Medicinska istraživanja 2024; 57(4):63-70 | DOI: 10.5937/medi57-53290

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

ORIGINAL ARTICLE

Oxidative stress and obstetric complications in pregnant women with inherited thrombophilia with and without low molecular weight heparin therapy

Dragana Maglić[1,2], Vesna Mandić-Marković[1,2], Jelena Bogdanović-Pristov[3], Rastko Maglić[1,2], Olivera Džatić-Smiljković[1,2], Radomir Aničić[1,2], Milica Mandić[2], Jelena Mitrović[2], Sabrina Škrijelj [2]

[1] University of Belgrade, Faculty of Medicine, Belgrade, Serbia

[2] Department for High-Risk Pregnancies, University Clinic for Gynecology and Obstetrics "Narodni front," Belgrade, Serbia

[3] Life Sciences Department, Institute for Multidisciplinary Research, University of Belgrade, Belgrade, Serbia

Recived: 11 September 2024

Revised: 22 October 2024

Accepted: 25 October 2024

Check for updates

Funding information:
Ministry of Education, Science, and Technological Development of the Republic of Serbia (Contract No. 451-03-66/2024-03/20053).

Competing interests:
The authors have declared that no competing interests exist

Correspondence to:
Dragana Maglić
45, Beogradska Street, 11000 Belgrade, Serbia
E-mail: dragana.maglic@gmail.com

Summary

Introduction: Inherited thrombophilia (IT) presents genetic conditions associated with the risk of deep vascular thrombosis (DVT) and obstetric complications (OC) such as preeclampsia (PE), fetal growth restriction (FGR), stillbirth and placental abruption (PA).

The aim of our study was to evaluate the frequency of OC and oxidative stress (OS) in women with IT during pregnancies with and without low molecular weight therapy (LMWH), compared to women with healthy pregnancies.

Material and methods: We evaluated 60 pregnant women with IT diagnosed before ongoing pregnancy based on previous DVT or OC (study group) and 60 healthy pregnant women (control group). Blood samples were collected before delivery, along with placental tissue from all subjects, to determine the activity of CAT, GPX, GH, SH, GR, CuZnSOD, and MnSOD enzymes.

Results: After the introduction of LMWH therapy, the total number of OC decreased significantly in women with IT. Analyzing the association between OC and different kinds of IT, we found significant association only between Factor V Leiden mutation and Protein C deficiency with GH/PE. Levels of SH are higher in IT; CAT, GPH and GR are three times more active in patients with IT with LMWH therapy compared to control group.

Conclusion: Values of OS parameters in pregnant women with IT during delivery may confirm increased OS in those patients indicating that introduction of antioxidant therapy may be advisable.

Key words: thrombophilia, obstetric complication, oxidative stress

Cite this article as: Maglić D, Mandić-Marković V, Bogdanović-Pristov J, Maglić R, Džatić-Smiljković O, Aničić R, Mandić M, Mitrović J, Škrijelj S. Oxidative stress and obstetric complications in pregnant women with inherited thrombophilia with and without low molecular weight heparin therapy; Medicinska istraživanja 2024; 57(4):63-70 DOI: 10.5937/medi57-53290

INTRODUCTION

Inherited thrombophilia (IT) present genetic conditions associated with the risk of deep vascular thrombosis (DVT) and obstetric complications (OC) and they are presented as deficiency in anticoagulant proteins - antithrombin III (AT III), protein C (PC) or protein S (PS), as well as gene mutations for Factor V Leiden (FVL), Factor II 20210A (FII), plasminogen activator inhibitor 1 (PAI-1) or methytetrahydrofolate reductase (MTHFR). (1) Diagnosis of IT is often made based on history of OC, such as habitual abortion (HA), preeclampsia (PE), severe fetal growth restriction (FGR), stillbirth and placental abruption (PA).[1] Both VT and obstetric complications are more likely in AT3, PS or PC deficiency or FVL and FII mutations, while the significance of PAI-1 and MTHFR is questionable (2,3).

The etiology and pathogenesis of OC in IT is not clearly defined, which is one of the reasons for the controversial views on therapy (2). Increased coagulability, endothelial disfunction, vasoconstriction and placental ischemia combined with pathological placentation cause decreased placental perfusion and inadequate fetal-maternal circulation. Subsequent vasculopathy and secondary thrombosis may cause inadequate intervillous perfusion, placental infarction and OC, such as PE, FGR, stillbirth and PA (4). However, OC still occur in a certain number of pregnancies with IT on low-molecular weight heparin (LMWH) therapy. Therefore, other pathological factors for OC should be considered in pregnancies with IT.

Studies have found that normal pregnancy is characterized by mild pro-oxidative changes in the status of maternal blood when compared to non-pregnant patients. In pregnant women with PE, an increase in the concentration of reactive oxygen species as well as reduced activity of protective enzymes against oxidative damage has been proven, resulting in hypoperfusion of the placenta, which increases oxidative stress (OS) (5,6). OS, characterized by an overproduction of reactive oxygen species (ROS), can significantly impair the function of these cells, thus instigating a cascade of events leading to thrombus formation. Impaired antioxidant defenses compound the prothrombotic state by allowing the accumulation of ROS, thereby contributing to OS-induced endothelial dysfunction. Most of vascular complications of pregnancy can be attributed to IT (7). OS have been related to the development of different OC, such as PE, FGR, miscarriage, and others.

The aim of our study was to evaluate the frequency of OC and OS in women with IT during pregnancies without LMWH therapy, and pregnancies with LMWH therapy and in women with healthy pregnancies.

MATERIAL AND METHODS

We conducted a longitudinal study evaluating 60 women with diagnosed IT and 60 healthy pregnant controls ate the University Clinic for Gynecology and Obstetrics "Narodni front", Belgrade.

The study has been approved by the Ethics Committee of the Faculty of Medicine in Belgrade in accordance with internationally accepted ethical standards (The Helsinki Declaration of 1964, as revised in 1975, 1983 and 1989) and each participant signed the informed consent form.

In the study group IT was diagnosed before ongoing pregnancy based on previous VTE or OC. All patients had a history of previous pregnancy without LMWH therapy. The most frequent inherited thrombophilia in our study was PAI-1 mutation (N=24; 40%); followed by FVL mutation (N=16; 26.7%); FII 20210A mutation (N=10; 16.6%); DPS (N-6; 10%); and DPC (N-4; 6.7%). We analyzed only patients with PAI homozygote mutations (4G/4G), because authors suggest that PAI-1 4G/5G alone is not responsible for obstetric complications. Other analyzed patients with inherited thrombophilia had mutation in heterozygous form.

During ongoing pregnancy doses of LMWH had been stared during early first trimester, after confirming the presence of the fetal heart rate. All patients had prophylactic or intermediate dose LMWH on recommendation of the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 196: Thromboembolism in Pregnancy. Obstet Gynecol. 2018 Jul;132(1):e1-e17.[23] The control group consisted of healthy pregnant women without previous risk for IT, who had uncomplicated pregnancies.

All pregnancies were single, with known gestational age and without a congenital anomaly, or congenital infection. All the patients were non-smokers. All the patients received 1000 mg of vitamin C and 5 mg of folate each day until gestational week 16; after that all patients received multivitamin supplement that contained 100 mg of vitamin C each day.

In all patients (both study and control group) before delivery, after admittance to the Delivery ward or Operating room for Cesarean section (CS), blood samples were collected and samples were taken in two vacutainers (1 serum and 1 plasma with EDTA as an anticoagulant), centrifuged at 1500 g for 10 min at 4^{0}C; divided into appropriate aliquots of 200 μL and stored for analysis at the temperature of -80^{0}C. Erythrocytes and plasma were separated by centrifugation (10 min. at 5000 rpm, 4^{0}C). The separated erythrocytes were washed three times with physiological solution by centrifugation (10 min. at 5000 rpm, 4^{0}C), and thus prepared samples were frozen at -80°C. We took cotyledons from placentas immediately after birth for the analysis of the activity of antioxidative

Table 1. Characteristics of the study group in the ongoing pregnancy and control group

	Study group N = 60	Control group N = 60
Maternal age	33.1+/-4,8	35.3±4.3
Parity, N (%)		
1	12 (20%)	26 (43.33%)
2	27 (45%)	18 (30%)
>3	21 (35%)	16 (25.67%)
BMI	25.1±5.6	24.9±4.6
Gestational age at delivery (week)	36.81 +/- 11,03	39.3±9.4 *
Cesarean section, N (%)	37 (61.1)	7 (11,67) *
Neonatal body weight	2855.59 +/- 689.47	3406.6 ±843.2 *
1-minute Apgar score	8.51 +/- 1.57	9.01±1.34
5-minute Apgar score	9.23± 1.65	9.93±1.10

* p< 0.05
Abbreviation: BMI – body mass index

enzymes. The activity of the enzymes catalase (CAT), glutathione peroxidase (GPH), sulfhydryl groups (SH) and glutathione reductase (GR), copper-zinc-superoxide dismutase (CuZnSOD), manganese superoxide dismutase (MnSOD) was determined.

We collected data on maternal age; parity; pre-pregnancy body mass index (BMI), calculated as weight in kilograms (kg) divided by height in meters (m) squared; pregnancy complications, such as DVT, miscarriage, preterm delivery (PTD), gestational hypertension (GH), PE, FGR, PA and stillbirth; and delivery data – gestational age at delivery, delivery mode (vaginal or CS), neonatal body weight, 1-minute and 5-minte Apgar score. In the study group we also evaluated history of previous pregnancies without LMWH therapy, and collected data on pregnancy complication.

We compared data between study group on LMWH therapy in current pregnancy, previous pregnancy without LMWH therapy and control group.

Statistical analysis of the obtained data was conducted by using descriptive statistics (mean value, standard deviation (SD), standard error (SE), Min-Max variation range and median (Med) and mode (Mod) values). The normality of distribution was tested by Kolmogorov-Smirnov and Shapiro-Wilk test, Student's t-test (parametric test). The minimum condition for the existence of a statistically significant difference was when the probability (p, level of significance) was less than or equal to 0.05. Statistical data processing was performed using the computer programs MS Excel and Medcalc (MedCalc ver. 11.4 Software, Belgium).

RESULTS

There were no differences in maternal age, parity and BMI between the groups. Gestational age, and neonatal body weight were higher in control group, while CS was more frequent in IT. There was no difference in Apgar score **(Table 1)**.

Pregnancy complications in patients with IT with and without LMWH therapy, and in control group are shown in Table 2. Distribution of complications in relation to the types of IT without with and LMWH therapy is shown in Table 3. After the introduction of LMWH therapy, the total number of obstetrics complications had decreased statistically significantly (X2=10.08; p=0.039). We didn't prove statistical significance between DVT in pregnant women with IT in pregnancies without LMWH therapy in relation to pregnancy with LMWH therapy and control group (p= 0.027505). Pregnant women with IT with LMWH therapy had significantly lower frequency of PTD in relation to pregnancy without LMWH and in control group (X2=23.835; p<0.00012). We didn't prove statistical significance of frequency of PE (X2=0.831; sign test z-0.46, p-0.64), PA (X2-0.12; p=0.73) and FGR (p>0.005) between pregnancies without LMWH therapy in relation to pregnancies with LMWH therapy and control group. Statistical frequency of GH was higher in pregnant women with IT without therapy (Ks2=8.85; P=0.003) in relation to pregnant women with LMWH therapy and control group. The rate of miscarriages was higher in pregnancies before LMWH therapy in relation to pregnancies with LMWH therapy and control group (X2=76.7 with Yates correction; p<0.001). LMWH therapy statistically reduce the rate of stillbirth in relation to pregnancies before therapy and control group (X2=14.70 with Yates correction; p<0,001). **(Table 2 and Table 3)**

Erythrocyte CAT activity during labor in patients with IT with LMWH therapy is lower compared to controls (p=0.04). Changes in glutathione peroxidase (GPX) enzyme activity were not detected before delivery, neither in the group of pregnant women with IT nor in the group of healthy pregnant women. Erythrocyte CuZnSOD activity does not differ between controls and patients with IT (p-0.014) **(Graph 1)**.

Table 2. Obstetric complication in the study group in pregnancies without LMWH therapy and pregnancies with LMWH therapy and in the control group

	IT without LMWH therapy N = 60	IT with LMWH therapy N = 60	Control Group N = 60	p
DVT, N (%)	9 (15)	2 (3.3)	0 (0)	0.027505
Preterm delivery, N (%)	18 (30)	8 (13.3)	4 (6.7)	<0,00012
PE, N (%)	5 (8.3)	4 (6.3)	0 (0)	0,73
GH, N (%)	32 (53.3)	22 (36.6)	2 (3.33)	0,003.
FGR, N (N%)	26 (43.33)	22 (36.67)	0 (0)	>0,005
Miscarriage, N (%)	53 (88.33)	5 (8.3%)	0 (0)	<0,001
PA, N (%)	5(8.3)	4(6.3)	2	0,73
Stillbirth, N (%)	17 (28.3)	3 (1.7)	0 (0)	<0,001

Abbreviations: IT-Inherited thrombophilia; LMWH-Low Molecular Weight Heparin; DVT-Deep Vascular Thrombosis; PE-Preeclampsia; GH-Gestational Hypertension; FGR-Fetal Growth Restriction, PA-Placental Abruption

Table 3. Distribution of complications in relation to types of IT without with and LMWH therapy

		GH/PE	FGR	PTD	MC	SB	PA	DVT	TOTAL
FVL mutation	I	13	8	5	14	3	1	3	47
	II	10	3	2	1	1	1	2	20
FII 20210A mutation	I	7	5	3	10	4	2	2	31
	II	3	3	1	1	1	0	0	9
DPC	I	0	1	1	3	0	0	0	5
	II	3	2	0	1	0	0	0	6
PAI-1 mutation	I	17	11	7	20	9	2	3	69
	II	8	12	4	2	1	3	0	30
DPS	I	0	0	2	6	1	0	1	10
	II	2	2	1	0	0	0	0	5
TOTAL	I	37	26	18	53	17	5	9	165
	II	26	22	8	5	3	4	2	70
p		0.64	0.5	<0.001	<0.001	<0.001	0.73	0.035	

Abbreviations: FVL – Factor V Leiden; FII – Factor II; DPC – Protein C deficiency; PAI – Plasminogen Activator Inhibitor; DPS – Protein S deficiency; GH-Gestational Hypertension; PE-Preeclampsia; FGR-Fetal Growth Restriction; PTD – Preterm Delivery; MC – Miscarriage; SB – Stillbirth; PA-placental abruption; DVT-Deep Vascular Thrombosis

Analyzing the association between OC and different kinds of IT, we found significant association only between FVL and DPC with GH/PE.

Table 4. Association between FVL and DPC with GH/PE

		Comparative Measures		
		95% Confidence Intervals		
		Value	Lower	Upper
FVL	Odds Ratio	3.14	0.995	9.92
	Relative Risk	1.33*	0.950	1.86
DPC	Odds Ratio	8.05	0.788	8.22
	Relative Risk	1.14[a]	0.958	1.35

Abbreviations: GH- Gestational Hypertension; PE – Preeclampsia; FVL – Factor V Leiden; DPC – Protein C deficiency; [a]Rows compared

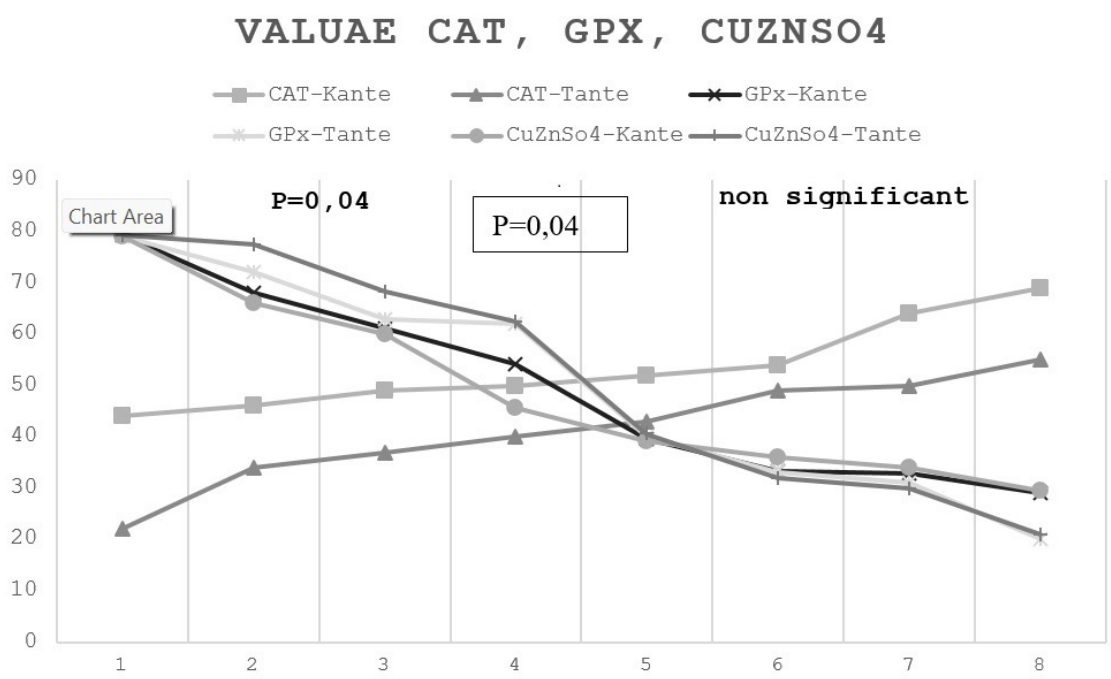
The level of SH groups in the plasma of patients with IT is higher compared to the values for controls **(Graph 2)**.

Ascorbyl radical is not detected in the plasma of control subjects before delivery (Kante) or in the plasma of patients with IT before delivery (Tante), indicating that there was no oxidative stress in both groups before delivery.

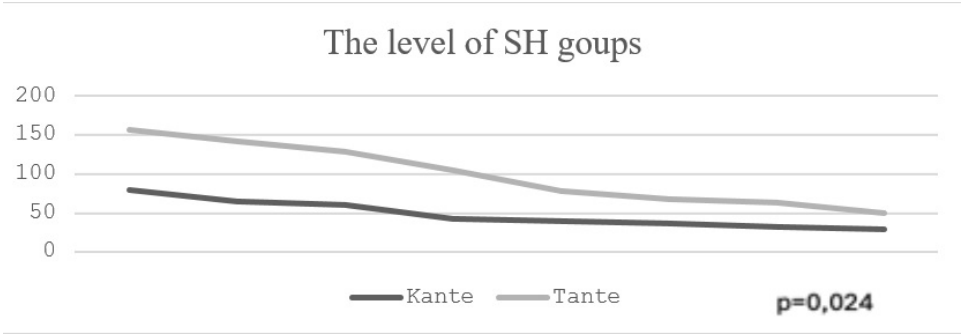
The results of enzyme activity in placental tissue show that the enzymes that use hydrogen peroxide (catalase, glutathione peroxidase and glutathione reductase), reducing the peroxide concentration, are three times more active patients with IT with LMWH therapy compared to control group. There was no difference in activity of MnSOD and CuZnSOD. This result indicates an increased hydrogen peroxide production in the placentas of patients with thrombophilia **(Graph 3)**.

DISCUSSION

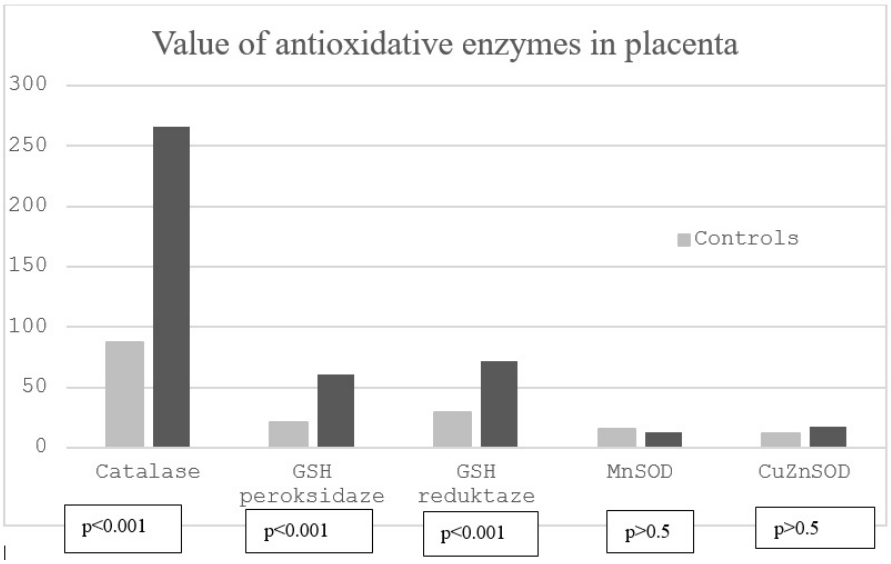
The most common IT in our study was PAI-1 mutation, followed by FVL mutation and FII G20210A mutation. Studies have shown different distribution of the most common IT among different populations; the most common appearance of PAI-1 and FVL mutations in Italian population;



Graph 1. Erythrocyte value of CAT, GPX and ZnCuSOD in patients with IT with LMWH therapy and control group before delivery
Abbreviations: CAT - Catalase activity; GPX - Glutathione peroxidase; ZnCuSOD - ZnCu superoxide dismutase; Tante – Patients with IT with LMWH therapy; Kante – Control group



Graph 2. Level of SH groups in plasma during delivery in pregnant women with IT with LMWH therapy and control group
Abbreviations: SH – sulfhydryl groups; Tante – Patients with IT with LMWH therapy; Kante – Control group



Graph 3. Activity of enzymes involved in the protection system against oxidative damage in placenta tissue of controls and patients with thrombophilia
Abbreviations: GSH – Glutathione; MnSOD – Manganese superoxide dismutase; CuZnSOD – Copper-zinc-superoxide dismutase

FVL, FII G20210A and MTHFR C677T mutations in Arab countries and MTFHR C677T and A1298C mutations, followed by the PAI-1 mutation in Romanian population (8-10). Variations in the prevalence of IT mutations among different populations can be attributed to different genetic profiles of the populations being studied. Therefore, determining the prevalence of these mutations in each population should assist in the development of thrombophilia screening protocols for the appropriate population.

CS was more frequent in patients with IT compared to controls. The most likely reason for completing a delivery by CS are OC and previous history. Other authors find that the increased frequency of CS is due to PTD and OC (FGR, PA, PE) (11).

In our study, the incidence of DVT in pregnancies prior to diagnosis of IT and prior to initiation of LMWH therapy had no statistical significance relative to the overall sample. A higher incidence of DVT in patients with IT, especially in pregnant women with FVL mutation, FII G20210A mutation, and DPS are reported (12,13). In our study, there was no statistically significant difference in the incidence of DVT in relation to the type of IT.

With the introduction of LMWH therapy, a statistically significantly lower number of early PTD (before 34 weeks) was registered. There was a statistically significant incidence of PTD between the LMWH treatment group compared to the control group. A higher incidence of PTD, especially late PTD, in patients with the FVL mutation is reported (11,12,14). In our group, the incidence of PTD was statistically significantly lower in patients with the FVL, F II G20210, and the PAI-1 mutations.

According to literature data, PA is more common in pregnant women with IT. There was no statistical significance in the occurrence of PA in pre- and post-LMWH therapy, indicating that LMWH therapy does not affect the occurrence of PA (12).

Most authors report an association between FGR and IT, especially the FVL mutation and DPS (8,15). The association between FGR and PAI-1 mutation has been reported as significant in case-controlled studies in general population of women with FGR (16, 17). On the contrary, Said et al. states that there was no association between the PAI-1 mutation and FGR (18). These discrepancies could be explained by huge differences regarding race and ethnicity between participants in conflicting studies.

The incidence of stillbirths has remained stable for decades, ranging from 4.9 to 10.4 per 1,000 births. In his study, Sarig found that pregnant women with IT had a higher incidence of sudden fetal death in the third trimester (66%) and particularly when associated with the FVL mutation. The most common IT in the stillbirth group was FII G20210A mutation. The number of stillbirths in pregnancies treated with LMWH was statistically significantly lower, only 1 patient had stillbirth with LMWH therapy, which justifies the use of LMWH in patients with a history of previous stillbirth (19).

GH/PE were the most common complication in group with IT. Most authors state that PE, early PE in particular, is associated with IT (10,20).

Thrombophilia, characterized by an increased tendency to form blood clots, presents a substantial risk during pregnancy, potentially impacting maternal and fetal outcomes. Specifically, endothelial dysfunction, driven by OS, emerges as a pivotal factor in thrombophilia, setting the stage for increased platelet activation and altered coagulation factors (21). Factors like FVL mutation, Prothrombin G20210A mutation, DPC and DPS contribute to the pro-thrombotic state observed in thrombophilia. Furthermore, inflammation, closely intertwined with OS, exacerbates the risk of blood clot formation. Inflammatory responses lead to endothelial activation, altered endothelial function, and increased adhesion molecules expression, disrupting the delicate balance between pro- and anti-coagulant factors. Chronic inflammatory conditions, such as autoimmune disorders, potentiate a persistent state of heightened clotting risk (21). Additionally, impaired antioxidant defenses compound the prothrombotic state by allowing the accumulation of reactive oxygen species, thereby contributing to OS-induced endothelial dysfunction. Understanding the interplay between these factors is crucial for tailored IT management, particularly in pregnancy. Treatment strategies encompass a multifaceted approach, including anticoagulant medications, lifestyle modifications, and targeted interventions to improve endothelial health. The complex nature of thrombophilia underscores the need for a collaborative healthcare approach, involving hematologists and high-risk pregnancy specialists.

The main reactive oxygen species in the blood of mothers with thrombophilia during childbirth is hydrogen peroxide (7,22). Superoxide dismutase is the main enzyme for the production of hydrogen peroxide in tissue. It can reach placental tissue from maternal or fetal circulation, amniotic fluid or uterine smooth muscle. The results of this research undoubtedly show that the placenta in IT patients is exposed to OS caused by an elevated concentration of hydrogen peroxide. Uncontrolled production of ROS is associated with the development of hypertension, which is the main symptom of PE (7,22).

AOS enzymes present in the placental tissue also protect the mother's blood from the increased amount of hydrogen peroxide produced in thrombophilia. If this defense loses effectiveness during pregnancy, prothrombotic conditions can lead to thrombosis. In the blood of pregnant women with thrombophilia on LMWH therapy, the level of some AOS enzymes (catalase, and the level of SH) was elevated compared to controls, which indicates a higher level of oxidative stress. Considering the lack of difference in the values of glutathione peroxidase, CuZnSOD, the question arises whether the administration of LMWH reduced the existence of oxidative stress in childbirth (7,22). After childbirth, when the placenta is rejected, its

protective function and filtering of the mother's blood is lost, and the production of hydrogen peroxide in the myometrium, endothelium and in the blood continues. In such conditions, thromboses can develop with a fatal outcome, which occur immediately after delivery (1,7).

CONCLUSIONS

Although many studies recommend only an expectant approach for patients with IT with possible prophylactic use of LMWH before and after delivery, our results indicate a positive effect of this therapy in reducing the frequency of PE, miscarriages and PTD. The most common intermediate thrombogenic thrombophilia are PAI gene mutations and F V Leiden mutations. Elevated values of catalase and SH and R-SH groups in the blood of pregnant women with thrombophilia during childbirth compared to controls may indicate increased OS in these pregnant women. The results of the activity of enzymes that reduce the concentration of peroxide with their activity are three times increased activity in the placenta tissue in subjects suffering from IT compared to control subjects. Therefore, the introduction of antioxidant therapy is also advisable in the therapy.

Acknowledgments

None

Author Contributions:

- The conception of the study was done by Dragana Maglić, Vesna Mandić-Marković, and Jelena Bogdanović-Pristov.
- The acquisition, analysis, and interpretation of data were done by Jelena Bogdanović-Pristov,
- Milica Mandić, Jelena Vugdelić and Sabrina Škrijelj.
- Draft version of the Manuscript was prepared by Rastko Maglić, Olivera Džatić-Smiljković and Radomir Aničić.

Ethical approval

The study has been approved by the Ethics Committee of the Faculty of Medicine in Belgrade (Approval No. 1382/2) in accordance with internationally accepted ethical standards (The Helsinki Declaration of 1964, as revised in 1975, 1983 and 1989) and each participant signed the informed consent form.

REFERENCES

1. Voicu DI, Munteanu O, Gherghiceanu F, Arsene LV, Bohiltea RE, Gradinaru DM, Cirstoiu MM. Maternal inherited thrombophilia and pregnancy outcomes. Exp Ther Med. 2020;20(3):2411-4. doi: 10.3892/etm.2020.8747. PMID: 32765725
2. Middeldorp S, Naue C, Köhler C. Trhombophilia, Thrombosis and Thromboprophylaxis in Pregnancy: For What and in Whom? Hamostaseologie. 2022;42(1):54-64. doi: 10.1055/a-1717-7663. PMID: 35196731
3. Ormesher L, Simcox L, Tower C, Greer IA. Management of inherited thrombophilia in pregnancy. Womens Health (Lond). 2016;12(4):433-4. doi: 10.1177/1745505716653702. PMID: 27638899
4. Regal JF, Lund JM, Wing CR, Root KM, McCutcheon L, Bemis LT, Gilbert JS, Fleming SD. Interactions between the complement and endothelin systems in ormal pregnancy and following placental ischemia. Mol Immun. 2019;144:10-8. doi: 10.1016/j.molimm.2019.06.015. PMID: 31326653
5. Pereira RD, De Long NE, Wang RC, Yazdi FT, Holloway AC, Raha S. Angiogenesis in the placenta: the role of reactive oxygen species signaling. Biomed Res Int. 2015; 2015:814543. doi. org/10.1155/2015/814543 PMID: 25705690
6. Ibrahim A, Khoo MI, Ismail EHE, Hussain NHN, Zin AAM, Noordin L, Abdullah S, Mahdy ZA, Lah NAZN. Oxidative stress biomarkers in pregnancy: a systematic review. Reprod Biol Endocrinol. 2024;22(1):93. doi: 10.1186/s12958-024-01259-x. PMID: 39095896
7. Bogdanović Pristov J, Opačić M, Bajčetić M, Mandić V, Maglić D, Miković Ž, Spasojević I. Oxidative status of maternal blood in pregnancies burdened by inherited thrombophilias. PLoS One. 2020;15(6):e0234253. doi: 10.1371/journal.pone.0234253. PMID: 32555583
8. Campello E., Spiezia L., Adamo A., Simioni P. Thrombophilia, risk factors and prevention. Expert Rev Hematol.2019;12(3):147–58. doi: 10.1080/17474086.2019.1583555. PMID: 30773075
9. Najjar, AA, Hassouna I, Srour MA, Ibrahim HM, Assi RY, Abd El Latif HM. Association of inherited thrombophilia mutations and their combinations among palestinian women with unexplained recurrent miscarriage. Thrombosis J. 2024;22(1):20. doi: 10.1186/s12959-024-00587-7. PMID: 38351006
10. Samfireag M, Potre C, Potre O, Moleriu LC, Petre I, Borsi E, Hoinoiu T, Preda M, Popoiu TA, Anghel A. Assessment of the Particularities of Thrombophilia in the Management of Pregnant Women in the Western Part of Romania. Medicina (Kaunas). 2023;59(5):85. doi: 10.3390/medicina59050851. PMID: 37241083
11. Simcox LE, Ormesher L, Tower C, Greer IA. Thrombophilia and Pregnancy Complications. International Journal of Molecular Sciences. 2015; 16(12):28418-28. doi: 10.3390/ijms161226104. PMID: 26633369
12. American College of Obstetricians and Gynecologists. ACOG practice bulletin No. 197: inherited Thrombophilias in Pregnancy. *Obstet Gynecol*. 2018;132(1):e18-e34. doi: 10.1097/AOG.0000000000002703. PMID: 29939939
13. Varrias D, Spanos M, Kokkinidis DG, Zoumpourlis P, Kalaitzopoulos DR. Venous Thromboembolism in Pregnancy: Challenges and Solutions. Vasc Health Risk Manag. 2023; 19:469-84. doi: 10.2147/VHRM.S404537. PMID: 37492280
14. Hiltunen LM, Laivuori H, Rautanen A, Kaaja R, Kere J, Krusius T, Rasi V, Paunio M. Factor V Leiden as a risk factor for preterm birth--a population-based nested case-control study. J Thromb Haemost. 2011;9(1):71-8. doi: 10.1111/j.1538-7836.2010.04104.x. PMID: 20946152
15. Mihai B-M, Salmen T, Cioca A-M, Bohîlțea R-E. The Proper Diagnosis of Thrombophilic Status in Preventing Fetal Growth Restriction. Diagnostics. 2023; 13(3):512. doi: 10.3390/diagnostics13030512. PMID: 36766616

16. Dugalić S, Petronijevic M, Stefanovic A, Jeremic K, Petronijevic SV, Soldatovic I, Pantic I, Djunic I, Jokic Z, Djokovic F, Dotlic J, Zaric M, Todorovic J. The association between IUGR and maternal inherited thrombophilias: A case-control study. Medicine (Baltimore). 2018;97(41):e12799. doi: 10.1097/MD.0000000000012799. PMID: 30313110

17. Mihai BM, Salmen T, Cioca AM, Bohîlțea RE. The Proper Diagnosis of Thrombophilic Status in Preventing Fetal Growth Restriction. Diagnostics (Basel). 2023 Jan 31;13(3):512. doi: 10.3390/diagnostics13030512.PMID: 36766616

18. Said JM, Higgins JR, Moses EK, Walker SP, Monagle PT, Brennecke SP. Inherited thrombophilias and adverse pregnancy outcomes: a case-control study in an Australian population. Acta Obstet Gynecol Scand. 2012 Feb;91(2):250-5.

19. Sarig G, Younis JS, Hoffman R, Lanir N, Blumenfeld Z, Brenner B. Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage Fertil Steril. 2002;77(2):342-7. doi: 10.1016/s0015-0282(01)02971-5. PMID: 11821094

20. Camacho Sáez B, Martínez-Taboada VM, Merino A, Comins-Boo A, González-Mesones B, Del Barrio-Longarela S, Riancho-Zarrabeitia L, López-Hoyos M, Hernández JL. Impact of Inherited Thrombophilia in Women with Obstetric Antiphospholipid Syndrome: A Single-Center Study and Literature Review. Biomedicines. 2024; 12(6):1174. doi: 10.3390/biomedicines12061174. PMID: 38927381

21. Stančiaková L, Brisudová K, Škorňová I, et al. Evaluating Thromboprophylaxis Strategies for High-Risk Pregnancy: A Current Perspective. Pharmaceuticals (Basel, Switzerland). 2024;17(6):773. doi: 10.3390/ph17060773. PMID: 38931440

22. Hussain T, Murtaza G, Metwally E, Kalhoro DH, Kalhoro MS, Rahu BA, Sahito RGA, Yin Y, Yang H, Chughtai MI, Tan B. The Role of Oxidative Stress and Antioxidant Balance in Pregnancy. Mediators Inflamm. 2021; 2021:9962860. doi: 10.1155/2021/9962860. PMID: 34616234

OKSIDATIVNI STRES I OPSTETRIČKE KOMPLIKACIJE KOD TRUDNICA SA NASLEDNOM TROMBOFILIJOM, SA I BEZ TERAPIJE HEPARINOM NISKE MOLEKULSKE TEŽINE

Dragana Maglić[1,2], Vesna Mandić-Marković[1,2], Jelena Bogdanović-Pristov[3], Rastko Maglić[1,2], Olivera Džatić-Smiljković[1,2], Radomir Aničić[1,2], Milica Mandić[2], Jelena Mitrović[2], Sabrina Škrijelj[2]

Sažetak

Uvod: Urođena trombofilija (UT) predstavlja stanje udruženo sa rizikom od duboke vaskularne tromboze (DVT) i obstetričkih komplikacija (OK) kao što su preeklampsija (PE), zastoj u rastu ploda (IUZR), mrtvorođenost i abrupcija placente (PA).

Cilj studije: procena učestalosti OC i oksidativnog stresa (OS) kod žena sa IT tokom trudnoće sa i bez terapije niske molekulske težine (LMVH), u poređenju sa ženama sa zdravim trudnoćama.

Metodologija: U studiju je uključeno 60 trudnica sa UT dijagnostikovanom pre aktuelne trudnoće na osnovu prethodne DVT ili OK (ispitivana grupa) i 60 zdravih trudnica (kontrolna grupa). Kod svih ispitanica uzet je uzorak krvi pre porođaja, kao i uzorak placentnog tkiva i određena je aktivnost CAT, GPX, GH, SH, GR, CuZnSOD i MnSOD.

Rezultati: Nakon uvođenja NMH u terapiju žena sa UT značajno je smanjen broj OK. Analizom povezanosti OK i različitih tipova UT, nađena je značajna povezanost samo između mutacije faktora V Leiden i deficit proteina C sa gestacijskom hipertenzijom/preeklampsijom. Nivo SH je povišen kod UT; CAT, GPH i GR pokazuju tri puta veću aktivnost kod žena sa UT na terapiji NMH u poređenju sa kontrolnom grupom.

Zaključak: Vrednosti parametara OS kod trudnica sa UT tokom porođaja mogu da potvrde prisustvo OS i ukažu na opravdanost primene antioksidativne terapije.

Ključne reči: trombofilija, opstetričke komplikacije, oksidativni stres

Primljen: 11.09.2024. I **Revizija:** 22.10.2024. I **Prihvaćen:** 25.10.2024.

Medicinska istraživanja 2024; 57(4):63-70