

Efficacy and Safety of Nadroparin and Unfractionated Heparin for the Treatment of Venous Thromboembolism During Pregnancy and Puerperium

Gorana Mitić¹, Mirjana Kovač², Ljubica Považan¹, Valentina Djordjević³, Vesna Ilić⁴, Iva Salatić¹, Radmila Lazić¹, Nebojša Antonijević⁵, Aleksandra Novakov-Mikić¹

¹ Clinical Centre of Vojvodina, Novi Sad, Serbia;

² Blood Transfusion Institute of Serbia, Belgrade, Serbia;

³ Institute of Molecular Genetics and Genetic Engineering, Belgrade, Serbia;

⁴ Military Medical Academy, Belgrade, Serbia;

⁵ Institute of Cardiovascular Diseases, Clinical Centre of Serbia, Belgrade, Serbia

SUMMARY

Introduction The optimal treatment of pregnancy associated VTE (venous thromboembolism) has not been established yet.

Objective The assessment of the efficacy and safety of low molecular weight heparin (LMWH) nadroparin and unfractionated heparin (UFH) used for the treatment of pregnancy and puerperium related VTE. Primary study goals were to analyze the incidence of recurrent VTE (proximal extension or pulmonary thromboembolism), thrombocytopenia, major and minor hemorrhages and skin allergic reactions. The study also included the incidence of miscarriages, stillbirth and neonatal abnormalities. We also studied the relationship between the presence of thrombophilia and the occurrence of complications during VTE treatment.

Methods Seventy-two women with antepartal VTE treated with s.c. LMWH during entire pregnancy and 88 women with postpartal VTE initially treated with either s.c. LMWH or i.v. UFH were under follow-up during the entire treatment. Thrombophilia testing included antithrombin, protein C and protein S activity levels, Activated protein C (APC) resistance, LA, ACL, FV Leiden, FII G20210A and MTHFR C677T mutations.

Results Twice a day weight based therapeutic regimen was applied for LMWH and activated partial thromboplastin time (aPTT) adjusted UFH dosages. After 2-6 weeks of antepartal deep vein thrombosis (DVT) treatment the dose of nadroparin was reduced to intermediate level. The duration of LMWH therapy during pregnancy was 1-35 weeks, on average 16 weeks. One case (0.62%) of DVT propagation into the vena cava occurred in a woman with antithrombin deficiency treated with LMWH. Two women (1.25%) had minor bleeding and 5 (3.125%) had minimal bleeding, while 3 (1.9%) had skin allergic reactions. The rate of successful pregnancy outcome was 97.2%. There were no cases of stillbirth or neonatal congenital abnormalities. Thrombophilia was found in 86 women (53.7%). No statistically significant correlation between the presence of thrombophilia and treatment complications were found.

Conclusion Nadroparin is both safe and effective for the treatment of DVT during pregnancy and puerperium.

Keywords: pregnancy; venous thromboembolism; low molecular weight heparin; nadroparin

INTRODUCTION

Venous thromboembolism (VTE) is an important cause of morbidity during pregnancy and postpartum [1]. Pulmonary thromboembolism (PTE) is the leading cause of maternal death in the developed countries [2]. The management of acute VTE and prevention of VTE are crucial factors in reducing maternal morbidity and mortality. Efficient initial treatment reduces the risk of recurrent VTE, as well as the development of post-thrombotic syndrome.

The optimal treatment of pregnancy associated VTE has not been established yet, particularly regarding optimal dosages after initial treatment. The use of vitamin K antagonists (VKA) for the treatment of pregnancy related VTE is associated with a significant risk of teratogenicity and bleeding. The risk of embryopathy is particularly high if VKA are used between 6 and 12 weeks of gestational age [3, 4]. The risk of fetal bleeding persists during entire pregnancy [5].

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) do not cross the placenta, which makes them safe for use in the treatment of pregnant women. Both intravenous and subcuta-

neous routes of administration of UFH are effective if an adequate starting dose is used [6]. LMWH have demonstrated some advantages over UFH, including lower risk of bleeding, lower incidence of heparin-induced thrombocytopenia and reduced risk of osteoporosis [7, 8].

OBJECTIVE

In order to assess the efficacy and safety of LMWH nadroparin and UFH used for the treatment of pregnancy and puerperium related VTE, we conducted a prospective cohort study in two centers in Serbia. The follow-up involved 160 women with pregnancy and puerperium related VTE disease who were treated at the Thrombosis and Haemostasis Unit, Institute of Laboratory Medicine, Clinical Centre of Vojvodina, Novi Sad and the Department of Haemostasis, National Blood Transfusion Institute, Belgrade, from 1998 to 2008; the study was conducted during the entire treatment of VTE. The objective of the study was to assess both maternal and fetal/neonatal safety. We analyzed the primary outcome and the rate of recur-

rent VTE (proximal extension of thrombus or PTE occurrence), development of heparin-induced thrombocytopenia (HIT), the frequency of major and minor bleeding and skin allergic reactions. Bleeding occurrence was classified as major, minor or minimal, according to the classification most commonly used to report bleeding severity, developed by the Thrombolysis in Myocardial Infarction (TIMI) study group [9]. Fetal outcomes were the incidence of miscarriages, stillbirth and neonatal congenital abnormalities. The relationship between the presence of thrombophilia and the occurrence of complications during VTE treatment was evaluated as well. The hypothesis was that bleeding complications during VTE treatment were less likely to occur in women with thrombophilia.

METHODS

We studied 72 women with antepartum VTE treated with s.c. LMWH during the entire pregnancy and 88 women with postpartum VTE initially treated with either s.c. LMWH or i.v. UFH. All women were tested for thrombophilia presence. None of them was either pregnant at the time of testing or taking hormonal contraceptive pills.

Antithrombin and protein C activities in plasma were determined by chromogenic assays using Instrumentation Laboratory kits (IL, Milan, Italy). Protein S activity was determined using ProS automated coagulation assay, which determines the functional activity of free protein S, manufactured by Instrumentation Laboratory, Milan, Italy. APC resistance was determined using Instrumentation Laboratory kits for APC-R detection. If the results of clotting tests were below the normal range, the assays were repeated from another plasma sample. Deficiency of antithrombin (AT), protein C and protein S were defined as plasma levels below 75%, 69% and 63%, respectively. Activated protein C resistance was defined as APC-R < 2.0. The presence of FV Leiden was screened in samples with APC-R < 2.44.

Factor V G1691A, Factor II G20210A and MTHFR C677T were detected by polymerase chain reaction as previously described in 120 patients, and by allelic discrimination in 40 patients [10, 11, 12]. Allelic discrimination was performed on the ABI Prism 7000 Sequence Detection System (Applied Biosystems, USA).

The serum anticardiolipin (ACL) IgG and IgM antibodies titer were determined by ELISA assay and the presence of the lupus anticoagulant (LA) was determined by activated partial thromboplastin time, kaolin clotting time, dilute prothrombin time, dilute Russell's viper venom time, and silica clotting time assays, as recommended, using Instrumentation Laboratory reagents [13].

Activated partial thromboplastin time (aPTT) for UFH dosing and monitoring was determined using SP Liquid aPTT reagent manufactured by the Instrumentation Laboratory.

Anti Xa activity was determined using the Instrumentation Laboratory HemosIL Heparin commercial kit. Blood samples for antiXa determination were taken 4 hours after LMWH application.

The automated coagulometer ACL 9000, manufactured by IL, Milan, Italy was used for all coagulation tests.

The comparison of the prevalence of thrombophilia in women with antepartum and postpartum VTE was performed using Chi square test. The presence of bleeding complications was compared between women with and without thrombophilia using Chi square test. P lower or equal to 0.05 was considered to be statistically significant.

The study was approved by the Medical Faculty Ethical Committee and signed informed consent was obtained from all participants.

RESULTS

Among 72 antepartum VTE events, 61 were DVT, 4 were PTE and 7 women had ascending superficial vein thrombosis of the leg. Among 88 postpartum VTE, 72 were DVT, while PTE occurred in 16 cases.

Nineteen episodes of antepartum VTE occurred during the first trimester, 9 of them at the gestational age between 4th and 10th week and 10 of them in the 12th week. Fourteen women experienced VTE during the second trimester, between the 14th and 24th week of gestational age, and 39 women were affected by VTE during the third trimester of pregnancy.

A twice daily weight based therapeutic regimen was applied for LMWH nadroparin and aPTT prolongation that corresponded to therapeutic level of anti Xa was applied for UFH dosing [14]. In 68 women with antepartum VTE LMWH was used from the beginning of treatment throughout the entire pregnancy, in 4 women i.v. UFH was used for initial treatment, and after 5-7 days LMWH was introduced and continued for the rest of the pregnancy.

The VTE treatment with nadroparin started with therapeutic dose (100 U/kg twice daily). After 2-6 weeks of antepartum VTE treatment the dose of nadroparin was reduced to intermediate level (75-100 U/kg daily, divided in two doses). All women were advised to stop nadroparin application at the onset of labor. For those who were planned for elective Caesarian section nadroparin was stopped 12-24 hours before the section and continued after 6-12 hours postpartum, depending on individual bleeding risk assessment.

The duration of antepartum VTE treatment varied from 1 to 35 weeks, on average 16 weeks. The platelet count was monitored twice weekly during the first month of treatment and every two weeks for the rest of the treatment. In 10 women treated with nadroparin the level of antiXa activity was monitored 1-2 weeks after the initiation of nadroparin and at 4 week intervals until delivery. The levels of anti Xa activity in these women determined 4 hours after s.c. nadroparin administration were between 0.54 U/ml and 0.84 U/ml.

The duration of superficial vein thromboses treatment was 4-6 weeks, with intermediate dose of nadroparin (75-100 U/kg daily).

Among 88 women with postpartum DVT, 51 were initially treated with i.v. UFH and 37 with LMWH. VKA were started as soon as possible and heparin was stopped after stable INR greater than 2.0 was achieved. The duration of postpartum heparin treatment was between 5 and 11 days, average 7 days.

All mothers were encouraged to breastfeed their babies while receiving anticoagulant therapy. The decision on the duration of postpartal anticoagulant treatment was based on an individual assessment, taking into account localization of thrombosis, type of thrombophilia and presence of other risk factors.

There were no cases of maternal death. Successful pregnancy outcome assessed as the delivery of a healthy baby occurred in 70 out of 72 pregnancies (97.2%) with antepartur VTE. Two pregnancies (2.8%) ended with pregnancy loss after VTE was diagnosed and treatment started, both in women with antithrombin deficiency. One of them was a woman with DVT propagation into the vena cava and opposite iliac vein, in whom DVT occurred at the 8th week of gestational age. Thrombus propagation occurred during treatment with nadroparin and the decision was made to perform an artificial abortion since it was estimated that the risk of fatal outcome was very high. The other was a woman with DVT that occurred at the 23rd week of gestational age; one week after the LMWH therapy was started pregnancy loss occurred.

There were no cases of thrombocytopenia during VTE treatment in pregnancy or postpartum. There were no cases of major bleeding. Two women (1.2%) had minor, clinically relevant bleeding. One of them had a haematoma on the Caesarian section site and the other had excessive postpartum vaginal bleeding that did not require blood transfusion and could be attributed to nadroparin, since the last dose of nadroparin was given 11 hours prior to delivery.

Minimal bleeding episodes, manifested as skin bruising at the sites of heparin application, occurred in 5 (3.12%) women.

There were no cases of stillbirth or neonatal abnormalities in any of the neonates.

Three cases (1.87%) of skin allergic reactions occurred. They were manifested as urticarial rash. In two women skin complications disappeared after a switch to another LMWH; in one of them they persisted during treatment with different LMWH.

The presence of thrombophilia was found in 86 women (53.7%). Among 72 women with antepartur VTE thrombophilia was found in 45 (62.5%) comparing to 41 of 88 (46.6%) women with postpartur VTE. Thrombophilic abnormalities were more frequent in women with antepartur VTE, but the difference was not statistically significant ($\chi^2=3.41$; $p=0.065$).

Both women with minor, clinically relevant bleeding had no thrombophilia, but there was no statistically significant correlation ($p=0.267$) between the absence of thrombophilia and occurrence of bleeding. We were also unable to demonstrate a statistically significant correlation between the absence of thrombophilia and minimal bleeding occurrence.

DISCUSSION

Venous thromboembolism is the leading cause of morbidity and mortality in pregnant women. The risk of VTE occurrence is additionally increased by the presence of inherited or acquired thrombophilia. Prevention and treatment of

venous thromboembolism during pregnancy are complicated since the antithrombotic drugs carry a certain risk to the mother, the fetus, or both. Vitamin K antagonists (VKA) cross the placental barrier and may be responsible for bleeding, teratogenicity and central nervous system abnormalities. The risk of embriopathy is particularly high if VKA are used between 6th and 12th weeks of gestation. UFH and LMWH do not cross the placenta, so they are safe for the fetus [15].

The use of LMWH is becoming more widespread. They have reliable pharmacokinetics, require less frequent injections than UFH and carry a lower risk of treatment complications. LMWH are safe and effective and they are replacing UFH as the anticoagulant of choice during pregnancy.

We evaluated the efficacy and safety of nadroparin and UFH used for treatment of 72 women with VTE that occurred during pregnancy and 88 women with postpartur VTE. Nadroparin was used for the initial treatment and secondary prevention in 68 cases of antepartur thromboses, and in four cases UFH was used for the initial treatment followed by nadroparin until delivery. The average duration of treatment with nadroparin was 16 weeks. The duration of nadroparin or UFH use for postpartur VTE treatment was much shorter, on average 7 days, since VKA were introduced as soon as possible.

The total number of treatment complications was acceptably low. The only woman with DVT propagation was diagnosed with antithrombin deficiency, which is considered to be the most severe thrombophilia. In both women with pregnancies that ended unfavorably, the antithrombin deficiency was found. Poor pregnancy outcomes could therefore rather be attributed to the type of thrombophilia present than to nadroparin treatment. The results of our study indicate that early diagnosis of antithrombin deficiency in women with pregnancy related VTE is of great importance since it identifies the patients who are at high risk of poor pregnancy outcome, which might be prevented by antithrombin concentrate administration.

Two women had minor bleeding episodes, one of them could reasonably be attributed to nadroparin use, since the period from nadroparin administration to the delivery was shorter than recommended [16,17]. The other bleeding episode could be caused by obstetrical reasons.

Our study demonstrated the absence of fetal complications during nadroparin treatment of pregnancy related VTE. It is particularly significant that there were no neonatal abnormalities in 19 women receiving nadroparin from the first trimester of pregnancy, especially since in 9 of them the treatment was commenced at early pregnancy, between the 4th and 10th week of gestational age.

There is increasing data to support the efficacy and safety of LMWH use during pregnancy. Several systematic reviews addressing this issue have been published, indicating that LMWH are efficient in the treatment of pregnancy related VTE, with acceptably low incidence of complications [14, 17]. Most of the published data evaluated safety profile of other LMWH than nadroparin, mostly enoxaparin and dalteparin [1, 18, 19, 20].

The incidence of bleeding complications related to LMWH in a study of 624 pregnancies was 1.3%, and the incidence

of VTE in the same study was 1.3% [21]. These results are similar to our findings regarding bleeding complications, with twice lower incidence of VTE in our study group.

Nadroparin was found to be safe and effective in pregnant women with mechanical heart valve prosthesis and in pregnant women with antiphospholipid syndrome [22, 23].

Several studies have evaluated the efficacy and safety of nadroparin in the treatment of pregnancy related VTE and thromboprophylaxis in high risk pregnancies. In a large review of LMWH use in 2777 pregnancies nadroparin was used for VTE treatment in 20 pregnancies with no complications [1].

The incidence of nadroparin related fetal or maternal complications was low in the study of 38 pregnancies with VTE with one case (2.63%) of maternal bleeding [24].

A Hungarian study of nadroparin use for thromboprophylaxis in 26 high risk pregnancies has shown a low incidence of complications; one VTE event in a woman with AT deficiency combined with APC resistance [25].

The incidence of skin complication occurrence in our study was very low, 1.9%, comparing to 4.29% in 420 preg-

nancies and 29% in 66 pregnancies published by other authors [1, 26]. Cross-reactivity occurred in one of three women who were switched from nadroparin to another LMWH, which is similar to literature findings [27].

Our study of antepartal VTE treatment with nadroparin is probably one of the largest published so far. The use of nadroparin for the treatment of VTE in pregnant women is associated with a very low incidence of maternal and fetal complications. DVT was effectively treated in all cases but one. Our results suggest that gestational DVT can be safely and effectively managed with LMWH nadroparin.

CONCLUSION

Nadroparin is both safe and effective for the treatment of DVT during pregnancy and puerperium, and UFH is safe and effective for the initial therapy of antepartal and immediate postpartal DVT and PTE.

REFERENCES

- Greer IA, Nelson-Piercy C. Low-molecular weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005; 106:401-7.
- Kher A, Bauersachs R, Nielsen JD. The management of thrombosis in pregnancy: Role of low-molecular-weight heparin. *Thromb Haemost*. 2007; 97:505-13.
- Bates SM, Ginsberg JS. How we manage venous thromboembolism during pregnancy. *Blood*. 2002; 100:3470-8.
- Snow V, Qaseem A, Barry P, Hornbake RE, Rodnick JE, Tobolic T, et al. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Int Med*. 2007; 146:1-17.
- Duhl AJ. Update on the use of antithrombotic agents in pregnancy. CME thrombosis; prophylaxis of venous thromboembolism; use of antithrombotic agents in pregnancy. *Am J Med*. 2004; 3-12.
- Ginsberg JS. Drug therapy: management of venous thromboembolism. *N Engl J Med*. 1996; 335:1816-28.
- Bauersachs R.M. Treatment of venous thromboembolism during pregnancy. *Thromb Res*. 2009; 123(Suppl 2):S45-50.
- Petilla V, Leinonen P, Markkola A, Hiilesmaa V, Kaaja R. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. *Thromb Haemost*. 2002; 87:182-6.
- Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Mahaffey KW, et al. A comparison of clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol*. 2006; 47:809-16.
- Bertina RM, Koeleman BPC, Koster T, Rosendaal FR, Driven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature*. 1994; 369:64-7.
- Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood*. 1996; 88:3698-703.
- Djordjevic V, Rakicevic Lj, Gagic M, Nikolic A, Savic A. Simultaneous detection of factor V Leiden and factor II G20210A variant by a multiplex PCR on whole blood. *Balc J Med Gen*. 2001; 4:15-7.
- Brandt JT, Triplett DA, Alving B, Scharer I. Criteria for the diagnosis of lupus anticoagulants: an update. *Thromb Haemost*. 1995; 74:1185-90.
- Mitić G, Spasić D, Považan Lj, Gnip S, Lazić R, Jurišić Đ, et al. Značaj određivanja heparinemije tokom laboratorijskog praćenja antitromboznog lečenja heparinom. *Bilt Transfuziol*. 2006; 52(2-3):135.
- Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, et al. Safety of low molecular weight heparin in pregnancy: a systematic review. *Thromb Haemost*. 1999; 81:668-72.
- James AH, Groteg CA, Branciazio LR. Thromboembolism in pregnancy: recurrence and its prevention. *Semin Perinatol*. 2007; 31:167-75.
- Greer IA. Venous thromboembolism and anticoagulant therapy in pregnancy. *Gend Med*. 2005; 2(Suppl A):10-7.
- Ensom MHH, Stephenson MD. Low-molecular-weight heparins in pregnancy. *Pharmacotherapy*. 1999; 19:1013-25.
- Rodie VA, Thomson AJ, Stewart FM, Quinn AJ, Walker ID, Greer IA. Low molecular weight heparin for the treatment of venous thromboembolism in pregnancy: a case series. *Br J Obstetr Gynaecol*. 2002; 109:1020-4.
- Rey E, Rivard GE. Prophylaxis and treatment of thromboembolic diseases during pregnancy with dalteparin. *Int J Gynecol Obstetr*. 2000; 71:19-24.
- Lepercq J, Conard J, Borel-Derlon A, Darmon JY, Boudignat O, Francoual C, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *Br J Obstetr Gynecol*. 2001; 108:1134-40.
- Lee JH, Park NH, Keum DY, Choi SY, Kwon KY, Cho CH. Low molecular weight heparin treatment in pregnant women with a mechanical heart valve prosthesis. *J Korean Med Sci*. 2007; 22:258-61.
- Ruffatti A, Favaro M, Tonello M, De Silvestro G, Pengo V, Fais G, et al. Efficacy and safety of nadroparin in the treatment of pregnant women with antiphospholipid syndrome: a prospective cohort study. *Lupus*. 2005; 14:120-8.
- Barillari G, Springolo F, Daminato R, Driul L, Turello M, Marchesoni D. Safety and efficacy of nadroparin for the management of venous thromboembolism or thrombophilia in pregnancy. *J Thromb Haemost*. 2007; 5(Suppl 2):P-S-623.
- Boda Z, Laszlo P, Pflieger G, Tornai I, Rejto L, Schlammadinger A. Thrombophilia, anticoagulant therapy and pregnancy. *Orv Hetil Hu*. 1998; 139:3113-6.
- Bank I, Libourel EJ, Middeldorp S, Van Der Meer J, Buller HR. High rate of skin complications due to low molecular weight heparins in pregnant women. *J Thromb Haemost*. 2003; 1:850-61.
- Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. *N Engl J Med*. 2008; 359:2025-33.

Ефикасност примене надропарина и нефракционисаног хепарина у лечењу тромбозе дубоких вена током трудноће и пуерперијума

Горана Митић¹, Мирјана Ковач², Љубица Поважан¹, Валентина Ђорђевић³, Весна Илић⁴, Ива Салатић¹, Радмила Лазић¹, Небојша Антонијевић⁵, Александра Новаков-Микић¹

¹ Клинички центар Војводине, Нови Сад, Србија;

² Институт за трансфузију крви Србије, Београд, Србија;

³ Институт за молекуларну генетику и генетски инжењеринг, Београд, Србија;

⁴ Војномедицинска академија, Београд, Србија;

⁵ Институт за кардиоваскуларне болести, Клинички центар Србије, Београд, Србија

КРАТАК САДРЖАЈ

Увод Оптималан начин лечења тромбоза дубоких вена насталих током трудноће још није потпуно дефинисан.

Циљ рада Циљ рада је био да се процене ефикасност и сигурност примене надропарина, хепарина мале молекуларне масе (енгл. *low-molecular-weight heparin* – *LMWH*), и нефракционисаног хепарина (енгл. *unfractionated heparin* – *UFH*) у лечењу венске тромбоемболијске болести у трудноћи и пуерперијуму. Такође су се желели утврдити учесталост рецидива тромбоза вена, учесталост тромбоцитопеније, крварења и алергијских реакција на кожи, учесталост губитка плода и рађања мртвог плода и појава конгениталних поремећаја код новорођенчета.

Методe рада У истраживање су укључене 72 жене с тромбозом вена насталом током трудноће које су лечене поткожном применом *LMWH* и 88 жена с тромбозом вена насталом постпартално које су лечене или са *LMWH* или интравенском применом *UFH*. Испитивање тромбофилије је обухватило одређивање нивоа антитромбина, активност протеина С и протеина S, одређивање резистенције активiranог протеина С, одређивање нивоа лупусног антикоагуланса и антикардиолипинских антитела и откривање мутација фактора V Лајден, *FII G20210A* и *MTHFR C677T*.

Резултати *LMWH* је примењиван два пута дневно, док је доза *UFH* подешавана према налазу активiranог парцијалног тромбoplastинског времена (*aPTT*). Након 2-6 недеља лечења, доза надропарина је смањена на интермедијарну. Лечење са *LMWH* током трудноће трајало је 1-35 недеља (просечно 16 недеља). Код једне болеснице с недостатком антитромбина дошло је до пропагирања дубоке венске тромбозе у доњу шупљу вену и контралатералну илијачну вену. Код две болеснице (1,25%) се јавило слабо крварење, а код пет болесница (3,12%) веома слабо крварење. Код три болеснице се јавила алергија по кожи. Трудноћа је успешно изведена код 97,2% испитаница. Није забележен ниједан случај рођења мртвог плода, нити су уочене конгениталне малформације плода. Тромбофилија је дијагностикована код 86 испитаница (53,7%). Није било статистички значајне повезаности тромбофилије и појаве компликација у вези с начином лечења.

Закључак Надропарин је ефикасан и сигуран лек који се може примењивати у лечењу тромбоза дубоких вена током трудноће.

Кључне речи: трудноћа; тромбозе вена; хепарин мале молекуларне масе; надропарин