Original Article,

Thrombophilia and newborn

Tatyana Itova[1],[2]

[1]University Hospital Medica Ruse Ltd, Ruse, Bulgaria
[2]University of Ruse „Angel Kanchev", Ruse, Bulgaria
Email Address taniaitova@abv.bg

Abstract:

Introduction: The term thrombophilia (TF) describes disorders associated with an increased predisposition of developing venous thromboembolism. Thrombotic accidents during pregnancy are now widely recognized as a cause of morbidity and mortality.

Objectives: To compare maternal and term newborn (NB) characteristics between healthy and thrombophilic pregnancies.

Methods: The study included 31 full-term newborns whose mothers were diagnosed with TF before the current pregnancy and treatment was carried out through it. In the control group were included 37 full-term NBs. NB indicators which were used are gender, gestation age, birth weight, Apgar score, morbidity during the early neonatal period, hospital stay, treatment during the early neonatal period. The indicators for the mothers are the type of TF, mechanism of childbirth, sequence of pregnancy and sequence of childbirth.

Results: In the observed groups of patients, we found that mothers with TF have an average higher age and have a higher number of unsuccessful pregnancies. They more often give birth by operation. The higher the number of maternal TF mutations, the more unsuccessful pregnancies. The NB of mothers with TF have a lower Apgar score, develop RDS more often during the early neonatal period and need a larger volume of therapeutic manipulations and have a significantly longer hospital stay.

Conclusions: TF in pregnant women, even when adequate treatment is administered during pregnancy, is associated with increased morbidity in their full-term NBs during the early neonatal period. This requires additional therapeutic measures in full-term newborns and is associated with a prolonged hospital stay.

Key Words: thrombophilia; newborn; pregnancy;

Introduction:

The term thrombophilia (TF) describes disorders associated with an increased predisposition to develop venous thromboembolism. It was first used by O. Egeberg in 1965 when it described the propensity to venous thrombosis in patients deficient in antithrombin III. Subsequent discoveries of other defects of the hemostasis system and their role in the development thrombotic complications contribute to the use of this term in clinical practice[1][2][3][4] .

The physiology of pregnancy is characterized by an increase in the synthesis of procoagulant factors (plasma coagulation factors II, VII, VIII, IX, X, fibrinogen, von Willebrand factor), a decrease in blood concentrations and the effects of natural anticoagulants (protein S and C). As a result, the coagulation potential – prothrombotic activity of the blood – is increased, which is evolutionarily necessary to prevent massive obstetric hemorrhages during childbirth and preserve the life of the woman[5] [6] .

Thrombotic accidents during pregnancy are now widely recognized as a cause of morbidity and mortality[7] . The increased risk of blood clotting can be caused by genetic factors, acquired changes in the clotting process or, more often, a combination of hereditary and acquired ones. Hereditary TF is the most common cause of thromboembolism in the mother. It is associated with an increased risk of adverse evolution during pregnancy, including fetal death in the second and third trimesters, abruptio, severe intrauterine fetal

hypotrophy and early, severe preeclampsia, premature birth[7] [8] .

The most prevalent hereditary TF were associated with pathological mutations localized in prothrombin gene mutation (factor II) at position G20210A, factor V Leiden gene mutation (FVL) at position G1691A, methylenetetrahydrofolate reductase (MTHFR) gene mutation at the C677T and A1298C positions and plasminogen activator inhibitor-1 (PAI-1) gene mutation. All these pathological mutations may increase the risk of developing thrombosis [9] [10] [4] .

Scientific searches and observations of pregnancy development against the background of TF are in most cases focused on the causes of intrauterine hypotrophy of the fetus and fetal loss [11][12][13][14] . Children born to mothers who have been treated for TF during pregnancy are most likely to have intrauterine hypotrophy, young for gestational age, or born prematurely. Early neonatal health problems can be foreseen by the anamnesis and pathology of the pregnancy in premature or hypotrophic newborn timely treatment can be carried out[15] [16] . However, long-term health problems in children born by mothers with TF are not entirely predictable. Behavioral abnormalities[17] , autism spectrum disorder, hyperactive behavior, eating disorder, delayed speech and psychomotor development are described in children whose mothers had antiphospholipid syndrome during the pregnancy[18] .

Objectives:
This study aimed to compare maternal and term newborn characteristics between healthy and thrombophilic pregnancies.

Material and methods:
The retrospective study included full-term NBs born from January 2021 to December 2023, treated in the Department for Neonatology of the University Hospital Medica Ruse Ltd., whose mothers were diagnosed with TF before the current pregnancy and treatment was carried out through it. The included full-term NBs meet the definition of such according to the International Classification of Diseases and Health Problems 10th revision – born at a gestation term of 37 full weeks to less than 42 full weeks[19] . The gestational age (GA) of the NB was determined by maternal amenorrhea and morphological criteria (New Ballard Score)[20] . For a control group we used full-term NBs born in August 2023 in our Department. The patient groups were designated as Group A – NBs of mothers with TF and Group B – control group NBs, respectively.

The study was approved by the Ethics Committee for the scientific activity of the University Hospital Medica Ruse (№ of approval 4/2024).

The included indicators for the NBs are gender, gestatoin age(GA), birth weight, Apgar score, leukocyte, platelets and erythrocytes from the first complete blood count, morbidity during the early neonatal period, hospital stay, treatment during the early neonatal period. The indicators for the mothers are a type of TF, mechanism of childbirth, sequence of pregnancy and sequence of childbirth, other concomitant diseases during pregnancy.

The data for the present study were obtained from the patient files of the newborns and their mothers, who were treated in the Department for Newborns and in the Department of Obstetrics, respectively, for the period 2021 - 2023.

The statistical processing of the data was carried out using a statistical processing program IBM SPSS Statistics version 23 and a spreadsheet program, part of the MS Office – Microsoft Excel package. For a significance level at which the null hypothesis is rejected, p <0.05 was chosen. The following methods were applied: descriptive analysis, tests to establish statistically significant difference, correlation and graphical analysis.

Results:
From the selected 36 parturients with TF and their NBs dropped out 5: one with stillbirth and 4 who gave birth to children before 37 weeks. The average age of the other 31 mothers with TF is 31.4 ±5.9 years and is significantly higher than the age of the control group B - 28.5±4.8 years (p=0.023). In Group A, the share of operative births SC (Cesarean section) is significantly higher – 82,7% compared to Group B – 37,8% (p=0.004)(Table 1). This difference is at the expense of more operative deliveries in Group A, due to aggravated obstetric history -37,9%, while in Group B this percentage is only 5,4%. The two groups do not differed in the proportion of resections - in Group A 27,6%, in Group B - in 24,3%. Incorrect presentation/pelvio-fetal disproportion as an indication of SC in the first group was registered slightly more often -13,8%, and in the second group – in 8,1%. Only in one case was an emergency operative birth permit required in Group A (Figure1).

Table 1. Demographic and obstetric indicators of the observed groups
(PN – partus normalis, SC - Cesarean section, GA – gestation age)

| Indicator		Group A	Group B	p
Count		31	37	
Mother's age(years)		31.4 ±5.9	28.5±4.8	0.023
Birth mechanism	SC/PN	26(82,7%) : 5(17,3%)	14(37,8%) : 23(62,2%)	0.004
Sequence of birth	1: >1	19(62%) : 12(38%)	23(62%) : 14(38%)	NS
Sequence of pregnancy	1:2:3:4	52%:17%:21%:10%	57%:43%:0%:0%	0.024
Gender	♂:♀	13(41%) : 18(59%)	22(60%):15(40%)	NS
Weight(gr.)		3197± 339	3233 ± 337	NS
GA(g.s.)		38.4 ± 1.0	38.7± 0.9	NS
Apgar 1min		7.7 ± 2.1	8.7 ± 0.9	0.010
Apgar 5min		8.7 ± 2.1	9.6 ± 0.6	0.022
Leukocytes (x10^9/l)		22.8 ± 7.2	22.4 ± 6.7	NS
Hemoglobin (g/L)		176 ± 22	169 ± 18	NS
Erythrocytes (x10^12/l)		5.0 ± 0.7	4.2 ± 1.8	0.034
Platelets (x10^9/l)		239 ± 59	305.0 ± 57.9	<0.001
Hospital stay (days)		4.6 ± 1.5	3.6 ± 1.0	0.002
Morbidity	Yes : no	55% : 45%	30% : 70%	0.033
Oxygen treatment	Yes : no	59% : 41%	16% : 84%	0.001
Intraamniotic infection	Yes : no	31% : 69%	11% : 89%	0.041
Phototherapy	Yes : no	21% : 79%	5% : 95%	0.066
Parenteral infusion	Yes : no	31% : 69%	8% : 92%	0.019
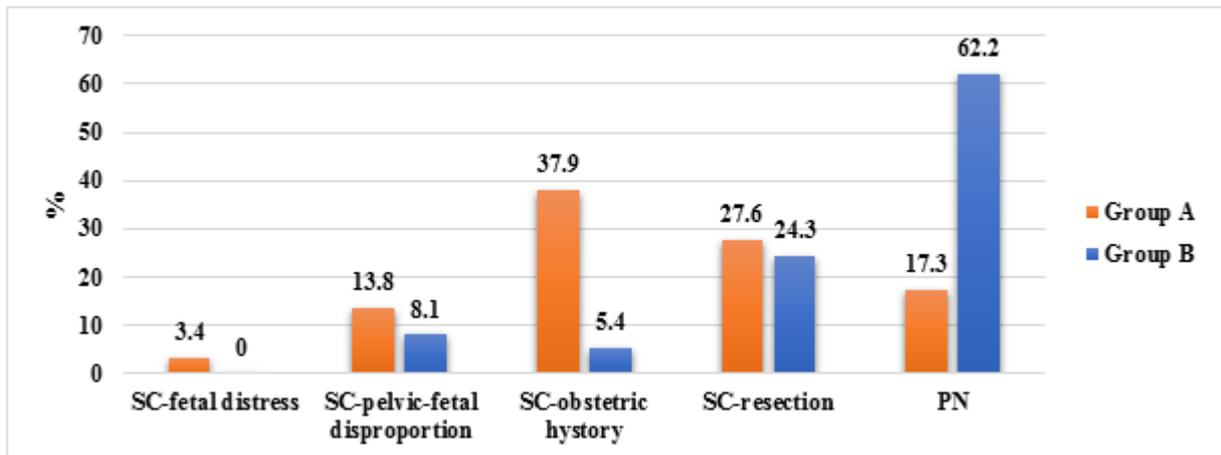
Figure 1. Mechanism of birth by group(in %)

The distribution according to the sequence of childbirth is the same in both groups of mothers – in 62% it is first and in 38% - second. The average number of pregnancies in women with TF is reliably greater - 1.9±1.1, against 1.4±0.5 in the control group of women (p=0.024). The distribution according to pregnancy sequence also shows a significant difference – in Group A women with first pregnancy are 52%, second – 17%, third – 21% and fourth – 10%, while in Group B with first are 57%, with second – 43% and there are none with third or fourth pregnancy (p=0.024) (Table 1) . The Pearson correlation coefficient for assessing the linear relationship between maternal TF and pregnancy sequence showed a much greater than typical positive correlation (p=(0.034 ; r=0.787).

Diagnosis of TF in 17(55%) of mothers is due to the search for the cause of a previous unsuccessful pregnancy. In 5 (16%) of the mothers of group A, a test for TF was made after establishing such a disease in a close relative. In

the course of treatment of infertility and preparation for IVF in 5(16%) cases, TF was proven. Four (13%) of the Group A mothers did their own tests before planning a pregnancy (Table 2).

Table 2. Reason for research on TF in mothers (TF - thrombophilia).

Reason for research	Count(%)
Unsuccessful pregnancies	17 (55%)
Mother/sister with TF	5 (16%)
Sterility treatment / IVF	5 (16%)
At your own will	4 (13%)

From the collected documentation from pregnancy keeping, it was found that 17(55%) of mothers are carriers of the mutant allele responsible for inhibition of plasminogen activator (PAI – 1 5G>4G), 7 are homozygous and 10 heterozygotes. Increased risk of venous thromboembolism due to hyperhomocysteinaemia (decreased activity of the enzyme MTHFR Mutation 677 C>T) was also found in 17(55%) of the studied women, 7 were homozygotes and 10 were heterozygotes. Increased levels of Factor II Prothrombin as heterozygous carrier of the mutant allele (Mutation 20210G>A), were found in one mother. Heterozygotes in the pathological allele for FactorV Leiden (FVL) associated thrombophilia (mutation R506Q) was detected in 5 (16%) cases (Table 3). Some of the patients had more than one form of TF. Using the Pearson correlation coefficient to estimate the linear relationship between established types of TF mutations in mothers and pregnancy sequence, we found a positive correlation ($p < 0.001$; $r=0.792$) that can be interpreted as much greater than the typical one.

Table 3. Established genetic variants of TF in mothers from Group A (TF – thrombophilia; HO - homozygote along the mutant allele; HE- heterozygote along the mutant allele)

Mutant allele	Plasminogen inhibitor activator PAI – 1 5G>4G		Hyperhomo-cysteinaemia MTHFR Mutation677C>T		NK Cells	Factor II Prothrombin Mutation 20210G>A	FactorV Leiden Mutation R506Q
	HO	HE	HO	HE	count	HE	HE
Count	7	10	7	10	4	1	5
Total(%)	17 (55%)		19 (55%)		4 (13%)	1 (3%)	5 (16%)

When comparing demographic indicators of NB in Group A and Group B, there was no significant difference between them by average birth weight, GA and sex. Children from Group A, however, had a significantly lower score on Apgar score at 1-th and 5-th minutes (7.7±2.1 and 8.7±2.1) compared to those from Group B (8.7±2.1 and 9.6±0.6) (p=0.022, p=0.010) (Table 1). In Group A there is one child with an Apgar score below 7 at 5 minutes, while in Group B there is none.
A comparison of NB's blood count from the first postnatal day showed no difference in the levels of mean leukocyte counts (Group A - 22.8±7.2x10^9/l and Group B - 22.4±6.7x10^9/l) and hemoglobin (Group A - 176±22g/L and Group B - 169±18g/L). Significantly higher were the levels of erythrocytes in Group A (5.0±0.7x10^12/l) compared to Group B (4.2±1.8x10^12/l) (p=0.034). On the other hand, in the NBs from Group A significantly lower average platelet count is registered (Group A 239±59x10^9/l and Group B 305.0±57.9x10^9/l) (p<0.001) (Table 1).
Pathology of NBs during an early neonatal period requiring therapy in both groups showed uneven distribution. In Group A, a higher proportion - 17(55%) vs. 11(30%) in Group B) of NB who received treatment (p=0.033). In the group of children of mothers with TF, oxygen therapy was much more common 18(59%) compared to the control group 6(16%) (p=0.001). In 3 patients (10%) from Group A, moderately respiratory

distress syndrome (RDS) was developed, and in one- severe RDS, while in Group B only one patient with moderate RDS was registered.

Verified intraamniotic infection (IAI) requiring an antibiotic course of treatment in Group A was recorded in 10(31%) of children, compared to only 4(11%) from Group B (p=0.041). Parenteral infusion was used significantly more frequently – 10(31%) in the first group vs.3 (8%) in the control group (p=0.019). We also reported a significantly longer hospital stay in the patients from Group A - 4.6±1.5 days than in Group B - 3.6±1.0 days (p=0.002).

Using Pearson's correlation coefficient an assessment was made of the linear relationship between maternal TF and morbidity of full-term NBs during the early neonatal period. We found a positive correlation (p=0.004; r=0.348) that can be interpreted as big or even bigger than the typical one.

Discussion:

In the group of patients we observed, we found that mothers with TF have an average higher age and have a higher number of unsuccessful pregnancies. They more often give birth by SC. As the number of mutations for the mother's TF increases, so does the number of unsuccessful pregnancies. The NBs of mothers with TF have a lower Apgar score, develop RDS more often during the early neonatal period and need a larger volume of therapeutic manipulations. These NBs have higher erythrocyte counts and lower platelet counts.

For Europe, according to a study by Dugalic et al, the most common forms of TF among the white population are FVL and MTHFR C677T gene mutation. The distribution of the type of TF in our Group A in labor is different, a smaller share is FVL mutations. The most common complications of TF in pregnant women in the European region are recurrent pregnancy loss, abortion, intrauterine fetal death, stillbirth, intrauterine fetal hypotrophy, preeclampsia, placental abruption, venous thromboembolism[4] . We also have one stillbirth in the initial cohort. In western Romania, observations in 200 mothers with TF found that they faced a significantly increased risk of giving birth to an underweight newborn. Their children had a lower Apgar score, similar to our results. The higher the BMI the mother with TF, the lower the Apgar score of NB [7] .

Dusek et al has screened 339 premature NBs with birth weights below 1500 g for carrying mutations for TF in the Czech Republic. They observed the Leiden mutation 2.5 times more frequently compared to the general population[10] . FVL is a disease that does not pose an immediate threat to NBs, however, this risk should not be ignored at a later age, especially in women, when other cumulative risks are present. Routine screening for thrombophilic defects in women without previous pregnancy complications is not currently recommended. However, the prevention of placenta-mediated complications such as recurrent miscarriages, early and late-onset fetal growth restriction, and stillbirth remains a major and topical health problem[8] .

Bremme et al in observation among 38 women with TF and their newborns in Sweden found similar to our results higher age within mothers with TF and a higher proportion of operative delivery in the group with hemostasis disorders. From the NB group, 16% had intrauterine hypotrophy or were SGA. There is one stillbirth. As in our observed TF group, they also had only one patient with an adverse Apgar score at 5 min. The mean NB's weight of mothers with TF was marginally lower compared to the control group, similar to our results [15] .

A study conducted in Cuba among 62 pregnant women and their children showed no association of TF type and maternal age with NB weight, but the later the treatment for TF was initiated, the lower the body weight of NB was[21]. Intrauterine hypotrophy complicates up to 10% of pregnancies, representing a major cause of morbidity and mortality in early childhood. This percentage reaches 25 in third world countries[12]. After birth, newborns with intrauterine hypotrophy are at increased risk of hypoglycemia, hypothermia, hyperbilirubinemia, necrotizing enterocolitis, intraventricular hemorrhage, seizures, respiratory distress syndrome, sepsis and neonatal death in extreme cases. Predisposition to certain diseases also remains significant in adulthood, including cognitive or neurological impairment, as well as cardiovascular or endocrine disorders such as stroke, coronary artery disease, dyslipidemia or even diabetes mellitus[11][22].

The risk of thrombosis in NB born after 37 weeks is significantly lower than in premature babies, and the risk of thrombosis correlates with the degree of prematurity: thrombotic complications

reach their peak in the group of children born 22–27 weeks. A serious risk factor for neonatal thrombosis is the presence of maternal TF and genetic forms of thrombophilia in newborns. Maternal thrombophilia can lead to increased coagulation potential and prethrombotic conditions during pregnancy, causing thrombotic vasculopathy at the placenta level[23][24].

In Group A, we associate the low total platelet count with the high proportion of registered congenital infections, because IAI tend to lead to increased consumption of platelets [25]. The higher levels of hemoglobin and erythrocytes on the first postnatal day in Group A are probably related to the lower Apgar score and hypoxemia of the newborns. Polycythemia may be due not only to intrauterine hypotrophy. Due to decreased tissue oxygenation, increased production of erythropoietin by the kidney is followed by an increasing number of erythrocytes and raised fetal blood volume[26].

Limitations of the study

The usual problems discussed in women with thrombophilia and current pregnancy are the risks of birth to premature or hypotrophic children and the pathology that these newborns have. Our retrospective study is of a small group of term neonates who developed with well-controlled maternal thrombophilia. There is clearly a difference in the pathology of the early neonatal period of this group of children. To make a more complete assessment, larger-scale observations and over a longer period of time are needed.

Conclusion:

TF in pregnant women, even when adequate treatment is administered during pregnancy, is associated with increased morbidity in their full-term NBs during the early neonatal period. This is manifested in a higher Apgar score, delayed cardiopulmonary adaptation, and a higher incidence of infectious pathology. They, in turn, require additional therapeutic measures in newborns and are associated with a prolonged hospital stay.

Acknowledgments:

References:

[1] Abildgaard U. Olav Egeberg--arvelig antitrombinmangel og trombofili [Olav Egeberg--hereditary antithrombin deficiency and thrombophilia]. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke* 2001;121(5): 604-5

[2] Fernández Arias M, Mazarico E, Gonzalez A, et al. Genetic risk assessment of thrombophilia in patients with adverse obstetric outcomes. *PLoS One*. 2019;14(2): e0211114.

[3] Arachchillage DRJ, Makris M. Inherited thrombophilia and pregnancy complications: should we test? *Seminars in Thrombosis and Hemostasis* 2019;45(1): e1.

[4] Dugalic S, Petronijevic M, Stefanovic A, et al. Perinatal complications related to inherited thrombophilia: review of evidence in different regions of the world. *The Journal of Maternal-Fetal & Neonatal Medicine* 2021;34(15): 2567-2576.

[5] Louis-Jacques AF, Maggio L, Romero ST. Prenatal screening for thrombophilias: indications and controversies, an Update. *Clinics in Laboratory Medicine* 2016;36(2): 421–34

[6] Bitsadze V, Khizroeva J, Alexander M, Elalamy I. Venous thrombosis risk factors in pregnant women. *Journal of Perinatal Medicine*. 2022;50(5): 505-518.

[7] Samfireag M, Potre O, Potre C, et al. Maternal and Newborn Characteristics—A Comparison between Healthy and Thrombophilic Pregnancy. *Life*. 2023; 13(10): 2082.

[8] Simcox LE, Ormesher,L, Tower C, Greer IA. Thrombophilia and Pregnancy Complications. *International Journal of Molecular Sciences*. 2015; 16: 28418–28428.

[9] Dobbenga-Rhodes Y. Shedding Light on Inherited Thrombophilias: The Impact on Pregnancy. *Journal of Perinatal and Neonatal Nursing*. 2016;30: 36–44.

[10] Dusek J, Nedvedova L, Scheinost O et al. Frequency of Leiden Mutation in Newborns with Birth Weight below 1500 g. *Healthcare* 2022;10: 865.

[11] Mihai B-M, Salmen T, Cioca A-M, Bohîlţea R-E. The Proper Diagnosis of Thrombophilic Status in Preventing Fetal

Growth Restriction. *Diagnostics*. 2023; 13(3): 512

[12] Vicoveanu P, Vasilache IA, Scripcariu IS et al. Feed-Forward Back Propagation Network for the Prediction of Small for Gestational Age Newborns in a Cohort of Pregnant Patients with Thrombophilia. *Diagnostics*. 2022;12(4):1009.

[13] Tsikouras P, Deftereou T, Anthoulaki X et al. Thrombophilia and Pregnancy: Diagnosis and Management [Internet]. *Embolic Diseases - Evolving Diagnostic and Management Approaches*. IntechOpen; 2020.

[14] Alecsandru D, Klimczak AM, Velasco JAG, Pirtea P, Franasiak JM. Immunologic causes and thrombophilia in recurrent pregnancy loss. *Fertility and sterility* 2021;115(3), 561-566.

[15] Bremme K, Lannemyr A, Tyni L, Chaireti R. Obstetric and neonatal outcomes in pregnant women treated with high-dose thromboprophylaxis: a retrospective, single-center study. *Journal of Maternal-Fetal & Neonatal Medicine*. 2021;34(10):1641-1644.

[16] Wahdan Y, Shalash A, Almassri T et al. The Evaluation of Behavioral and Medical Outcomes of Infants When Low Molecular Weight Heparin is Used in Pregnancy: Systematic Review. *SSRN* 4664313.

[17] Boffa M-C, Lachassinne E, Boinot C, et al. European registry of babies born to mothers with antiphospholipid syndrome: a result update. *Lupus*. 2009;18(10):900-904

[18] Mekinian A, Lachassinne E, Nicaise-Roland P et al. European registry of babies born to mothers with antiphospholipid syndrome. *Annals of the rheumatic diseases* 2013;72(2): 217-22.

[19] International Statistical Classification of Diseases and Related Health Problems. https://www.who.int/standards/classifications/classification-of-diseases

[20] Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. *The Journal of Pediatrics*. 1991;119(3): 417–23.

[21] Castillo-González DC, Huerta-Perdomo S, Averhof-Hernández F, et al. Characterization of neonates of mothers with hypercoagulability in thromboprophylactic regimen. *Revista Cubana de Hematología, Inmunología y Hemoterapia* 2019;35(4): 1-13.

[22] Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). *American Journal of Obstetrics & Gynecology*. 2020;223(4):B2-B17

[23] Makatsariya A, Bitsadze V, Khizroeva J, et al. Neonatal thrombosis. *Journal of Maternal-Fetal & Neonatal Medicine*. 2022;35(6):1169-1177.

[24] Demirel G, Celik I H, Zergeroglu S, Erdeve O, Dilmen U. Neonatal outcome of the pregnancies associated with placental villous thrombosis – thrombophilic status of the mothers and the infants. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2012;25(11): 2225–2229.

[25] Esiaba I, Mousselli I, Faison GM, Angeles DM, Boskovic DS. Platelets in the Newborn. Neonatal Med, 2019, 10: 1-31.

[26] Brucknerová I, Ujházy E, Dubovický M, Mach M. Early assessment of the severity of asphyxia in term newborns using parameters of blood count. *Interdisciplinary toxicology*. 2008. 1.3-4: 211-213.