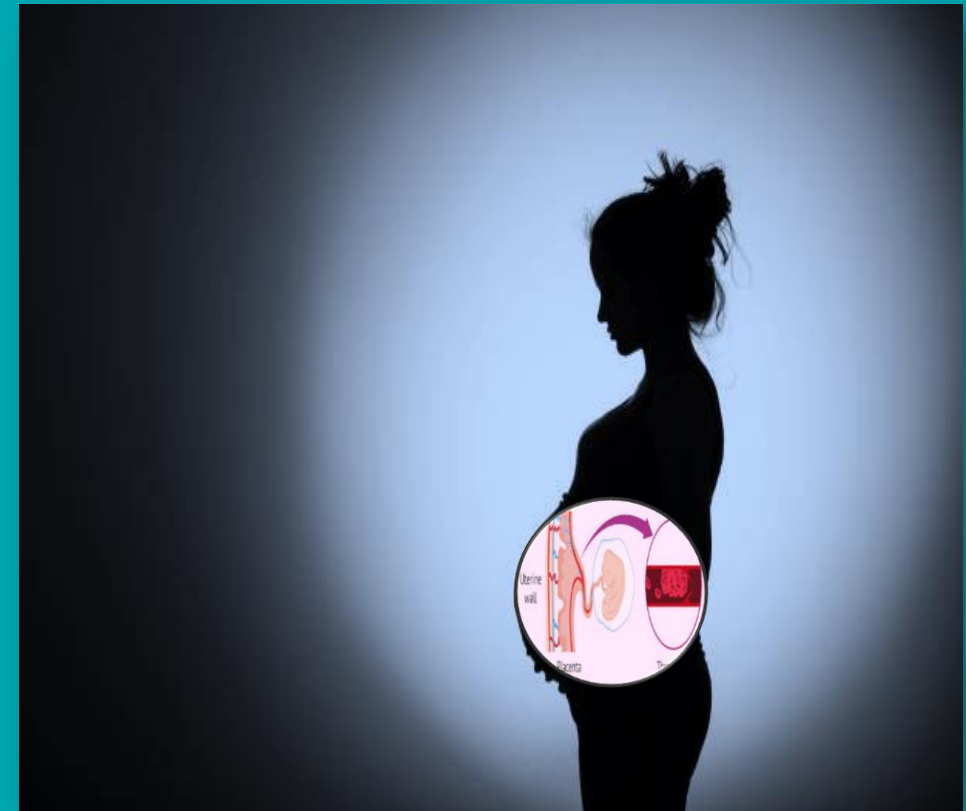




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Tok, nadzor i ishod trudnoće komplikovane trombofilijom

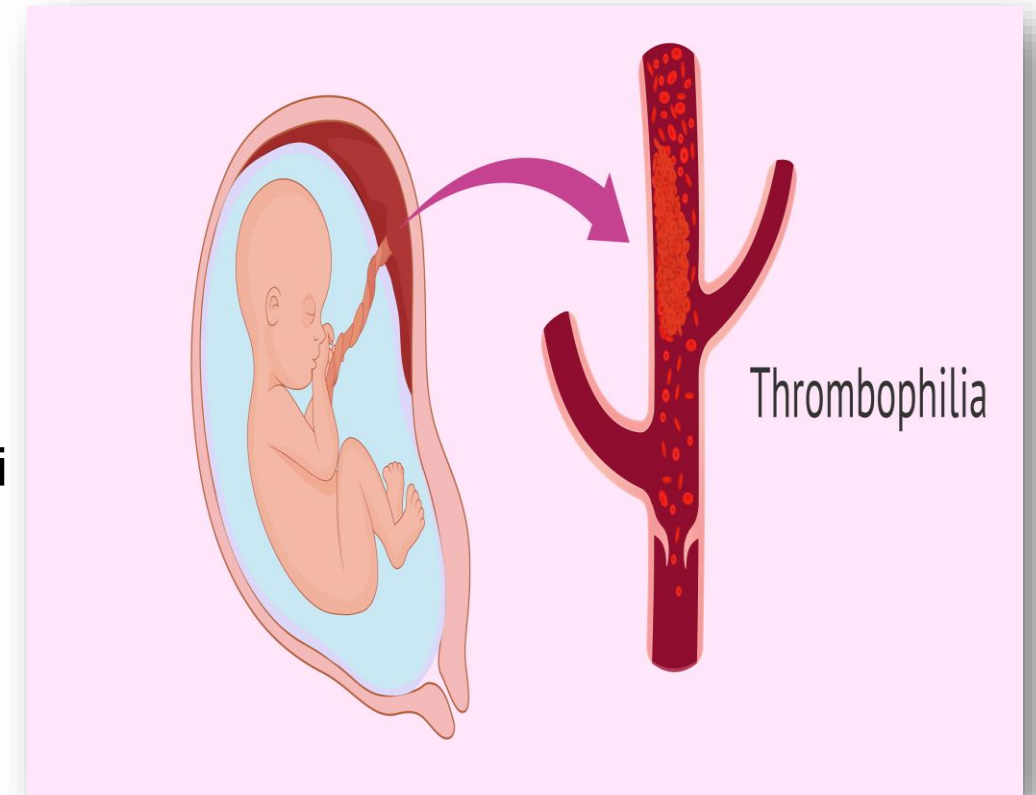
Dr Dejana Milojević



Trombofilija, trudnoća i komplikacije

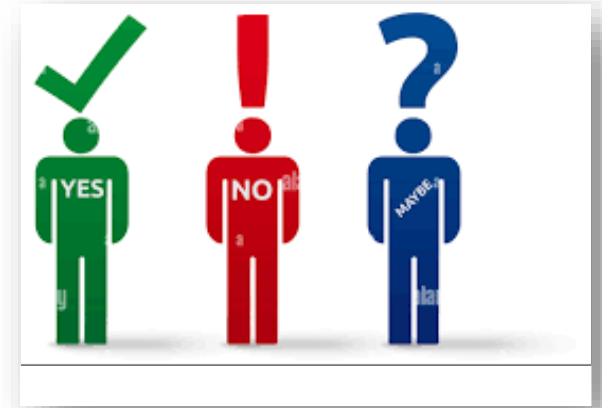
- Fiziološke promene u trudnoći
- Trudnoća i hiperkoagulabilnost krvi
- Etiopatogenetski mehanizam

- **Obstetričke komplikacije**
 - Ponavljani spontani pobačaji tokom prvog i drugog trimestra
 - Intrauterusna smrt ploda
 - Preeklampsija
 - Težak zastoj u rastu ploda
 - Abrupcija placente



Urođene trombofilije i neuspeh trudnoće ??

- **Jaka veza** - u manjim, retrospektivnim kohortnim i „case-control“ studijama
- **Slaba/nepostojeće veza** - u velikim, prospektivnim studijama
 - Urođena trombofilija je slabo i nesigurno povezana sa povećanim rizikom od neuspeha trudnoće, ali može biti doprinoseći faktor za pojavu komplikacija u trudnoći (gubitak ploda, preeklampsija, abrupcija, placentalna insuficijencija)





Vrste trombofilija i neuspeh trudnoće

Thrombophilia	First-Trimester Loss	Late Fetal Loss	Preeclampsia	Abruption	Fetal Growth Restriction
Factor V Leiden, homozygous	2.71 (1.32-5.58)*	1.98 (0.4-9.69)	1.87 (0.44-7.88)	8.43 (0.41-171.20)	4.64 (0.19-115.68)
Factor V Leiden, heterozygous	1.68 (1.09-2.58)*	2.06 (1.1-3.86)*	2.19 (1.46-3.27)*	4.70 (1.13-19.59)*	2.68 (0.59-12.13)
Prothrombin, heterozygous	2.49 (1.24-5.00)*	2.66 (1.28-5.53)*	2.54 (1.52-4.23)*	7.71 (3.01-19.76)*	2.92 (0.62-13.70)
MTHFR C677T, homozygous	1.40 (0.77-2.55)	1.31 (0.89-1.91)	1.37 (1.07-1.76)*	1.47 (0.40-5.35)	1.24 (0.84-1.82)
Antithrombin deficiency	0.88 (0.17-4.48)	7.63 (0.3-196.36)	3.89 (0.16-97.19)	1.08 (0.06-18.12)	N/A
Protein C deficiency	2.29 (0.20-26.43)	3.05 (0.24-38.51)	5.15 (0.26-102.22)	5.93 (0.23-151.58)	N/A
Protein S deficiency	3.55 (0.35-35.72)	20.09 (3.7-109.15)*	2.83 (0.76-10.57)	2.11 (0.47-9.34)	N/A
Anticardiolipin antibodies	3.40 (1.33-8.68)*	3.30 (1.62-6.70)*	2.73 (1.65-4.51)*	1.42 (0.42-4.77)	6.91 (2.70-17.68)*
Lupus anticoagulant	2.97 (1.03-8.56)*	2.38 (0.81-6.70)	1.45 (0.76-2.75)	N/A	N/A
Acquired APCR	4.04 (1.67-9.76)*	0.90 (0.21-3.86)	1.80 (0.70-4.61)	1.25 (0.36-4.37)	N/A
Hyperhomocystinemia	6.25 (1.37-28.42)	0.98 (0.17-5.55)	3.49 (1.21-10.11)*	2.40 (0.36-15.89)	N/A

*Statistically significant



Trombofilija i trudnoća

- Dijagnostikovanje
- Praćenje i lečenje
- Smernice za primenu antikoagulantne terapije

Doza antikoagulanata			
Lek	Profilaksa	Intermedijarna	Terapijska
Heparin	5000IJx2	10000x2	/
Clexan	40mg/24h	40mg/12 1mg	1mg/kg/12h
Fragmin	5000IJ	5000/12	100IJ/kg/12h
Fraxiparin	3800IJ	3800/12	100IJ/kg/12h

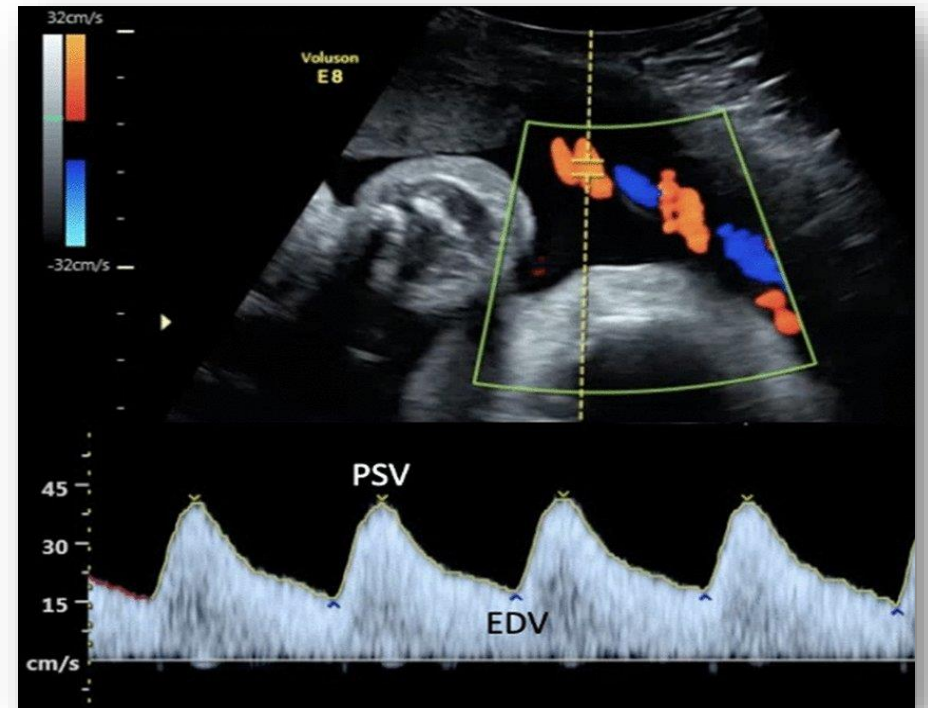
- Vrednost D dimera

Praćenje trudnica sa trombofilijom

1. Fetoplacentna cirkulacija
2. Uteroplacentna cirkulacija
3. Amnionski index

Smanjen amnionski index
Poremećaj fetoplacentne
i uteroplacente cirkulacije

Smanjena vrednost ph fetalne krvi
niži Apgar skor



Prikaz slučaja



- Pacijentkinja stara 27. god u 8 g.n. druge po redu trudnoće
- Prva trudnoća ostvarena prirodnim putem u 25. god napredovala normalno do 33 g.n. kada je konstatovana intrauterina smrt ploda
- PH pregled pokazao infarkte u posteljici
- Hematološkim ispitivanjem ustanovljeno postojanje FII 20210A mutacije (heterozigot)
- Rezultati svih ostalih ispitivanja normalni

ZAKLJUČAK : *Urođena trombofilija*

Uzrok gubitka ploda u prethodnoj trudnoći???

„Ništa ne brinite, sa Fraxiparinom će sve biti u najboljem redu!“

Prikaz slučaja

- Pacijentkinja stara 27. god u 8 g.n. druge po redu trudnoće.
- **U drugoj trudnoći** dobijala **LMW heparin** i uspešno se porodila
- **Treća trudnoća** godinu dana kasnije
- **LMW heparin** u profilaktičkim dozama od početka trudnoće
- **FMU u 32-oj nedelji gestacije uprkos terapiji ca LMWH**



Dileme

Da li je uspešna trudnoća zaista rezultat primene LMWH ??



Da li je urođena trombofilija prava meta?





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Prothrombin Gene *G20210A* Mutation and Obstetric Complications

Robert M. Silver, MD, Yuan Zhao, MS, Catherine Y. Spong, MD, Baha Sibai, MD, George Wendel Jr, MD, Katharine Wenstrom, MD, Philip Samuels, MD, Steve N. Caritis, MD, Yoram Sorokin, MD, Menachem Miodovnik, MD, Mary J. O'Sullivan, MD, Deborah Conway, MD, Ronald J. Wapner, MD, and Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (NICHD MFMU) Network
Departments of Obstetrics and Gynecology at the University of Alabama at Birmingham, Birmingham, Alabama; the University of Chicago, Chicago, Illinois; the University of Cincinnati

- Ispitivano prisustvo FII 20201A mutacije kod **4167 žena** u prvom trimestru trudnoće
- **Mutacija je nađena kod 157 (3.8%) žena** i one su imale sličnu učestalost gubitaka ploda, preeklampsije i abrupcije kao i žene bez mutacije



Regular Article

THROMBOSIS AND HEMOSTASIS

Comparative incidence of pregnancy outcomes in thrombophilia-positive women from the NOH-APS observational study

Sylvie Bouvier,¹⁻³ Éva Cochery-Nouvellon,^{1,2} Géraldine Lavigne-Lissalde,^{1,2} Érick Mercier,¹⁻³ Pascale Fabbro-Peray,⁴ Jean-Pierre Balducchi,⁵ Pierre Marès,⁶ and Jean-Christophe Gris¹⁻³

¹Department of Hematology, University Hospital, Nîmes, France; ²Research team EA2992 "Dysfonction des Interfaces Vasculaires," University of Montpellier 1, Nîmes, France; ³Laboratory of Hematology, Faculty of Pharmacy and Biological Sciences, Montpellier 1 University, Montpellier, France; and ⁴Department of Biostatistics, Epidemiology and Medical Information, ⁵Department of Internal Medicine, and ⁶Department of Gynecology and Obstetrics, University Hospital, Nîmes, France

Primena LMW heparina kod žena sa prethodnim gubitkom ploda posle 10-te nedelje gestacije i sa FV Leiden ili FII 20210A mutacijom povećala je za oko 20% procenat uspešnih trudnoća

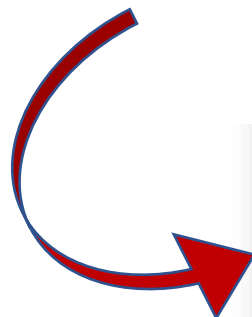


Table 3. Outcomes of new pregnancy attempts in women from the thrombophilia group and no-thrombophilia group with prior fetal death

Group, N	Thrombophilia, 186		No-thrombophilia, 313		RR (95% CI)*	P
	n/N	Incidence	n/N	Incidence		
New pregnancies	185/186	0.995	311/313	0.994		
Prophylactic LMWH treatment during pregnancy	185/185	1	0/311	0		
Spontaneous abortions before 10 WG	36/185	0.195	83/311	0.267	0.750 (0.533-1.056)	.0998
Ongoing pregnancies at 10 WG	149/185	0.805	228/311	0.740	1.090 (0.989-1.202)	.0835
Fetal deaths (% of new pregnancies)	19/185	0.103	72/311	0.232	0.444 (0.277-0.712)	.0007
Fetal deaths (% of ongoing pregnancies at 10 WG)	19/149	0.128	72/228	0.313	0.407 (0.257-0.646)	.0001
Ongoing pregnancy at 20 WG (% of new pregnancies)	139/185	0.751	180/311	0.579	1.299 (1.145-1.475)	.0001
Live births (% of new pregnancies)	130/185	0.703	156/311	0.502	1.385 (1.198-1.600)	<.0001
Live births (% of ongoing pregnancies at 10 WG)	130/149	0.872	156/228	0.684	1.270 (1.142-1.413)	<.0001
Preterm live births <37 WG (% of live births)	16/130	0.123	39/156	0.250	0.499 (0.292-0.850)	.0106
Preterm live births <34 WG (% of live births)	7/130	0.054	19/156	0.122	0.448 (0.194-1.032)	.0593



Meta analiza 8 studija/483 trudnica

Poređenje grupa (sa LMWH vs bez LMWH) žena sa urođenom TF koje su prethodno imale kasne (>10 gn) ili ponovljane rane (<10gn) gubitke trudnoća

Evidence-Based Focused Review

A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia

Leslie Skeith,^{1,2} Marc Carrier,¹⁻³ Risto Kaaja,⁴ Ida Martinelli,⁵ David Petroff,⁶ Ekkehard Schleußner,⁷ Carl A. Laskin,⁸⁻¹⁰ and Marc A. Rodger^{1-3,11}

¹The Ottawa Blood Disease Centre, Division of Hematology and ²Department of Medicine, University of Ottawa and The Ottawa Hospital, Ottawa, ON, Canada; ³Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada; ⁴Department of Medicine, University of Turku and Turku University Hospital, Turku, Finland; ⁵A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy; ⁶Clinical Trial Centre, University of Leipzig, Leipzig, Germany; ⁷Department of Obstetrics and Gynecology, Friedrich Schiller University Hospital, Jena, Germany; ⁸LifeQuest Centre for Reproductive Medicine, Toronto, ON, Canada; ⁹Department of Medicine and ¹⁰Department of Obstetrics and Gynecology, University of Toronto, Toronto, ON, Canada; and ¹¹Department of Obstetrics and Gynecology, University of Ottawa and The Ottawa Hospital, Ottawa, ON, Canada

We performed a meta-analysis of randomized controlled trials comparing low-molecular-weight heparin (LMWH) vs no LMWH in women with inherited thrombophilia and prior late (≥10 weeks) or recurrent early (<10 weeks) pregnancy loss. Eight trials and 483 patients met our inclusion criteria. There was no significant difference in livebirth rates with the use of LMWH compared with no LMWH (relative risk, 0.81; 95% confidence interval, 0.55-1.19; $P = .28$), suggesting no benefit of LMWH in preventing recurrent pregnancy loss in women with inherited thrombophilia. (*Blood*. 2016;127(13):1650-1655)

Zaključak: bez značajne prednosti terapija LMWH u prevenciji ponavljanih gubitaka trudnoća kod žena sa urođenom trombofilijom





U svakodnevnoj praksi

„Zamislite, doktor mi čak nije ni predložio da testiram trombofiliju?!“

Trombofilija = hematološki + psihološki fenomen

- Pacijenti retko čitaju vodiče i preporuke
- Vode se emocijama i željom da veruju u „čarobni“ lek
- Za ženu čija se prijateljica sa 4G/4G varijantom na PAI-1 genu porodila uz primenu Fraxiparina to je snažniji dokaz od svih prospektivnih studija zajedno
- IZLAZ IZ BEZIZLAZNE SITUACIJE

I na kraju

Testiranje urođene trombofilije - **GENETSKO TESTIRANJE** sa mogućim dalekosežnim posledicama na:

- osobu koja se testira
- porodicu
- potomstvo
- genetska stigmatizacija

Odluku o testiranju i lečenju **NE** bi trebalo donositi na osnovu:

- pritiska bolesnika
- postupka iz očajja
- anegdotskih slučajeva
- najboljih želja i očekivanja





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Hvala!