

Treatment of Venous Thromboembolism during Pregnancy and Puerperium

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://um.nsk.hr/um:nbn:hr:220:019548>

Rights / Prava: [Attribution-NonCommercial-NoDerivatives 4.0 International/Imenovanje-Nekomercijalno-Bez prerada 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2024-09-13**



Repository / Repozitorij:

[Repository of the Sestre milosrdnice University Hospital Center - KBCSM Repository](#)

TREATMENT OF VENOUS THROMBOEMBOLISM DURING PREGNANCY AND PUERPERIUM

Petar Gaćina¹, Dubravka Čaržavec¹, Vladimir Stančić¹ and Vlatko Pejša²

¹Department of Hematology, Sestre milosrdnice University Hospital; ²Department 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 age¹, 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 thrombosis². The third trimester and post-

partum 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 periods³. 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 state¹⁶. 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 activation¹⁶⁻¹⁹. 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 normal²⁰. 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 studies²⁶. 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 teratogenicity²⁶. 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 osteoporosis²⁷. 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 LMWH²⁸. 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/mL²⁹⁻³¹. 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 mothers³⁷. Warfarin is also considered safe during lactation because it does not accumulate in breast milk to a substantial degree³⁸. Therefore, OACs should be used postpartum, particularly to avoid the risk of osteoporosis associated with prolonged LMWH administration³⁹. 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 patients⁴⁰. 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 agents⁴⁰.

Embolectomy is indicated for patients with massive PE who are hemodynamically unstable despite anticoagulation and their life is threatened⁴¹. 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.

References

1. National Institutes of Health Consensus Development Conference Prevention of venous thrombosis and pulmonary embolism. *JAMA* 1986;256:744-9.
2. ROSENDAAL FR. Risk factors for venous thrombotic disease. *Thromb Haemost* 1999;82:610-9.
3. PABINGER I, GRAFENHOFER H, KYRLE PA, QUEHENBERGER P, MANNHALTER C, LECHNER K *et al.* Temporary increase in the risk of recurrence during pregnancy in women with a history of venous thromboembolism. *Blood* 2002;100:1060-2.
4. LINDQVIST PG, SVENSSON PJ, MARSAAL K, GRENNER L, LUTERKORT M, DAHLBACK B. Activated protein C resistance (FV Q506) and pregnancy. *Thromb Haemost* 1999;81:532-7.
5. MARTINELLI I, SACCHI I, LANDI G, TAOLI E, DUCA F, MANNUCCI PM. High risk of cerebral vein thrombosis in carriers of prothrombin gene mutation and in users of oral contraceptives. *N Engl J Med* 1998;338:1793-7.
6. CONRAD J, HORELLOU MH, Van DREDEN P, LECOMPTE T, SAMAMA M. Thrombosis and pregnancy in congenital

- deficiencies in AT III, protein C or protein S. Study in 8 women. *Thromb Haemost* 1990;63:319-20.
7. FRIEDERICH PW, SANSON BJ, SIMIONI P, ZANARDI S, HUISMAN MV, KINDT I *et al.* Frequency of pregnancy and related venous thromboembolism in anticoagulant deficient women: implication for prophylaxis. *Ann Intern Med* 1996;125:955-60.
 8. HELLGREN M, TENGBORN L, ABILDGAARD U. Pregnancy in women with congenital antithrombin III deficiency. Experience of treatment with heparin and antithrombin. *Gynecol Obstet Invest* 1982;14:127-41.
 9. De STEFANO V, LEONE G, MASTRANGELO S, TRIPODI A, RODEGHIERO F, CASTAMAN G *et al.* Thrombosis during pregnancy and surgery in patients with congenital deficiency of antithrombin III, protein C, protein S. *Thromb Haemost* 1994;71:799-800.
 10. GINSBERG JS, WELLS PS, BRILL-EDWARDS P, DONOVAN D, MOFFATT K, JOHNSTON M *et al.* Antiphospholipid antibodies and venous thromboembolism. *Blood* 1995;86:3685-91.
 11. GERHARDT A, SCHARF RE, BECKMANN MW, STRUVE S, BENDER HG, PILLNY M *et al.* Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. *N Engl J Med* 2000;342:374-80.
 12. GRANDONE E, MARGAGLIONE M, COLAIZZO D, D'ANDREA G, CAPPUCCI G, BRANCACCIO V *et al.* Genetic susceptibility to pregnancy-related venous thromboembolism. Roles of factor V Leiden prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations. *Am J Obstet Gynecol* 1988;179:1324-8.
 13. SIMIONI P, SANSON BJ, PRANDONI P, TORMENE D, FRIEDERICK PW, GIROLAMI B *et al.* Incidence of venous thromboembolism in families with inherited thrombophilia. *Thromb Haemost* 1999;81:198-202.
 14. MARTINELLI I, BUCCIARELLI P, MARGAGLINE M, De STEFANO V, CASTAMAN G, MANNUCCI PM. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. *Br J Haematol* 2000;111:1223-9.
 15. Mc COLL MD, RAMSAY JI, TAIT JD, WALKER ID, Mc COLL F, CONKIE JA *et al.* Risk factors for pregnancy associated venous thromboembolism. *Thromb Haemost* 1997;78:1183-8.
 16. GREER IA. Thrombosis in pregnancy: maternal and fetal issues. *Lancet* 1999;353:1258.
 17. GREER IA. Epidemiology, risk factors and prophylaxis of venous thromboembolism in obstetrics and gynaecology. *Baillieres Clin Obstet Gynaecol* 1997;11:403-30.
 18. CLARK P, BRENNAND J, CONKIE JA *et al.* Activated protein C sensitivity, protein C, protein S and coagulation in normal pregnancy. *Thromb Haemost* 1998;79:1166-70.
 19. GREER IA. Haemostasis and thrombosis in pregnancy. In: BLOOM AL, FORBES CD, THOMAS DP, TUDDENHAM EGD, eds. *Haemostasis and thrombosis*, 3rd ed. Edinburgh: Churchill Livingstone, 1994;987-1015.
 20. FRIEND JR, KAKKAR VV. The diagnosis of deep venous thrombosis in the puerperium. *J Obstet Gynaecol Br Commonw* 1970;77:820-3.
 21. FRANCALANCI I, COMEGLIO P, ALESSANDRELLO A, LIOTTA A, CELLAI AP, FEDI S *et al.* D-dimer concentrations during normal pregnancy, as measured by ELISA. *Thromb Res* 1995;78:399-405.
 22. CHAN WS, CHUNILAL SD, BATES S, NAGUIT I, SOOD R, JOHNSTON M *et al.* The prevalence of positive soluble fibrin and D-dimer results in healthy asymptomatic pregnant women. *Blood* 1999;94:20.
 23. PROIETTI AB, JOHNSON MJ, PROIETTI FA, REPKE JT, BELL WR. Assessment of fibrin(nogen) degradation products in preeclampsia using immunoblot enzyme-linked immunosorbent assay, and latex-bead agglutination. *Obstet Gynecol* 1991;77:696-700.
 24. GINSBERG JS, BATES SM. Management of venous thromboembolism during pregnancy. *J Thromb Haemost* 2003;1:1435-42.
 25. CHAN WS, GINSBERG JS. Diagnosis of deep vein thrombosis and pulmonary embolism in pregnancy. *Thromb Res* 2002;107:85-91.
 26. SANSON BJ, LENSING AWA, PRINS MH, GINSBERG JS, BARKAGAN ZS, LAVENNE-PARDONGE E *et al.* Safety of low-molecular-weight heparin in pregnancy: a systemic review. *Thromb Haemost* 1999;81:668-72.
 27. BATES SM, GREER IA, HIRSH J, GINSBERG JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126 (3 Suppl):627S-44S.
 28. CASELE HL, LAIFER SA, WOELKERS DA, VENKATARAMANAN R. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. *Am J Obstet Gynecol* 1999;181:1113-7.
 29. CROWTHER MA, SPITZER K, JULIAN J *et al.* Pharmacokinetic profile of a low-molecular weight heparin (Reviparin) in pregnant patients: a prospective cohort study. *Thromb Res* 2000;98:133-8.
 30. RODIE VA, THOMSON AJ, STEWART FM *et al.* Low molecular weight heparin for the treatment of venous thromboembolism in pregnancy: case series. *Br J Obstet Gynecol* 2002;109:1020-4.
 31. THOMSON AJ, GREER IA. Thromboembolic disease in pregnancy and the puerperium: acute management. London: Royal College of Obstetricians and Gynecologists, Guideline No. 20, 2001.
 32. SEPHTON V, FARQUHARSON RG, TOPPING J, QUENBY SM, COWAN C, BACK DJ *et al.* A longitudinal study of maternal dose response to low-molecular-weight heparin in pregnancy. *Obstet Gynecol* 2003;101:1307-11.
 33. BOUNAMEAUX H, De MOERLOOSE P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. *J Thromb Haemost* 2004;2:551-4.

34. GINSBERG JS, HIRSH J, TURNER C, LEVINE MN, BURROWS R. Risks to the fetus of anticoagulant therapy during pregnancy. *Thromb Haemost* 1989;61:197-203.
35. HALL JG, PAULI RM, WILSON KM. Maternal and fetal sequelae of anticoagulants during pregnancy. *Am J Med* 1980; 68:668-72.
36. ITURBE-ALESSIO I, Del CARMEN FONESCA M, MUTCHNIK O, SANTOS MA, ZAJARIAS A, SALAZAR E. Risks of anticoagulant therapy in pregnant women with artificial heart valves. *N Engl J Med* 1986;315:1390-3.
37. FLESSA HC, KLAPOSTROM AB, GLUECK MJ, WILL J. Placental transport of heparin. *Am J Obstet Gynecol* 1965; 93:570-3.
38. BATES SM, GINSBERG JS. How we manage venous thromboembolism during pregnancy. *Blood* 2002;100:3470.
39. THOMSON AJ, WALKER ID, GREER IA. Low-molecular-weight heparin for immediate management of thromboembolic disease in pregnancy. *Lancet* 1998;352:1904.
40. AHEARN GS, HADJILIADIS D, GOVERT JA *et al.* Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator: a case report and review of treatment options. *Arch Intern Med* 2002;162:1221-7.
41. STONE SE, MORRIS TA. Pulmonary embolism during and after pregnancy. *Crit Care Med* 2005;33 (10 Suppl):S294-300.

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 nuspojave, 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*