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# THROMBOPHILIA IN PREGNANCY – CURRENT ISSUE OF MODERN PERINATOLOGY

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Pregnancy is a condition of increased affinity to blood clotting. The most important changes of coagulation system in pregnancy involve the increase of the following coagulation factors: fibrinogen production, level of numerous blood coagulation factors- FII, FVII, FVIII, FX, FXII, acquired activated protein C resistance, and the decrease of: fibrinolysis due to the increase of a large number of fibrinolytic activator inhibitors PAI-1 and PAI-2, thrombin activatable fibrinolysis inhibitor TAFI, and levels of proteins S and C. This disease is not a disease on its own, but a group of inherited and acquired coagulation disorders that increase the predisposition to thrombosis. The treatment of choice in pregnancy are low-molecular-weight heparins (LMWHs) which are derived from standard heparin by controlled hydrolysis, thus obtaining heparins of a lower molecular mass. The most commonly used LMWHs are: dalteparin sodium, enoxaparin, nadroparin-calcium, reviparin. LMWH is given in prophylactic doses - low and medium doses in therapeutic doses. Thromboprophylaxis in pregnancy is implemented as: intrapartal, intra- and postpartum according to the official recommendations of the American Association of Obstetricians and Gynecologists (ACOG). Specific recommendations of ACOG refer to the treatment of hereditary thrombophilia in pregnancy. *Acta Medica Medianae 2015;54(3):54-58.*

***Key words**: pregnancy, thrombophilia, thromboprophylaxis, low molecular weight heparins*

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## Introduction

Pregnancy is a condition of increased affinity to blood clotting. The most important changes of coagulation system in pregnancy involve the increase in the following coagulation factors: fibrinogen production, level of numerous blood coagulation factors- FII, FVII, FVIII, FX, FXII, and acquired activated protein C resistance.

During the pregnancy, there is a decrease in: fibrinolysis due to increase of large number of fibrinolytic activator inhibitors PAI-1 and PAI-2, thrombin activatable fibrinolysis inhibitor TAFI, and levels of proteins S and C (1).

Additional risk factors for the development of deep venous thrombosis (DVT) include the following comorbidities: systemic lupus erythematosus (SLE), sickle cell anemia, obesity, smoking, immobility (2).

Thrombophilias is not a disease on its own but a group of inherited and acquired coagulation disorders that increase the predisposition to thrombosis.

## Inherited thrombophilia

Inherited thrombophilia affects 15% of the population in Western countries, half of which is pregnancy-associated VTE.

Low risk inherited thrombophilias are heterozygosity for the FV Leiden, heterozygosity for prothrombin gene G20210A, protein C or protein S deficiency.

High risk inherited thrombophilias are related to antithrombin deficiency, simultaneous presence of heterozygosity for factor V Leiden and prothrombin G20210A mutation, homozygosity for factor V Leiden or homozygosity for prothrombin G20210A mutation (3-5).

**Table 1**. Recommendations for therapy of inherited thrombophilia based on assigned risk category

| | High | Intermediate | Low |
|---|---|---|---|
| Type of thrombophilia | Factor V Leiden homozygous, prothrombin gene homozygous, Compound heterozygous, Antithrombin deficiency, any thrombophilia + history of VTE | Low-risk thrombophilia with a strong family history of VTE | Factor V Leiden heterozygous, prothrombin gene mutation heterozygous, protein C or S deficiency, no personal/family history of VTE |
| Management | Intermediate or therapeutic low molecular weight heparin antepartum and for 4–6 weeks postpartum | Prophylactic dosing of low molecular weight heparin antepartum and 4–6 weeks postpartum | Clinical surveillance antepartum and anticoagulation for 4–6 weeks postpartum |

**Acquired thrombophilia**

Antiphospholipid syndrome (APS)

It is a non-inflammatory autoimmune disease characterized by thrombosis or pregnancy-related complications, along with autoimmune thrombocytopenia and antiphospholipid antibodies (lupus anticoagulant-LAC, anticardiolipin antibodies-ACL, antibodies to beta-2 glycoprotein).

Clinical criteria for the diagnosis of APS:

- One or more VTE episodes or a history of three or more early miscarriages before the $10^{th}$ gestational week (GW);
- One or more fetal loss after $10^{th}$ GW or pre-term birth before the $34^{th}$ GW due to pre-eclampsia or placental insufficiency.
- Laboratory criteria for the diagnosis of APS:
- LAC present in plasma on two occasions at least 12 weeks apart or
- Anticardiolipin antibodies IgG and IgM present with medium or high titre,
- Anti β2-glycoprotein antibody of IgG and IgM on two occasions at least 12 weeks apart (6).

This is the only thrombophylia confirmed to directly cause pregnancy loss, but when treated, pregnancy outcomes can be improved (7).

On the contrary, the debates on inherited thrombophilia have still been going on. So far, low-molecular-weight heparin LMWH, aspirin, unfractionated heparin, corticocosteroids and intravenous immunoglobulin have been used as treatment. The outcomes of pregnancies in women with inherited thrombophilia are generally good, even without therapy interventions.

"Since there is a strong association between inherited thrombophilia and venous thromboembolism, timely detection of these mutations is a logical prevention strategy. However, an association between inherited thrombophilias and uteroplacental thrombosis that can lead to adverse pregnancy outcomes, such as fetal loss, preeclampsia, fetal growth restriction, and placental abruption is still controversial. Although there has been no confirmation of treatment benefits yet, and since our understanding of thrombophilias is still limited, this possible association, based on previous clinical experiences, has resulted in increased screening for thrombophilias in pregnancy", the author of the ACOG journal quotes (8).

Who should be tested?

- Women who are pregnant or plan pregnancy having personal or family history of venous thrombosis.
- Women who have had the history of fetal loss during pregnancy, fetal growth restriction, severe early preeclampsia, placental abruption, habitual miscarriages, fetal neural tube defect from a previous pregnancy (9).

Treatments during pregnancy are:

Low-molecular-weight heparins (LMWH) which are derived from standard heparin by controlled hydrolysis, thus obtaining heparins of a lower molecular mass (the mean molecular weight of 4000-6000 daltons). The important difference between standard heparins and low-molecular-weight heparins is that LMWHs mostly inhibit factor Xa, but do not affect thrombin and platelet aggregation (10).

The most commonly used LMWH are: dalteparin sodium, enoxaparin, nadroparin-calcium, reviparin.

**Antepartal thromboprophylaxis**

The Pregnancy and Thrombosis Working Group recommends no pharmacological thromboprophylaxis antepartum or postpartum for patients with the following thrombophilias with no history of VTE and no history of adverse pregnancy out-comes, unless there are some other reasons for VTE prophylaxis, such as cesarean section. They are:

- Factor V Leiden heterozygote
- Prothrombin G20210A heterozygote
- Antiphospholipid antibodies
- Protein C deficiency
- Protein S deficiency
- Hyperhomocysteinemia.

Patients with PROM, preeclampsia, pyelo-nephritis or other pathologic disorders in pregnancy require longer bed rest because pregnancy itself is an additional risk factor for VTE. The combination of compulsory bed rest and pregnancy is a sufficient reason for VTE prophylaxis (11,12).

Monitoring of pregnant women who were treated with LMWH.

The risk for heparin-induced thrombocytopenia (HIT) has been considered to be low with the application of LMWH, still the periodic monitoring of platelet count and evaluation of renal function are recommended (13,14).

Antepartum thromboprophylaxis is recommended for the history of (12):

1. A single VTE event with no longer present transient risk factor;
2. A single idiopathic episode of VTE without rece-iving long term anticoagulants;
3. A single episode of VTE pregnancy or estrogen-related;
4. VTE with family anamnesis of VTE;
5. VTE with the following thrombophilias:
- Factor V Leiden heterozygote
- Prothrombin G20210A heterozygote
- Protein C deficiency
- Protein S deficiency
- Hyperhomocysteinemia
6. Two or more episodes of VTE;
7. Antiphospholoid syndrome without the history of VTE;
8. Thrombophilia with unfavourable pregnancy outcomes, two or more pregnancies early losses, one or more late pregnancy losses, preeclampsia, intrauterine growth restriction (IUGR), or placental abruption.

Antepartum therapy is recommended for (15, 16):

1. Thrombophilias with or without family anamnesis of VTE:
- Factor V Leiden homozygote
- Prothrombin G20210A homozygote
- Antithrombin III deficiency
- Compound heterozygote of factor V Leiden and prothrombin G20210A
2. Antiphospholipid antibodies with or without the anamnesis of VTE;
3. Active arterial and/or venous embolism;
4. Multiple (two or more) episodes of VTE and/or women undergoing long-term anticoagulants the-rapy (e.g. single episode of VTE that can be either idiopathic or associated with thrombophilia);
5. Rheumatic heart disease with atrial fibrillation;
6. Patients with mechanical heart valve:

Therapy dose, twice daily LMWH during entire pregnancy in doses adjusted either to keep a 4-hour anti-Xa heparin level at approximately 1.0 to 1.2 U/mL (preferred) or according to weight LMWH (as above) until the 13$^{th}$ week, warfarin until the mid of the 3$^{rd}$ trimester, then again the restart UFH or LMWH.

**Intrapartal thromboprophylaxis**

It is advisable to discontinue prophylactic LMWH 12 hours before planned labor induction or cesarean section. Also, full dosing of LMWH should be discontinued 24 hours before planned induction or cesarean section.

When delivery is anticipated, LMWH heparin should be discontinued if spinal or epidural anesthesia is used. "Insertion of a spinal needle or epidural catheter should be delayed until the anticoagulant effect of the medication is minimal. This is usually at least 18 h after one prophylactic dose of LMWH daily. Anesthesiologist should be consulted.

Pneumatic compression devices intrapartum are to be used and continued until the patient is fully ambulatory (17).

**Postpartum thromboprophylaxis**

Removal of epidural catheter should be done when the anticoagulant effect of thromboprophylaxis is at its minimum, continuation of anticoagulant thromboprophylaxis should be delayed for at least 2 h after the removal of spinal needle or catheter.

Patients who undergo cesarean delivery with thrombophilias without a history of VTE, or with adverse pregnancy outcomes, should receive prophylactic LMWH for 6 weeks postpartum.

Patients receiving prophylactic doses of LMWH should continue receiving the same dose for 6 weeks postpartum.

Patients on adjusted dose of LMWH may be restarted on receiving heparin and warfarin of 5 mg at the same time. Heparin is not to be discontinued until INR has been within the therapeutic range for at least 2 days. It is usually achieved in 5 to 7 days, but sometimes may take longer (18).

Hematologist is to be consulted for patients on long-term anticoagulation therapy.

**Prophylactic dose of LMWH**

Low-dose LMWH prophylaxis:

For prophylaxis anti-Xa maximum range (3-4 hours after dosing) is 0.2-0.4 IU/mL. Minimal value (12 hours after dosing) is 0.1-0.3 IU/mL (15,19).

Prophylactic doses of LMWH are:

- Dalteparin (Fragmin) 5.000 U SC every 24 hours or
- Enoksaparin (Clexane) 40 mg SC every 24 hours

(although modification of dose may be required in patients with extreme body weight).

Intermediate dose of LMWH:

- Dalteparin 5.000 U SC every 12 hours, or
- Enoksaparin (Clexane) 40 mg SC every 12 hours.

**Therapeutic doses of LMWH**

For therapeutic treatment, antifactor Xa maximum range (3 to 4 hours after dosing) is 0.5-1 IU/mL (upper range 0.8-1 IU/mL). Minimal value (12 hours after dosing) is 0.2-0.4 IU/mL (>0.5 IU /mL for highest risk):

- Dalteparin 100 U/kg every 12 hours, or

- Enoxaparin (Lovenox) 1 mg/kg every 12 hours.

Adjust doses for body weight greater than 100 kg and for renal diseases as well for CrCl less than 30 mL/min.

Specific recommendations of American College of Obstetricians and Gyneacologists (ACOG) regarding management of inherited thrombophilias in pregnancy include:

Screening for inherited thrombophilias include factor V Leiden mutations, prothrombin G 20210A mutations and antithrombin, protein C and protein S deficiencies (level C recommendations, based on consensus and expert opinion of the particular field); for women with inherited thrombophilia individualized risk assessment is recommended, which can modify management decisions; women who breastfeed may receive LMWH (20).

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# TROMBOFILIJE U TRUDNOĆI – AKTUELNI PROBLEM MODERNE PERINATOLOGIJE

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Trudnoća je stanje povećane sklonosti ka zgrušavanju krvi. Najvažnije promene koagulacionog sistema u trudnoći su: stvaranje fibrinogena, nivo brojnih faktora zgrušavanja krvi- FII, FVII, FVIII, FX, FXII, stečena rezistencija na aktivirani protein C. Tokom trudnoće smanjena je fibrinolitička aktivnost zbog porasta velikog broja inhibitora fibrinolitičke aktivnosti PAI I i PAI II, aktivirajući fibrinolitički inhibitor TAFI, kao i nivoi proteina S i C. Trombofilije nisu bolest same po sebi, već je to grupa naslednih i stečenih koagulacionih poremećaja koji povećavaju sklonost ka trombozi. Terapija izbora u trudnoći su niskomolekularni heparini (LMWH) koji se dobijaju ograničenom hidrolizom standardnog heparina. Najčešće korišćeni LMWH su: dalteparin natrijum, enoksaparin, nadroparin-kalcijum, reviparin. LMWH se daje u profilaktičkim niskim, srednjim i terapijskim dozama. Tromboprofilaksa se u trudnoći sprovodi kao: antepartalna, intrapartalna i postpartalna prema zvaničnim preporukama Američkog udruženja opstetričara i ginekologa (ACOG). Specifične preporuke ACOG odnose se na postupak sa naslednom trombofilijom u trudnoći. *Acta Medica Medianae 2015; 54(3):54-58.*

***Ključne reči**: trudnoća, trombofilija, tromboprofilaksa, niskomolekularni heparini*