



СПИСАНИЕ НА МАКЕДОНСКОТО ЛЕКАРСКО ДРУШТВО
Мак. мед. преглед, 2024; 78(1)

JOURNAL OF THE MACEDONIAN MEDICAL ASSOCIATION
Mac. Med. Preview, 2024; 78(1)

UDK: 61+061.231=866=20

CODEN: MKMPA3

ISSN: 0025-1097

**МАКЕДОНСКИ
МЕДИЦИНСКИ
ПРЕГЛЕД**

**MACEDONIAN
MEDICAL
REVIEW**

Основано 1946
Founded 1946

1/24

MMP

Мак Мед Преглед

Списание на Македонското
лекарско друштво

Journal of the Macedonian Medical
Association

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tel. 02/3162 577

www.mld.org.mk / mld@unet.com.mk

Жиро сметка / Bank Account

300000000211884 - Komercijalna banka Skopje

Печати: Бранко Гапо графичко производство - Скопје

Македонски медицински преглед се печати три пати годишно. Претплатата за списанието изнесува
10 евра за лекари, 50 ера за установа, странство 80 евра.

Основано 1946

Founded 1946

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UTERINE ARTERY DOPPLER AND SERUM LEVEL OF IMMUNOBIOMARKERS IN PREECLAMPSIA - OUR EXPERIENCE

ДОПЛЕР НА УТЕРИНА АРТЕРИЈА И СЕРУМСКО НИВО НА ИМУНИТЕ БИОМАРКЕРИ КАЈ ПРЕЕКЛАМПСИЈА - НАШЕ ИСКУСТВО

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Abstract

Introduction. Important mechanisms are known to be involved in the immunomodulatory pathways which are crucial for maintaining an adequate utero-placental circulation in pregnancy. Its disbalance brings to impaired tolerance, which leads to inflammation and autoimmune processes in preeclampsia.

Aim. The aim of this study was to find if inadequate uteroplacental hemodynamic was associated with improper fetomaternal immune adaptation. The risk of developing preeclampsia can be predicted by combining use of uterine artery flow and cytokine values. The aim was to show their combination as a predictive indicator of preeclampsia in the second trimester of pregnancy.

Methods. This study enrolled 96 pregnant patients in the second trimester (patients were between the 14th and 20th gestational weeks). Their history data, routine foetal ultrasound, bilateral uterine artery Doppler ultrasound and cytokines were evaluated. All patients were followed up till the end of pregnancy. Half of the pregnant women consisted the study group (N=48), which had presence of notch of the uterine artery. In the control group (N=48), there was an absence of uterine artery notch. In all patients, Doppler of the uterine artery, pulsatility index (PI) and resistance index (RI) were made and determined. The pro-inflammatory cytokines (TNF- α , IL-1 α , IL-2 and IL-6) and anti-inflammatory cytokines (IL-4 and IL-10) from patient's serum were analyzed.

Results and Discussion. In the study group (N=48), 32 patients had changes in the cytokine serum levels. Increased pro-inflammatory biomarkers (IL-6, TNF- α , IL-1 α) were with sensitivity of 78 to 91.2%. According to this, high predictive value was found. Of these 32 patients, 21 developed preeclampsia. When the sensitivity of pro- and anti-inflammatory biomarkers together with the uterine artery Doppler ultrasound was

combined, a sensitivity resulted in 81.5%. Multivariate regression analysis detected that IL-6 was the most significant predictive parameter. This result is similar to that presented in the study by Teran and Hentschke *et al.*

Conclusion. Using predictive tests is important to detect undeveloped preeclampsia in a timely manner that would prevent possible developmental complications. After abnormal Doppler results, cytokines should be investigated as a predictive method.

Keywords: preeclampsia, cytokines, immunobiomarkers, pregnancy

Анстракт

Вовед. Важни механизми се вклучени во имуномодулаторните патишта, што е од клучно значење за одржување на адекватна утеро-плацентарна циркулација во бременоста. Нивниот дисбаланс доведува до нарушена толеранција, што доведува до инфламација и автоимуни процеси кај прееклампијата.

Цел. Целта на оваа студија е да открие дали несоодветната утеро-плацентарна хемодинамика е поврзана со неправилна фетоматернална имунолошка адаптација. Ризикот од развој на прееклампија може да се предвиди со комбинирање на употребата на протоколот на утерината артерија и вредностите на цитокините. Целта е да се прикаже нивната комбинација како предиктивен индикатор како ризик за прееклампија во вториот триместар од бременоста.

Методи. Оваа студија опфати 96 бремени пациентки во вториот триместар (пациентките беа помеѓу 14 и 20 гестациска недела). Беа евалуирани податоците од нивната историја, рутински ултразвук на фетусот, билатералниот доплер на утерината артерија и вредностите на цитокините. Сите пациентки биле следени до крајот на бременоста. Кај сите пациентки беа вклучени Доплер на утерината артерија, индекс на пулсатилност (PI) и резистенс индекс (RI). Половина од трудниците кои ја сочинуваат испиту-

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ваната група (N=48) имаа присуство на notch на утерината артерија. Кај пациентките од контролната група (N=48) имаше отсуство на notch на утерината артерија. Пронинфламаторните цитокини (TNF- α , IL-1 α , IL-2 и IL-6) и антиинфламаторните цитокини (IL-4 и IL-10) беа анализирани од серумот на пациентките.

Резултати и дискусија. Во испитуваната група (N=48), 32 пациентки имале промени во серумските вредности на цитокините. Зголемените пронинфламаторни биомаркери (IL-6, TNF- α , IL-1 α) беа со сензитивност од 78 до 91,2%, резултат со висока предиктивна вредност. Од нив, 21 развија прееклампија. Кога сензитивноста на про и антиинфламаторните биомаркери заедно со утериниот артериски Доплер беше комбинирана, сензитивноста резултираше со 81,5%. Од мултиваријатната регресиона анализа откриено е дека IL-6 е најзначајниот параметар за предикција. Овој резултат е сличен на студијата на Теран и Хенчке и колегите.

Заклучок. Користењето на предиктивни тестови е важно за навремено откривање на неразвиена прееклампија што би ги спречило можните развојни компликации. По абнормални Доплерови резултати, вредностите на цитокините треба да се испитаат како метод за предвидување.

Клучни зборови: прееклампија, цитокини, имунобиомаркери, бременост

Introduction

Maternal immunological tolerance in pregnancy towards the semi-allogenic fetus is crucial for maintaining a normal pregnancy. Immune imbalance may lead to a higher risk of developing pregnancy complications such as preeclampsia. Preeclampsia is a multisystem disorder that occurs in 3 to 7% of pregnancies [1], and it is the most common cause of maternal and perinatal morbidity and mortality worldwide. According to American College of Obstetricians and Gynecologists (ACOG) [2], preeclampsia is defined as hypertensive disorder after 20 gestational weeks with presence of proteinuria at previously normotensive women, or absence of proteinuria but with other clinical manifestations expressed. There are several important mechanisms known that are involved as immunogenic and immunomodulatory pathways crucial for maintaining balance, and their loss leads to weakened tolerance, strong inflammation and autoimmunity, thus describing preeclampsia [3].

The vascular layers of the myometrium are properly invaded by the extravillous trophoblast to precede uterine spiral artery remodulation. The process is dependent on the balance in the produced immunological biomarkers from the deciduas. sFlt-1 (soluble fms-like

tyrosine kinase-1 factor) is expressed by the foetal tissue (trophoblast) and maternal tissue (endothelium) [4]. In preeclampsia, it is well known that exacerbation of clinical symptoms is a result of increased levels of pro-inflammatory and decreased level of anti-inflammatory cytokines [5].

The activity of the antigen presentation is weakened, therefore the immune tolerance towards the fetus is inadequate [6]. It is reflected in the shallow nidation of the extravillous trophoblast [7,8]. Because of the immunological changes during nidation at the level of extravillous trophoblast according to findings in the literature, there are antiangiogenic and pro-inflammatory factors released in circulation as a result of poor placental perfusion [9]. This imbalance leads to ischemia that leave consequences due to a multiorgan dysfunction [10].

IL-6 together with TNF- α stimulates the production of endothelin 1, reactive oxygen species and antibodies, like a ROS and AT1-AA 1, and IL-10 decreased values exacerbate hypertension and endothelial dysfunction [11]. Changes of uterine artery flow results in impaired uteroplacental circulation, an insufficient vascular arborisation in tertiary placental villi. The notch is examined, with a lower sensitivity value, but also PI and RI with higher sensitivity in relation to the prediction of vascular deviations.

According to literature data, preeclampsia which is developed before 34 g.w. is mostly dependent on the placental insufficiency, whereas after 34 weeks of gestation the maternal etiological factors are more expressed.

Aim

The aim of this study was to find if inadequate uteroplacental hemodynamic was associated with improper fetomaternal immune adaptation. The risk of developing preeclampsia can be predicted by combining the use of uterine artery flow and cytokine levels. The aim was to show their combination as a predictive indicator for preeclampsia in the second trimester of pregnancy.

Material and methods

Pregnant patients were recruited successively for this prospective cohort study. They were between 14 to 20 weeks of pregnancy, a total number of 96 patients. The study was performed at the University Clinic for Gynecology and Obstetrics in Skopje, RN Macedonia in a period of 12 months (the year 2019). An approved consent to participate in the study was signed by each patient. The study was approved by the Research Ethics Committee at the University Clinical Center in Skopje. This study enrolled 96 pregnant patients in the second trimester (patients were between the 14th and 20th gestational weeks). Their history data, routine foetal ultrasound, bilateral uterine artery Doppler ultrasound

and cytokines were evaluated. All patients were followed up till the end of pregnancy. Half of the pregnant women consisted the study group (N=48), which had presence of the uterine artery notch. In the control group (N=48), there was an absence of uterine artery notch. In all patients, Doppler of the uterine artery, pulsatility index (PI) and resistance index (RI) were made and determined. The pro-inflammatory cytokines (TNF- α , IL-1 α , IL-2 and IL-6) and anti-inflammatory cytokines (IL-4 and IL-10) from patient's serum were analysed.

Inclusion criteria were: single pregnancy, normotensive patient before pregnancy, live foetus - without malformation. Exclusion criteria were multiple pregnancy and stillbirth.

In patients, the data were obtained from patient history, family history and previous comorbidities. After an ultrasound assessment of the fetal biometry (14-20 g.w.) normal appearance of foetus was confirmed without ultrasound visible malformation, as well as placenta and amniotic fluid and umbilical cord. By Doppler method, Mindray Dc 7, Voluson 8, according to the ultrasound software, examined the flow of the uterine artery, where in addition to the presence of notch, the values of pulsatility (PI) and resistance (RI)

indexes were measured (according to the reference values of the ultrasound software). Serum levels of pro-inflammatory cytokines (TNF- α , IL-1 α , IL-2 and IL-6) and anti-inflammatory cytokines (IL-4 and IL-10) were examined using the ELISA methodology (Magnetix Luminex Assay multiplex kit) at the Institute of Immunobiology and Human Genetics of the Faculty of Medicine, Ss. Cyril Methodius University in Skopje. Patients were followed by ultrasound and other additional diagnostic procedures according to clinical protocol until delivery. The obtained data were statistically processed (STATISTICA 21, SSPS for Windows).

Results

Of a total number of 96 patients, regarding the history data (Table 1), statistical significance was found in the study group compared to the control group regarding history of previous pregnancy with preeclampsia, for was $p < 0.05$ (16.67% vs. 4.17%). In the study group, 27.08% were smokers versus 10.42% in the control group ($p = 0.03$).

Ne se točno numerirani tabelite, da se sredat

Table 1. Characteristics of patients

Characteristics of patients	Study group (48)	Control group (48)	P- value
Parity: nulliparous	28 (58.33%)	21 (43.75%)	0.15
Multiparous	20 (41.67%)	27 (56.25%)	0.15
Diabetes	6 (12.50%)	3 (6.25%)	0.29
Smokers	13 (27.08%)	5 (10.42%)	0.03
Previous pregnancy with PE	8 (16.67%)	2 (4.17%)	0.04
BMI	24.5	22.2	0.56
Systemic lupus erythematosus (SLE)	2 (4.17%)	0	0.15
Morbus von Willebrand	2 (4.17%)	0	0.15
Family history of PE	7 (14.58%)	2 (4.17%)	0.08

Regarding the results of the flow indexes, a significant result was obtained in terms of RI and PI values between the two groups for $p = 0.005$ (Table 2). The mean PI value in the study group was 1.95, and 1.43 in

the control group, showing a statistical significance. The mean RI value in the study group was 0.64, and in the control group 0.51, which demonstrated a statistical significance ($p = 0.007$).

Table 2. Doppler evaluation (PI and RI)

Presence of notch	Number of patients	Average value	Стандардна девијација (SD)	Стандардна грешка (SE)	T	Df	P (2-tailed)
PI study group	48	1.9585	0.15269	0.02204	11,959	94	0.005
PI control group	48	1.4327	0.26359	0.03805		75.351	
RI study group	48	0.6498	0.10558	0.01524	8,649	59.455	0.007
RI control group	48	0.5094	0.03878	0.00560			

Increased resistance in PI and RI values above 1.75 and 0.68, respectively, and the presence of a diastolic notch were abnormal results.

Of the 48 pregnant patients from the study group, 32 had changes in cytokine levels. Pro-inflammatory biomarkers (IL-6, TNF- α , IL-1 α) were elevated, and anti-inflammatory biomarker (IL-10) was decreased. There

were changes in IL4 level in the study group, but no changes in the control group. Also, there were no changes in the minimum and maximum IL-2 levels, but little difference in the mean level.

The analysis of the cytokines showed that the result obtained for IL-6 represented the most significant predictive indicator in comparison with other cytokines.

Statistical analysis with Pearson's coefficient with correlation confirmed an increase in the pro-inflammatory biomarkers (IL-6, TNF- α , together with IL-6 and TNF- α in correlation IL-1 α with $p < 0.001$).

By using ANOVA test and logistic multivariate regression analysis, IL 6 had highest influence as a pro-inflammatory cytokine (described in statistical procedures 1, 2 and 3).

ssion analysis, IL 6 had highest influence as a pro-inflammatory cytokine (described in statistical procedures 1, 2 and 3).

Ne moze dva pati 1, 2???? Najverojatno ke bide ili 3 ili 3,4,5????neka odluci avtorot

Statistical procedure 1. Sum value

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.452	0.204	0.160	0.46

a) Predictors : (Constants), IL - 2, IL - 4, IL - 6, IL - 10, T N F - α

Statistical procedure 2. ANOVA for analysis of cytokine variations in preeclampsia

Model	Sum of Squares	Df	Mean Square	F	P
Regression	4.882	5	0.976	4.61	0.001
Residual	19.024	90	0.211		
Total	23.906	95			

Dependent variable: patients with preeclampsia; Predictors (Constant): IL-2, IL-4, IL-6, IL-10, TNF- α

Statistical procedure 3. Result of the Logistic multivariate regression analysis

Model	Unstandardized Coefficients		Standardized Coefficients		T	P
	B	Std. Error	Beta			
(Constant)	1.817	0.360			5.044	0.000
TNF- α	0.008	0.041	0.020		0.197	0.844
IL-6	-0.072	0.016	-0.432		-4.351	0.000
IL-10	0.002	0.002	0.122		1.279	0.204
IL-4	-0.010	0.008	-0.124		-1.313	0.192
IL-2	-0.017	0.033	-0.050		-0.519	0.605

Mutual interaction of the pro-inflammatory cytokines in the study group showed a sensitivity of 78% to 91.2% in detecting the risk of preeclampsia. The combined usage of the Doppler method with immunobiomarkers resulted in: sensitivity of 81.5% (69.2-90.2%), specificity of 45.7% (32.2-60.1%), negative predictive value of 67.7% (50-81%) and positive predictive value of 63.8% (52-74%), which was a reliable predictive indicator.

The anti-inflammatory cytokines resulted in high sensitivity (95%) but low specificity (25%) for IL-10. IL-4 had no valuable range changes.

Of the 48 patients in the study group, 32 had elevated levels of pro-inflammatory and decreased levels of anti-inflammatory cytokines; in 16 patients there were no changes in the levels. In the third trimester, 21 patients (43.75%) developed preeclampsia. Of these, six patients (12.5%) had preterm birth (mean of 34.4 gestational weeks), versus the control group (38.3 gestational weeks). Complications had occurred in one patient having eclamptic seizure (2.08%), one patient had HELLP syndrome and pulmonary oedema (2.08%). Four patients had abruption of the placenta in partum (8.33%) and three foetuses had IUGR (6.25%). Six patients did not have complications (12.5%). In the same group with the presence of notch and elevated cytokines, three patients had gestational hypertension (6.25%) and three had gestational diabetes (6.25%), 5

resulted false positive. In those with presence of notch and normal cytokine range, two patients had SLE (4.17%), two had M. Von Willebrand (4.17%) and 12 resulted false positive (25%). In the control group, three patients had gestational hypertension (6.25%), two had gestational diabetes (4.17%) and two foetuses were diagnosed with IUGR (4.17%). There were 41 patients (85.42%) without complications.

Discussion

Preeclampsia is a multifactorial disorder which includes maternal, genetic, immunological, environmental, oxidative stress and angiogenic factors.

According to Mannisha Kar *et al.* [12] and ISSHP guidelines [13], multiparametric approach is required for detection of the risk for developing preeclampsia. Also, maternal factors are important in prediction preeclampsia such as previous pregnancies with preeclampsia and those who had been smokers.

Doppler measurement had sensitivity from 34 to 76%. Implementation of biomarkers are increasing the sensitivity of detection of patients which will develop preeclampsia in the second trimester [14,15].

The values obtained for flow indexes (PI above 1.75 and RI above 0.68) correspond to those from ISUOG where cut-off values are proposed for each trimester.

Between 14th and 20th gestational weeks, studies emphasize that a score of 1.75 for PI and 0.68 for RI indicates a risk of developing preeclampsia. According to Plasencia, PI in the first, as well as in the second trimester, a sensitivity of 77% for early preeclampsia and 27% for late preeclampsia were detected [16]. The value of 95 percentile for PI was associated with a risk of developing more serious complications as we found in our study [17].

Goma detected PI value greater than or equal to 1.75 representing a sensitivity of 99%, and by using cytokines, he measured a sensitivity of 88.6% and specificity of 100% detection rate. [18] This corresponds to the findings in our study. Of all pro-inflammatory cytokines, single sensitivity of IL-6 was 85% [19].

The results of the combined usage of the uterine artery Doppler ultrasound together with pro-inflammatory and anti-inflammatory cytokines showed sensitivity of 81.5%, and the mutual correlation of the pro-inflammatory cytokines was 78 to 91.2%. This as a predictive tool in the second trimester, from the 14th to the 20th gestational week, which is applied in patients who are prone to develop preeclampsia after 28 weeks of gestation in the third trimester.

Teran [20] and Hentschke *et al.* [21] verified an increase in IL-6 in preeclampsia. Also, IL-6 analyzed with multivariate regression analysis was the most significant predictive parameter. In line with the results of this study, we should be more vigilant in monitoring these patients. The risk is detectable according to FMF in the first trimester of pregnancy [22] and the patients should be given Aspirin (120-160mg) as soon as we confirm the risk [23]. The final target is appropriate time for admission in tertiary care facility.

Conclusion

Usage of predictive test in the early second trimester for preeclampsia will help an appropriate monitoring of patients who have a risk of developing preeclampsia. If abnormal Doppler result is obtained, especially in patients with a known risk of preeclampsia, we suggest levels of cytokines, especially IL6, to be measured. Thus, we can prevent unfavourable outcome of development of preeclampsia and its complications.

Different therapeutic modalities and predictive methods can improve the overall health of both, the mother and the foetus. Taking into account that preeclampsia is a multifactorial disorder, the investigations for the disease never stop. Preeclampsia will be a field of research in the years to come. Our study is a little contribution to this issue, with the results obtained in our patients.

Conflict of interest statement. None declared.

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