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

<table>
<thead>
<tr>
<th>Type of thrombophilia</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Intermediate or therapeutic low molecular weight heparin antepartum and for 4–6 weeks postpartum</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Prophylactic dosing of low molecular weight heparin antepartum and 4–6 weeks postpartum</td>
</tr>
<tr>
<td>Low</td>
<td>Clinical surveillance antepartum and anticoagulation for 4–6 weeks postpartum</td>
</tr>
</tbody>
</table>

**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 10th gestational week (GW);
- One or more fetal loss after 10th GW or pre-term birth before the 34th 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 thrombophilia 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, corticosteroids and intra venous 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 thromb oembolism, timely detection of these mutations is a logical prevention strategy. However, an association between inherited thrombophilias and utero-placental 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, pyelonephritis 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 receiving 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. Antiphospholipoid 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 therapy (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 13th week, warfarin until the mid of the 3rd 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 Gynecologists (ACOG)
regarding management of inherited thrombophilias
in pregnancy include:

Screening for inherited thrombophilias inclu-
de 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 parti-
cular field); for women with inherited trombophilia
individualized risk assessment is recommended,
which can modify management decisions; women
who breastfeed may receive LMWH (20).

References

1. Bremme KA. Haemostatic changes in pregnancy. Best
[CrossRef] [PubMed]

2. James AH, Jamison MG, Brancazio LR, Myers ER.
Venous thromboembolism during pregnancy and the
postpartum period: incidence, risk factors, and
15. [CrossRef] [PubMed]

3. Robertson L, Wu O, Langhorne P, Robertson L, Wu O,
Langhorne P et al. Thrombosis: Risk and Economic
Assessment of Thrombophilia Screening (TREATS)
Study. Thrombophilia in pregnancy: a systematic
[CrossRef] [PubMed]

S, Di Giampaolo F. Coagulation disorders in
pregnancy: acquired and inherited thrombophilias.
Ann N Y Acad Sci 2010; 1205: 106–17. [CrossRef]
[PubMed]

5. Kocher O, Cirovic C, Malynn E, Rowland CM, Bare LA,
Young BA et al. Obstetric complications in patients
with hereditary thrombophilia identified using the LCx
microparticle enzyme immunoassay: a controlled
study of 5,000 patients. Am J Clin Pathol 2007;
127(1): 68–75. [CrossRef] [PubMed]

6. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey
RL, Cervera R et al. International consensus statement
on an update of the classification criteria for definite
antiphospholipid syndrome (APS). J Thromb Haemos

7. Opatrny L, David M, Kahn SR, Shrier I, Rey E.
Association between antiphospholipid antibodies and
recurrent fetal loss in women without autoimmune
2214–21. [PubMed]

8. Bates SM, Greer A, Middeldorp S, Veenestra D,
Prabulos AM, Vandvik PO. VTE, thrombophilia,
antithrombotic therapy, and pregnancy—
antithrombotic therapy and prevention of thrombosis,
9th ed: American College of Chest Physicians
evidence-based clinical practice guidelines. Chest
2012; 141(2) (Suppl): e691S–e736S. [PubMed]

9. Thrombophilia: Laboratory Support of Diagnosis and
Management. [Internet]. [updated 2015 Nov].
com/testcenter/testguide.action?d=CF_Thrombophi
la#top.

10. Mantha S, Bauer KA, Zwicker JI. Low molecular weight
heparin to achieve live birth following unexplained
pregnancy loss: a systematic review. J Thomb
Haemos 2010; 8(2): 263–8. [CrossRef] [PubMed]

11. 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-644S.
[CrossRef] [PubMed]

12. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama
CM, Lassen MR et al. Prevention of venous
thromboembolism: American College of Chest
Physicians Evidence-Based Clinical Practice Guidelines
[PubMed]

BELZONI Investigators Group. The incidence of
heparin-induced thrombocytopenia in medical
patients treated with low-molecular-weight heparin:
a prospective cohort study. Blood 2005; 106(9):
3049-54. [CrossRef] [PubMed]

14. Martel N, Lee J, Wells PS. Risk for heparin-induced
thrombocytopenia with unfractionated and low-
molecular-weight heparin thromboprophylaxis: a
[CrossRef] [PubMed]

15. Duhl AJ, Paisadis MJ, Ural SH, Branch W, Casele H,
Cox-Gill J et al. Antithrombotic therapy and
pregnancy:consensus report and recommendations
for the prevention of venous thromboembolism and
adverse pregnancy outcome. Am J Obstet Gynecol
2007; 197: 147.e1-21. [CrossRef] [PubMed]

16. Barbour LA. ACOG Committee on Practice Bulletins-
Obstetrics. ACOG practice bulletin. Thromboembolism
203-12. [PubMed]

**TROMBOFILIJE U TRUDNOĆI – AKTUELNI PROBLEM MODERNE PERINATOLOGIJE**

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

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