE) is approximately 1 *per* 1500 deliveries. Despite achievements with thromboprophylaxis in other areas, over the past 20 years there has been an increase in the incidence of deep venous thrombosis (DVT) in pregnant women. This increase may be explained by the risk factors including older age, cesarean section, a history of VTE, and presence of thrombophilia. In pregnant women, the risk of VTE is five-fold that in non-pregnant women of similar age[1], and is higher after cesarean section than after vaginal delivery. In the Leiden Thrombophilia Study, pregnancy was associated with a four-fold risk and puerperium with a 14-fold risk of thrombosis[2]. The third trimester and postpartum period are the most likely times for VTE to occur.

Women with previous VTE have an approximately 3.5-fold risk of recurrent VTE during pregnancy compared to non-pregnant periods[3]. The risk of VTE is additionally increased in pregnant women who have inherited thrombophilias such as factor (F) V Leiden mutation, prothrombin gene (G20210A) mutation, homozygosity for C667T methylene tetrahydrofolate reductase (MTHFR) mutation, deficiencies of antithrombin (AT), protein C (PC) or protein S (PS), presence of antiphospholipid antibodies (APLA), and those with known antiphospholipid syndrome[4-15].

Pathophysiology

Pregnancy and the postpartum period may be marked by the presence of all three components of Virchow's triad: venous stasis and atonia due to hormonal effects and the enlarging uterus, endothelial injury, and a hypercoagulable state[16]. The physiologic changes in the

Correspondence to: *Petar Gaćina, MD*, Department of Hematology, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: petar.gacina@zg.htnet.hr

Received January 27, 2006, accepted February 28, 2006

hemostatic system include acquired functional resistance to activated protein C, elevation of fibrinogen levels and F VIII activity, a decrease in PS, increases in plasminogen activator inhibitor 1 and 2 (PAI-1, PAI-2) that decrease fibrinolysis, and platelet activation[16-19]. These changes occur throughout pregnancy and persist for up to 6 weeks postpartum.

Diagnosis of VTE during Pregnancy

Prompt diagnosis and treatment of VTE in pregnancy and puerperium can greatly reduce the associated morbidity and mortality. The diagnosis of VTE during pregnancy is difficult as many of the signs and symptoms also occur in healthy pregnant women, and pulmonary emboli may arise from the pelvic veins while the leg veins remain normal[20]. The elevation of plasma levels of D-dimers during pregnancy may be unrelated to VTE[19,20-23].

Compression ultrasonography (CUS) is the test of choice for DVT. A normal CUS does not exclude calf DVT, so the test should be repeated 1-2 days after referral (day 2 or 3) and, if normal, again 1 week later (days 6-8) to exclude the possibility of extending calf-vein thrombosis. If the test is normal, or if it is unsuccessful and the clinical suspicion of isolated iliac DVT is high, complete venography without a lead-lined apron or magnetic resonance imaging (MRI) should be considered in order to make a definitive diagnosis[24,25].

The approach to suspected pulmonary embolism (PE) in pregnancy is similar to the approach in non-pregnant patient. Ventilation/perfusion (V/Q) lung scan is the first line test, followed by CUS if the results are non-diagnostic. The combination of chest roentgenography, V/Q scanning, and pulmonary angiography exposes the fetus to less than 5000 μGy (0.5 rad). Exposure to radiation of less than 50,000 μGy (5 rad) has not been associated with a significant risk of fetal injury in most studies[26]. Helical computed tomography (hCT) and MRI are now more commonly used for the diagnosis of PE.

Treatment of VTE during Pregnancy

The therapeutic options in pregnancy are limited to the use of either unfractionated heparin (UFH) or low molecular weight heparins (LMWHs). The available evidence shows that LMWHs are at least as effective and safe as UFH in the prevention and treatment of VTE during pregnancy and puerperium. Oral anticoagulants such as warfarin are relatively contraindicated for use during pregnancy for the treatment of VTE because they freely cross the placenta, and can be associated with adverse fetal effects.

LMWHs are widely used in pregnancy and puerperium for treatment of VTE because they do not cross the placenta barrier and therefore do not cause fetal bleeding or teratogenicity[26]. LMWHs have a longer half-life and greater bioavailability than UFH, which allows for once or twice daily subcutaneous injection. LMWHs also have a substantially lower incidence of maternal heparin induced thrombocytopenia (HIT), bleeding and osteoporosis[27]. Danaparoid, a heparinoid with limited immunologic cross-reactivity with heparin, should be substituted if heparin-associated thrombocytopenia develops.

If LMWH is used for acute treatment of VTE, a weight-adjusted dose regimen (as *per* the recommendations of the manufacturer) should be used. In pregnancy there are physiologic changes in cardiovascular, hemostatic, renal function and production of placental heparinase, which lead to changes in the maternal dose response to LMWH[28]. As the pregnancy progresses (and most women gain weight), the volume of distribution of LMWH changes. Therefore, some centers advocate weight-adjusted doses with simply altering the dose in proportion to any weight change, whereas others recommend measurement of anti-factor Xa taken 3-4 h after morning dose as a guide to reaching the desired level of 0.5 to 1.2 U/mL[29-31]. Treatment is usually provided for at least 6 months and at least until 6 weeks after delivery.

However, the need to adapt the LMWHs dosage to the weight of pregnant women or to monitor LMWH treatment during pregnancy remains controversial[32,33]. It also remains unclear whether the dose of LMWH can be reduced after an initial period of full anticoagulation. It has been suggested to maintain initial heparin therapy throughout pregnancy because of the ongoing risk of recurrent VTE during this time period.

In order to avoid bleeding complications during delivery (especially with neuroaxial anesthesia) in women receiving LMWH, the American College of Chest Physicians recommends discontinuing LMWH treatment 24 h prior to elective induction of labor or cesarean section. The optimum management of pregnant women with a very high risk of recurrent VTE (thrombophilia, prior pregnancy complications, and/or prior VTE) is still unknown, but trials of anticoagulant therapy are ongoing.

In contrast to UFH and LMWHs, coumarin derivatives cross the placenta and have the potential to cause fetal teratogenicity and bleeding[34,35]. Oral anticoagulants (OACs) are usually safe during the first 6 weeks of gestation, but if coumarin derivatives are taken between 6 and 12 weeks of gestation, there is the risk of embryopathy which consists of nasal hypoplasia and/or stippled epiphyses[35,36]. Central nervous system anomalies can occur in any trimester[34,35]. OACs should also be avoided in the weeks before delivery because of the risk of serious perinatal bleeding caused by the intrapartum trauma to the anticoagulated fetus.

Treatment of VTE during Puerperium

UFH and LMWHs are not secreted into breast milk and can be given safely to nursing mothers[37]. Warfarin is also considered safe during lactation because it does not accumulate in breast milk to a substantial degree[38]. Therefore, OACs should be used postpartum, particularly to avoid the risk of osteoporosis associated with prolonged LMWH administration[39]. Postpartum, LMWH together with warfarin therapy should be recommended as soon as it is safe to do so, usually within 12 h of delivery. LMWH is continued until the International Normalized Ratio (INR) of 2.0 or greater is reached. Anticoagulants should be given for at least 6 weeks following delivery.

Treatment of Unstable Pulmonary Embolism during Pregnancy and Puerperium

In case of unstable or massive pulmonary embolism, vena cava filters, thrombolytics or embolectomy may be useful. Insertion of a vena caval filter may rarely be indicated during pregnancy and puerperium. The indications for the placement of an inferior vena cava filter are the same as in non-pregnant patients[40]. These include: (a) patients with acute VTE in whom conventional anticoagulation is contraindicated (active bleeding, recent surgery, hemorrhagic stroke); (b) patients with acute VTE in whom conventional anticoagulation has proven ineffective; and (c) patients who are critically ill and at risk of recurrent embolism, in whom recurrent embolism is likely to be fatal. Placement of a vena cava filter does not negate the need of anticoagulation.

There is no experience with thrombolytic therapy in pregnant patients. Its use is associated with the risk of maternal or fetal bleeding, teratogenesis, and fetal loss. Thus, thrombolytic therapy should be reserved for those cases with unstable PE in which the life of mother is threatened. Recombinant tissue plasminogen activator and streptokinase are the recommended agents[40].

Embolectomy is indicated for patients with massive PE who are hemodynamically unstable despite anticoagulation and their life is threatened[41]. The data are limited, however, available case reports suggest that embolectomy may be associated with a higher incidence of fetal loss than thrombolytic therapy.

Conclusion

Venous thromboembolism remains the leading cause of maternal death in industrialized countries. In recent years, LMWHs have become the therapeutic agents of choice for both prophylaxis and management of maternal VTE. The available evidence indicates that LMWHs are of at least equivalent efficacy but have a better safety profile compared with UFH for thromboprophylaxis and treatment of VTE during pregnancy and puerperium. There is, however, poor consensus and wide disparity of views among experts with regard to the appropriate dose for the varying indications, the duration of treatment, and whether and how LMWHs should be monitored because of the lack of an evidence basis. Large prospective trials are still required to resolve these remaining problems.

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Sažetak

LIJEČENJE VENSKE TROMBOEMBOLIJE ZA VRIJEME TRUDNOĆE I BABINJA

P. Gaćina, D. Čaržavec, V. Stančić i *V. Pejša*

Venska tromboembolija (VTE) nije učestala, ali ostaje vodećim uzrokom smrtnosti za vrijeme trudnoće i babinja u razvijenim zemljama. Rizik VTE je oko 4-5 puta veći u trudnica nego u žena iste dobi bez trudnoće. Nastanak VTE je povezan s venskom stazom, oštećenjem endotela vena zdjelice uslijed poroda, te povećanom sklonošću zgrušavanju krvi za vrijeme trudnoće i babinja. Najčešći rizični čimbenici VTE za vrijeme trudnoće i babinja su prethodna tromboza(e), nasljedna sklonost trombozi, trudnice starije od 35 godina, debljina i porod operacijskim zahvatom. Duboka venska tromboza za vrijeme trudnoće i babinja je češće lijevostrana (85% nasuprot 55% u žena iste dobi koje nisu trudne) i iliofemoralna (72% u trudnica nasuprot 9%). Heparini male molekularne težine su lijekovi izbora u liječenju VTE za vrijeme trudnoće i babinja, jer su djelotvorni i imaju znatno manje nuspojava, kao trombocitopeniju potaknutu heparinom, krvarenje i osteoporozu te pouzdaniju protutrombotsku aktivnost u odnosu na nefrakcionirani heparin.

Ključne riječi: *Venska tromboza – etiologija; Trudnoća – komplikacije; Venska tromboza – terapija; Čimbenici rizika*