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RESEARCH ARTICLE

The role of active perinatology in the prevention of spontaneous loss of conceptus and birth rate drop

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Summary

Introduction: Modern perinatology demands continuous improvement of doctrines and protocols. The loss of conceptus is unforgivable when the possibility to sustain such pregnancy would elevate the level of birth rate that we aspire as a society. The aim of this study was to show the role of low molecular weight heparin in prevention of poor pregnancy outcomes.

Methods: The study included all women with inherited thrombophilia referred to the Clinic for Gynecology and Obstetrics of the Clinical Centre of Serbia between 2016 and 2018 who were followed-up until delivery. The patients were divided into two groups.

Results: The total number of 180 patients were pregnant for the first time, while 178 patients had had previous pregnancies. In 153 out of 178 patients, the previous pregnancy had poor outcome. 12 patients with AC therapy had FMU in previous pregnancies, 49 patients had missed abortion, 54 patients had second trimester miscarriage, 4 patients had both FMU and missed abortion, 9 patients had missed abortion and second trimester miscarriage while one patient had FMU, missed abortion and second trimester miscarriage. In previous pregnancies, 92 babies were born out of 313 pregnancies while in the current pregnancies treated with therapy there were 173 babies from 151 pregnancies.

Conclusions: Patients with anticoagulant treatment in current pregnancy have had significant burden of previous pregnancy losses.

Keywords: pregnancy, pregnancy loss, inherited thrombophilia.

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INTRODUCTION

Modern perinatology demands continuous improvement of doctrines and protocols. The loss of conceptus is unforgivable when a possibility to sustain such pregnancy would elevate the level of birth rate that we as a society wish for.

The recommendations for testing to congenital thrombophilia and antiphospholipid syndrome given by the Clinic for Hematology of the Clinical Centre of Serbia state that congenital thrombophilia is an increased tendency for thrombosis as a result of gene mutation for different factors in the haemostatic syndrome (1).

Within the frames of perinatology, at the moment there is no absolute consensus for testing against congenital thrombophilia. Testing is recommended only for individuals with a previous diagnosis of deep venous thrombosis and venous thromboembolism (VTE) which represent the leading causes of mortality in women (2).

Recently, the indications have been broadened to existing obstetrics history (habitual miscarriages in the second trimester and sudden fetal death). We are striving to improve the process of protocols modernization by scientifically proven data (3–6).

Prompted by obvious birth rate drop, we have analyzed publicly available data (the Institute of Public Health of Serbia) in pre-COVID period. These data show the difference between 2016 and 2017: the number of live births 35,047 vs. 35,564; the number of still births 222 vs. 209; the number of deaths 48,037 vs. 49,402, the number of live births -12,963 vs. -13,838.

If we excluded the population that migrated and delivered in Serbia and concentrated only to the data on population inhabiting Serbia for a longer period of time, it would be possible to obtain even more statistically significant data (7).

The comparison between 2016 and 2017: stillbirths 151 vs. 182. The number of live births against still births per 1,000 people goes from 9.8 to 10. The birth rate per 1,000 people goes from 3.6 to 3.9.

METHODS

The study included all women with inherited thrombophilia referred to the Clinic for Gynecology and Obstetrics of the Clinical Centre of Serbia between 2016 and 2018 who were followed-up until delivery. The patients were divided into two groups. The first group included 137 pregnant women with one or more forms of congenital thrombophilia and no use of anticoagulant therapy. The second group included 221 pregnant patients with one or more forms of thrombophilia with administered anticoagulant therapy. The following was examined: demographics, family and personal history, presence of pregnancy complications, type and presence of thrombophilia, perinatal outcome of previous pregnancies, type of anticoagulant therapy, mode of delivery in previous and current pregnancies, laboratory and sonography parameters and perinatal outcome (newborn body weight and Apgar Score at birth). The following pregnancy complications were analyzed: miscarriage (early – up to the 10^{th} week of gestation and late – between the 10^{th} and the 20^{th} week of gestation), preterm deliveries (between the 20^{th} and the 37^{th} week of gestation), intrauterine growth restriction (IUGR), intrauterine fetal death, preeclampsia, placental abruption and deep venous thrombosis.

Exclusion criteria were the following: patient's age over 40, egg donation, joined presence of both congenital and acquired thrombophilia, congenital uterine body anomalies, conditions after gynecological surgeries, perinatal infections (TORCH – toxoplasmosis and others such as syphilis, varicella, mumps, parvovirus and HIV, rubella, cytomegalovirus, herpes simplex), type I diabetes mellitus, chronic hypertension, kidney transplantation, morbid obesity (BMI>40), the use of anticoagulant therapy for other comorbidities, abnormal screening tests in the first trimester (Double and/or Triple test) and pathological karyotype, confirmed fetal anomalies, as well as central placenta praevia and pathological degree of placental nidation (suspected accrete, increta and percreta).

The study was approved by the Ethic Committee (decision No 2650/IV-13) of the Faculty of Medicine, University of Belgrade. A written informed consent was obtained from all study participants.

STATISTICAL ANALYSIS

Descriptive statistics were reported as mean with standard deviation for numerical data. Numbers with percentages were used for categorical data. Differences between groups were analyzed using Pearson Chi Squared test for categorical variables. All tests were 2-tailed. $P<0.05$ was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS, version 21).

RESULTS

The study included 358 pregnant patients with diagnosed trombophilia and mean age 33.67±4.01. The characteristics of the study group are presented elsewhere (6)previous studies regarding LMWH prophylaxis for APO in women with inherited thrombophilia were performed in high risk patients with previous adverse health outcomes in medical, family and/or obstetric history. Therefore, the aim of this study was to investigate the effects of LMWH prophylaxis on pregnancy outcomes in women with inherited thrombophilias regardless of the presence of previous adverse health outcomes in medi-

cal, family, and obstetric history.Prospective analytical cohort study included all referred women with inherited thrombophilia between 11 and 15 weeks of gestation and followed-up to delivery. Patients were allocated in group with LWMH prophylaxis (study group.The total number of 180 patients had their first pregnancy while 178 patients had had previous pregnancies. In 153 out of 178 patients, the previous pregnancy had poor outcome. In the total sample of patients, significantly higher number of patients had poor outcomes in previous pregnancies (χ^2 =36.888; p<0.001). A total number of 129 out of 151 patients with anticoagulant therapy had poor previous pregnancy outcome.

Table 1. Previous pregnancies

Outcome	Total	With AC therapy
Delivery	25 (14.0%)	22 (14.6%)
Poor outcome	153 (86.0%)	129 (85.4%)
Total	178 (100%)	151 (100%)

When comparing previous pregnancies with current pregnancy, 129 out of 151 patients with AC therapy (85.4%) had poor outcomes in the past while they were not present in the current pregnancy. 12 patients with AC therapy had FMU in previous pregnancies, 49 patients had missed abortion, 54 patients had second trimester miscarriage, 4 patients had both FMU and missed abortion, 9 patients had missed abortion and second trimester miscarriage while one patient had FMU, missed abortion and second trimester miscarriage **(Table 2)**.

Table 2. Poor outcomes in previous and current pregnancy, with AC therapy(n=129)

	Past	Current
FMU	12 (9.3%)	0 (0%)
Missed abortion	49 (38.0%)	0 (0%)
Second trimester mis.	54 (41.9%)	0 (0%)
FMU+Missed abortion	4 (3.1%)	0 (0%)
Misc.+Missed	9 (7.0%)	0 (0%)
FMU,Missed ab.,Misc.	1 (0.8%)	0 (0%)

The total number of previous pregnancies was 379 (313 in the group of patients with AC therapy. The total number of losses in the past was 273 (19 FMU, 107 missed abortions, and 147 second trimester miscarriages). The total number of 73 patients had one loss, 51 patients had two losses, 20 patients had three losses, and 7 patients had four losses, while there were 2 patients with 5 previous pregnancy losses. Poor outcomes were statistically significantly more common (72%) in previous pregnancies (χ^2 =73.586; p<0.001). The pregnant patients in the AC therapy group had a total number of 223 (71.2%) poor outcomes in previous pregnancies.

The pregnant patients that received AC therapy had 18 FMU in previous pregnancies(8.1%), 205 missed abortions and miscarriages(91.9%) which was not present in their current pregnancies. In previous pregnancies, 92 babies were born out of 313 pregnancies while in the current pregnancies, where patients were treated, there were 173 babies from 151 pregnancies.

Table 3. Previous pregnancies outcome

Outcome	Total	With AC therapy
Delivery	106 (28%)	90 (28.8%)
Poor outcome	273 (72%)	223 (71.2%)
Total	379 (100%)	313 (100%)

Table 3. Poor outcomes in pregnant patients with therapy, previous and current pregnancy

	Past (n=223)	Current (n=151)
FMU	18 (8.1%)	0 (0%)
Missed ab., miscarriage	205 (91.9%)	0 (0%)

DISCUSSION

In the group of patients where we administered AC therapy for pregnancies burdened by congenital thrombophilia, almost half of the patients could already have had offspring. Half of the patients previously lost a conceptus, had a handicap. The society missed a possible birth rate increase.

If we analyze the available data from the Institute of Public Health of Serbia, by observing birth rate and mortality on the territory of Belgrade only in the past two years, the trend shows drama and a decrease in population. The quality of newborn population is a subject per se, i.e. fetal programming and prevention of adult age diseases through appropriate monitoring of the course and outcome of pregnancy.

Comparing the period of 2016 to the period of 2017, the ratio is as follows: live births 17,967 to 18,000 migrations; still births 88 to 90; deaths 20,803 to 21,768. Birth rate ranging from -2,836 to -3,768. Newborn deaths ranging from 96 to 73. Birth rate in 1,000 people ranging from -1.7 to -2.2.

If we compare the number of deliveries in 2016 and 2017 at the Clinic of Gynecology and Obstetrics of the Clinical Centre of Serbia (Visegradska) only, we come up with the following numbers: in 2016 there were 3,999 vaginal deliveries and 2,298 Cesarean Sections (the total in 2016 – 6,288); in 2017, there were 3,691 vaginal deliveries and 2,230 Cesarean Sections (the total in 2017 – 5,921). In 2018, there were 5,602 deliveries – 3,576 vaginal deliveries and 2,026 Cesarean Sections.

By observing the parameters related to the incidence of diagnosed thrombophilia in women and the effects of administered anticoagulant therapy, we came to an astonishing number of lost conceptuses. Possibilities of increasing birth rate by timely diagnosis of thrombophilia as a possible risk factor for the loss of conceptus and therefore lack of offspring are obvious, both in quantita-

tive and statistical analyses.

The birth rate is evidently dropping. When encouraging an increase in birth rate, not only quantity is important, but quality as well if we want healthy offspring. By losing a conceptus, birth rate decreases. Morbidity (personal, physical and emotional) is increased, as well as social morbidity in relation to family as a societal entity and in relation to the society as a whole.

When observed from the financial aspect, the cost of the loss of potential offspring is high, together with the costs of treatment and late diagnosis. The costs of healthcare system and the burden on it are unreasonably pilling.

Such a stand does not lead to the other extreme that includes unnecessary diagnostic procedures. There are aspects related to sub-specialist perinatology knowledge that are indicators of a possible need for diagnosing congenital thrombophilia and the therapy of certain forms of thrombophilia.

We know that the basic aspect of placental function is its size, but also the intensity of nidation and vascular connection of uteroplacental unit. The size of placenta is determined during the first trimester when definitive chorioallantoic placenta and membranes (chorion leave) are separated before the start of uteroplacental blood flow. By recognizing the phenomenon of chorion regression, with the use of ultrasonography in the second trimester, severe perinatal outcome and thrombotic placental damage are anticipated. Once the definite placenta is formed, invasive extravillous trophoblastic cells transform the spiral arteries in order to establish low-resistance uteroplacental circulation or more efficient flow. This step in the development may be diagnosed by Doppler examination of uterine artery and is the main risk factor for inadequate placentation. In one large study, Franco et al found histological evidence of uteroplacental (maternal) vascular pathology superimposed to placental infarction in 78.7% of cases(8).

From the physiological point of view, placenta has the auto-anticoagulation ability. External area of placental villi is covered by special syncitiotrophoblast layer which is actively involved in the local hemostasis. Decreased placental expression of otherwise physiological glial cells type 1 and poor development of placental villi with defect syncytialization are key characteristics of placental disorder. Invasive extravillous trophoblast normally excludes maternal T-cells by secreting an enzyme indoleamin-2,3-dioxigenase which catalyzes tryptophan. Poor trophoblast invasion and differentiation to secret indoleamin-2,3-dioxigenase or maternal immune overreaction which removes these cells by apoptosis, result in aberrant invasion of maternal T-cells. Maternal T-cells invasion, leading to vitilis, is a further example of abnormal placental development(8).

Iserman et al. conducted a study where they observed animal model pregnancies, pointing to the role of thrombomodulin in the growth and survival of trophoblast. By studying mice with impaired coding of thrombomodulin gene, at the fetal-maternal junction, they observed the thrombomodulin deficit related to embryo abortion. This study showed the basic role of thrombomodulin in the growth and survival of trophoblast. At the feto-maternal junction, thrombomodulin deficit stimulates procoagulant cascade, therefore prompting mass cell death of trophoblast and leading to trophoblast cell growth cessation(9).

In order to properly understand the establishing of correct flow in the uteroplacental unit, the fact that placenta itself has procoagulant characteristics, expressed in trophoblast cells, should not be neglected (10).

However, there are also inhibitory mechanisms, such as endothelial protein C receptor, thrombomodulin, annexin V and tissue coagulation factor inhibitor, which increase starting from the 10th week of gestation (11–14).

According to the literature data, congenital thrombophilia affects 3-11% of the population. Several forms of mutations have been established, classified into most common groups (15–28).

Factor V Leiden (FVL)

1. Factor II (prothrombin) G20210A
2. Protein C deficiency
3. Protein S deficiency
4. Antithrombin deficiency
5. Dysfibrinogenemia
6. Hyperhomocysteinemia, methylenetetrahydrofolate reductase gene, MTHFR 677 T
7. PAI-1 and angiotensin converting enzyme (ACE)

Placental insufficiency is considered to be the cause of the following perinatal complications in pregnancy: preeclampsia, fetal growth restriction (FGR) and still birth. The most common placental lesion is the infarction of placental villi. The frequency of infarction incidence is positively correlated to the perinatological tests for monitoring of uteroplacental circulation, and successive pathologies of the flow through fetal body. Such observations of clinicians perinatologists, as a part of observational studies, prompted the hypothesis and led to testing for thrombophilia in mothers(8).

Thus, it was established that pregnancies destined to end before the 32nd week of gestation with severe preeclampsia or FGR often had abnormal test results for placental function observed between the 12th and the 22nd week of gestation. However, this included false positive results of maternal serum for Down syndrome, smaller placental size and decreased uteroplacental blood flow. In case of two or more abnormal test categories of placental function, placental infarction may be predicted with high certainty. However, maternal thrombophilia was proven as an unusual finding in patients with documented thrombotic placental disorder (8). It is important to mention that the most precise tests and biological credibility of such findings were based primarily on animal models (9).

Adequate placental circulation is necessary for the successful development of pregnancy. Inadequate placental perfusion in conditions surpassing physiological level of coagulability leads to microthrombosis forming and decreases the possibility of trophoblast invasion. Thus, primarily established inadequate perfusion is superimposed to incidence of chronic hypoxia. Clinical manifestations of pathological conditions such as fetal growth restriction, intrauterine fetal death, second and third trimester pregnancy loss, placental abruption and preeclampsia, add to the fact that placental invasion was limited through the process of hypercoagulability surpassing the level of tolerance.

CURRENT GUIDELINES

The lack of strong and consistent evidence base for clinical guidelines has led to different recommendations for clinicians. Regarding thromboprophylaxis, the recommendations of the American College of Chest Physicians (ACCP), compared to recommendations of the Royal College of Obstetricians and Gynecologists (RCOG), do not have absolute consensus(29,30).

Considering the weak correlation between the most common types of thrombophilia and VTE, the incidence of VTE diagnosis in family history has been monitored. ACCP recommendations suggest LMWH prophylaxis in two groups of women: 1) without family history of VTE who are either homozygote FVL or prothrombin gene mutation; and 2) women with family history of VTE in combination with any other congenital thrombophilia.

ACCP guidelines do not recommend prophylactic use of LMWH for those with congenital thrombophilia and with the absence of previous pregnancy complications. This is justified by the lack of evidence to support outcome improvement with LMWH in women with congenital thrombophilia and recurrent pregnancy loss. However, ACCP recommends aspirin for women who are under high risk of developing preeclampsia, regardless their thrombophilia history. This is in accordance with RCOG and supported by a strong evidence base.

Similarly, RCOG guidelines recommend considering antenatal prophylaxis with LMWH in patients who are homozygote FVL and prothrombin G20210A. These guidelines also recommend prophylactic LMWH in women with antithrombin deficiency, proten C or protein S deficiency, despite the lack of family/personal history of VTE, which differs from ACCP recommendations. RCOG further stratifies the risk as per pragmatic accumulation of the risk factors: if FVL heterozygote or prothrombin gene mutation is present with two or three other risk factors, or there is a complex heterozygote, prophylactic LMWH may be administered even before delivery. The other difference is that RCOG guidelines applies stratification of risks to further difference in dosing, pointing to the fact that women with antithrombin deficit and previous VTE should have 50-100% dose of therapy antenatally and 6 weeks postnatally (9).The studies of Gris et al. (31,32)we investigated the effectiveness of enoxaparin, a low-molecular-weight heparin, in preventing these complications. Between January 2000 and January 2009, 160 women from the NOHA First cohort, with previous abruptio placentae but no foetal loss during their first pregnancy and negative for antiphospholipid antibodies, were randomised to either a prophylactic daily dose of enoxaparin starting from the positive pregnancy test (n=80 on the prevention of negative outcomes of pregnancies in women with history of preeclampsia and abruption, treated by LMWH, showed a significant benefit.

ACCP and RCOG are the only two examples of internationally available guidelines. The variations between these two guidelines are only examples of the lack of adequate evidence base

CONCLUSIONS

Previous pregnancy poor outcomes were statistically significantly more common when anticoagulant therapy was not administered (72%).

Pregnancy complications such as preeclampsia, hypertension, placental abruption, and thrombocytopenia were more common in pregnant patients without the anticoagulant therapy, but with no statistical significance.

More pregnancies were delivered by means of surgery, especially in patients with previous pregnancy poor outcomes. The patients with anticoagulant therapy had vaginal deliveries more often, with statistical significance, compared to a higher number of Cesarean Sections in the group without the therapy.

REFERENCES:

1. Републичка стручна комисија за израду и имплементацију водича добре клиничке праксе. Национални водић добре клиничке праксе. Акутна и хронична обољења вена. 2013.
2. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk J, et al. Saving Lives , Improving Mothers ' Care. Oxford; 2014.
3. Dugalic S, Petronijevic M, Stefanovic A, Stefanovic K, Perovic M, Pantic I, et al. Perinatal complications related to inherited thrombophilia: review of evidence in different regions of the world. J Matern \& Neonatal Med [Internet]. 2021;34(15):2567–76. Available from: https://doi.org/10.1080/14767058.2019.1669017
4. Gojnic MG, Dugalic S V, Stefanovic AO, Stefanovic K V, Petronijevic MA, Petronijevic SMV, et al. Combined hereditary thrombophilias are responsible for poor placental vascularization development and low molecular weight heparins (LMWH) prevent adverse pregnancy outcomes in these patients. J Matern \& Neonatal Med [Internet].

2020;0(0):1–8. Available from: https://doi.org/10.1080/14767058.2020.1849116

5. Dugalić S, Petronijevic M, Stefanovic A, Jeremic K, Petronijevic SV, Soldatovic I, et al. The association between IUGR and maternal inherited thrombophilias: A case-control study. Medicine (Baltimore). 2018;97(41).
6. Dugalic S, Petronijevic M, Stefanovic A, Stefanovic K, Petronijevic SV, Stanisavljevic D, et al. Comparison of 2 approaches in management of pregnant women with inherited thrombophilias: Prospective analytical cohort study. Medicine (Baltimore). 2019 Aug;98(34):e16883.
7. Републички завод за статистику. СРБ 189 СН 60 090721 Статистика становништва Унутрашње миграције, 2020 . Београд; 2021.
8. Franco C, Walker M, Robertson J, Fitzgerald B, Keating S, McLeod A, et al. Placental infarction and thrombophilia. Obstet Gynecol. 2011 Apr;117(4):929–34.
9. Ormesher L, Simcox L, Tower C, Greer IA. Management of inherited thrombophilia in pregnancy. Womens Health (Lond Engl). 2016 Jul;12(4):433–41.
10. Aharon A, Brenner B, Katz T, Miyagi Y, Lanir N. Tissue factor and tissue factor pathway inhibitor levels in trophoblast cells: implications for placental hemostasis. Thromb Haemost. 2004 Oct;92(4):776–86.
11. Greer IA, Aharon A, Brenner B, Gris J-C. Coagulation and placenta-mediated complications. Rambam Maimonides Med J. 2014 Oct;5(4):e0034.
12. Greer IA, Brenner B, Gris J-C. Antithrombotic treatment for pregnancy complications: which path for the journey to precision medicine? Br J Haematol. 2014 Jun;165(5):585–99.
13. Szecsi PB, Jørgensen M, Klajnbard A, Andersen MR, Colov NP, Stender S. Haemostatic reference intervals in pregnancy. Thromb Haemost. 2010 Apr;103(4):718–27.
14. Aharon A, Lanir N, Drugan A, Brenner B. Placental TFPI is decreased in gestational vascular complications and can be restored by maternal enoxaparin treatment [6]. J Thromb Haemost. 2005;3(10):2355–7.
15. Paidas MJ, Ku D-HW, Arkel YS. Screening and management of inherited thrombophilias in the setting of adverse pregnancy outcome. Clin Perinatol. 2004 Dec;31(4):783–805, vii.
16. Pabinger I, Nemes L, Rintelen C, Koder S, Lechler E, Loreth RM, et al. Pregnancy-associated risk for venous thromboembolism and pregnancy outcome in women homozygous for factor V Leiden. Hematol J Off J Eur Haematol Assoc. 2000;1(1):37–41.
17. Fatini C, Gensini F, Battaglini B, Prisco D, Cellai AP, Fedi S, et al. Angiotensin-converting enzyme DD genotype, angiotensin type 1 receptor CC genotype, and hyperhomocysteinemia increase first-trimester fetal-loss susceptibility. Blood Coagul fibrinolysis an Int J Haemost Thromb. 2000 Oct;11(7):657–62.
18. Buchholz T, Lohse P, Rogenhofer N, Kosian E, Pihusch R, Thaler CJ. Polymorphisms in the ACE and PAI-1 genes are associated with recurrent spontaneous miscarriages. Hum Reprod. 2003 Nov;18(11):2473–7.
19. Said JM, Tsui R, Borg AJ, Higgins JR, Moses EK, Walker SP, et al. The PAI-1 4G/5G polymorphism is not associated with an increased risk of adverse pregnancy outcome in asymptomatic nulliparous women. J Thromb Haemost. 2012 May;10(5):881–6.
20. Yang C, Fangfang W, Jie L, Yanlong Y, Jie W, Xuefei L, et al. Angiotensin-converting enzyme insertion/deletion (I/D) polymorphisms and recurrent pregnancy loss: a meta-analysis. J Assist Reprod Genet. 2012 Nov;29(11):1167–73.
21. Facchinetti F, Marozio L, Frusca T, Grandone E, Venturini P, Tiscia GL, et al. Maternal thrombophilia and the risk of recurrence of preeclampsia. Am J Obstet Gynecol [Internet]. 2009;200(1):46.e1-46.e5. Available from: http://dx.doi.org/10.1016/j.ajog.2008.07.032
22. Facco F, You W, Grobman W. Genetic Thrombophilias and Intrauterine. Obs Gynecol. 2009;113(6):1206–16.
23. Foka ZJ, Lambropoulos AF, Saravelos H, Karas GB, Karavida A, Agorastos T, et al. Factor V leiden and prothrombin G20210A mutations, but not methylenetetrahydrofolate reductase C677T, are associated with recurrent miscarriages. Hum Reprod. 2000 Feb;15(2):458–62.
24. Bezemer ID, Doggen CJM, Vos HL, Rosendaal FR. No association between the common MTHFR 677C->T polymorphism and venous thrombosis: results from the MEGA study. Arch Intern Med. 2007 Mar;167(5):497–501.
25. Kosmas IP, Tatsioni A, Ioannidis JPA. Association of C677T polymorphism in the methylenetetrahydrofolate reductase gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. J Hypertens. 2004 Sep;22(9):1655–62.
26. Chen Z, Xu F, Wei Y, Liu F, Qi H. Angiotensin converting enzyme insertion/deletion polymorphism and risk of pregnancy hypertensive disorders: a meta-analysis. J Renin Angiotensin Aldosterone Syst. 2012 Mar;13(1):184–95.
27. Wu X, Zhao L, Zhu H, He D, Tang W, Luo Y. Association between the MTHFR C677T polymorphism and recurrent pregnancy loss: a meta-analysis. Genet Test Mol Biomarkers. 2012 Jul;16(7):806–11.
28. Subrt I, Ulcova-Gallova Z, Cerna M, Hejnalova M, Slovanova J, Bibkova K, et al. Recurrent pregnancy loss, plasminogen activator inhibitor-1 (-675) 4G/5G polymorphism and antiphospholipid antibodies in Czech women. Am J Reprod Immunol. 2013 Jul;70(1):54–8.
29. Goecke T, Voigt F, Rath W. Thromboprophylaxis following cesarean section–a nation-wide survey from Germany. J Matern Neonatal Med. 2020;33(14):2359–65.
30. ACOG Practice Bulletin No. 197 Clinical Management Guidelines for Inherited Thrombophilias in Pregnancy. ACOG Pract Bull. 2018;132(1):e18–34.
31. Gris J-C, Chauleur C, Faillie J-L, Baer G, Marès P, Fabbro-Peray P, et al. Enoxaparin for the secondary prevention of placental vascular complications in women with abruptio placentae. The pilot randomised controlled NOH-AP trial. Thromb Haemost. 2010 Oct;104(4):771–9.
32. Gris J-C, Chauleur C, Molinari N, Marès P, Fabbro-Peray P, Quéré I, et al. Addition of enoxaparin to aspirin for the secondary prevention of placental vascular complications in women with severe pre-eclampsia. The pilot randomised controlled NOH-PE trial. Thromb Haemost. 2011 Dec;106(6):1053–61.

ULOGA AKTIVNE PERINATOLOGIJE U PREVENCIJI NEPOTREBNOG GUBITKA KONCEPCIJE I PADA NATALITETA

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Sažetak

Uvod: Savremena perinatologija zahteva kontinuirano unapređenje doktrina i protokola. Gubitak trudnoće se smatra neoprostivim, a mogućnost za održavanje rizičnih trudnoća bi mogao da utičena povećanje stope rađanja, kojoj težimo kao društvo. Cilj ovog istraživanja bio je da se prikaže uloga niskomolekularnog heparina u prevenciji loših ishoda trudnoće.

Metod: U istraživanje su uključene sve **žene** sa naslednim trombofilijama upućene na Kliniku za Ginekologiju i akušerstvo, Kliničkog Centra Srbije između 2016 i 2018. godine, koje su praćene do porođaja. Pacijentkinje su podeljene u dve grupe.

Rezultati: Ukupno je 180 pacijentkinja bilo u svojoj prvoj trudnoći, dok je njih 178 imalo prethodne trudnoće. Ukupno je 153 od 178 njih imalo gubitak prethodne trudnoće. 12 pacijentkinja sa antikoagulantnom terapijom imalo je FMU, 49 je imalo missed pobačaj, 54 je imalo spontani pobačaj u drugom trimestru, 4 pacijentkinje sui male i FMU i missed, 9 njih je imalo missed i spontani pobačaj u drugom trimestru, jedna pacijentkinja je imala sva tri nepovoljna ishoda. U svim prethodnim trudnoćama, ukupno je rođeno 92 bebe iz 313 trudnoća, dok je sa antikoagulantnom terpaijom rođeno 173 bebe iz 151 trudnoće.

Zaključak: Pacijenkinje sa antikoagulantnom terapijom imaju značajno visoko opterećenje sa prethodnim gubicima trudnoće.

Ključne reči: trudnoća; gubitak trudnoće; nasledne trombofilije.

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