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¹Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

²Department of Gynecology, Obstetrics and Reproductive medicine, School of Medicine, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina

³Department of Obstetrics and Gynecology, Medical School University of Zagreb, Zagreb, Croatia

Corresponding author: Edin Medjedovic MD, PhD. Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina. E-mail: medjedovic.e@gmail.com; ORCID ID: <https://orcid.org/0000-0003-2357-9580>.

The Importance of Doppler Analysis of Uterine Circulation in Pregnancy for a Better Understanding of Preeclampsia

Edin Medjedovic^{1,2}, Asim Kurjak^{2,3}

ABSTRACT

Background: The etiology of preeclampsia has still not been completely explained. Early identification of women with the risk of developing preeclampsia is a key goal of antenatal care. **Objective:** To investigate risk factors for preeclampsia from the history, laboratory and ultrasound findings (Doppler). **Methods:** Pregnant women with normal Doppler sonography in the second trimester of pregnancy were classified as a control group, while pregnant women with impaired Doppler in the second trimester were considered as the investigated group with presumably increased risk for preeclampsia. A total number of 80 patients was included in the study (40 patients in each group). **Results:** The difference of urea, uric acid and lactate dehydrogenase (LDH) in the serum of the control and investigated group was statistically significant, while the differences were not statistically significant for creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The presence of a notch sign during assessment of blood flow in uterine arteries in subjects in the investigated group with the diagnosis of preeclampsia had the specificity of 47.62%, and sensitivity of 88.89%. The positive predictive value of a notch sign during assessment of blood flow in uterine arteries as a marker for diagnosis of preeclampsia in the second trimester of pregnancy was 90.91%, and its negative. Systolic and diastolic blood pressure are dependent variables which are predicting preeclampsia, whilst a notch sign in uterine arteries was designated as an independent variable predicting preeclampsia. **Conclusion:** From the laboratory tests the following parameters were considered as the risk factors for preeclampsia: increasing levels of urea, uric acid, and LDH. Notch sign was considered to be a very strong predictor of preeclampsia, especially if present bilaterally. Doppler sonography in the second trimester of pregnancy is a good predictor for early diagnosis of preeclampsia.

Keywords: ultrasound, hypertension, pregnancy.

1. BACKGROUND

Preeclampsia is defined as hypertension (systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg) after the 20th week of gestation, with one or more of the following symptoms: proteinuria, organ dysfunction (including kidney, hepatological, hematological or neurological complications), and sometimes the presence of fetal growth restriction. It is the cause of increased morbidity for the mother, and mortality and morbidity of the mother and fetus, and newborn (1). The incidence of cerebrovascular disease after birth is higher in women who previously had preeclampsia in a pregnancy (2). Preeclampsia is a systemic disease which includes a large number of disturbances in the organism of a pregnant woman and within the fetoplacental unit. There are differing epidemiological data on the prevalence of preeclampsia, varying from 0.5% to 15% of all pregnancies, and symptoms usually occur at the end of the second and the beginning of the third trimester of pregnancy (1). The etiology of preeclampsia has still not been completely explained. Early identification of women with the risk of developing preeclampsia is a key goal of antenatal care. Biochemical tests, Doppler sonography of the uterine arteries plays a major role in predicting preeclampsia (3). Many studies have tried to link the Doppler findings of the blood flow in the uterine blood vessels with the possible early prediction and detection of preeclampsia (4). During a normal pregnancy physiological changes take place to the spiral arteries with development of physiologically reduced resistance to blood flow,

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which is directly affecting the resistance of blood flow in the uterine arteries (3). Blood flow resistance in the uterine arteries is usually lower on the placental than on the side opposite to the placenta (3,4). Ultrasound of the uterine arteries has become a useful method for indirect assessment of the uteroplacental circulation in early pregnancy (4,5,6). Although the procedures for prediction of preeclampsia are missing, Doppler of the uterine arteries is the most often used in everyday clinical practice and for the research (4).

2. OBJECTIVE

The aim of the study was to investigate risk factors for preeclampsia from the history, laboratory and ultrasound findings (Doppler).

3. PATIENTS AND METHODS

Patients and study design

The study was divided into two parts, retrospective, and prospective, and it included 80 pregnant women in the second trimester of pregnancy who were either hospitalized at the Department of Gynecology and Obstetrics at the Clinical Center of the University of Sarajevo or followed-up at the Outpatient Clinic of Gynecology and Obstetrics at the Clinical Center of the University of Sarajevo. The retrospective part of the study enrolled pregnant women whose pregnancy was followed-up during the period of 01/02/2012 to 30/12/2019. We received permission for the research from the ethics committee and a certificate of the feasibility of the study at the Clinical Center of the University of Sarajevo. Pregnant women with normal Doppler sonography in the second trimester of pregnancy were classified as a control group, while pregnant women with impaired Doppler in the second trimester were considered as the investigated group with presumably increased risk for preeclampsia. In patients referred by primary care physicians Doppler of uterine arteries was prospectively monitored during regular follow-up visits by fetal medicine subspecialist. Those of the patients with impaired Doppler of uterine arteries were considered as high-risk. All patients were divided into two equal groups after the 22nd week of gestation: the control group (n = 40) and the investigated group (n = 40).

Methods

Minimum required calculated initial number of patients (sample size) for this study by Kelsey is 76 and by Fleiss it is 72. At the beginning of the research we have enrolled 90 patients (45 in each group), while 10 of them were excluded for various reasons (see exclusion criteria). A total number of 80 patients was included in the study (40 patients in each group). Inclusion criteria for the control group were: second trimester of pregnancy (after the 22 weeks of gestation), normal RI of the uterine arteries on the placental side, and the side opposite to the placenta (the RI=0.39-0.52 on the placental side were considered normal; the RI=0.37-0.61 on the side opposite to the placenta were considered normal). Inclusion criteria for the investigated group of patients were: second trimester of pregnancy (after 22 weeks

of gestation), abnormal RI of the uterine arteries (the RI \geq 0.53 on the placental side were considered abnormal; the RI \geq 0.62 on the side opposite to placenta were considered abnormal). Exclusion criteria were: a history of arterial hypertension before 20th week of gestation and/or essential arterial hypertension before pregnancy, chronic cardiovascular and renal diseases, loss from follow-up due to various reasons like change of the health-care provider, spontaneous or induced termination of pregnancy, or early premature birth before the completion of the study. At the beginning of the study, based on the uterine artery Doppler, patients who fulfilled inclusion criteria were included in one of the two groups. In addition to the ultrasound examination, comprehensive history of previous pregnancies and laboratory findings were taken, when appropriate. The following data were assessed:

Data from the history: age, number of births, the delivery method in previous pregnancy/pregnancies, complications related to previous pregnancy/pregnancies, pre-existing disease before the pregnancy.

Body mass index–BMI (before pregnancy and in the second trimester of pregnancy; malnutrition up to 19 kg/m², normal body weight 19–24 kg/m², overweight 24–30 kg/m², obesity over 30 kg/m²)

Systolic and diastolic blood pressure (mmHg).

Laboratory findings: creatinine (reference 63 – 107 μ mol/L), uric acid (reference 134 – 337 μ mol/L), blood glucose (reference 4.4 – 6.2 mmol/L), aspartate transaminase (AST) (reference 12-38 IU/L), alanine transaminase (ALT) (reference 7-41 IU/L), lactate dehydrogenase (LDH) (reference 115-221 IU/L), complete urine examination (with proteins). The laboratory findings were performed once a month in the control and every three weeks in the investigated group of patients.

Statistical analysis

Chi-square test (χ^2 -test) was used as a non-parametric test for two groups, where the observed and expected frequencies were compared; and model-non-parametric χ^2 -test for the homogeneity of two samples with frequencies arranged in 2 x 2 contingency tables (when N was less than 40 but more than 20, Yates correction was used). The Shapiro-Wilk test was used to test the significance of the differences if the distribution was not normal. The Mann-Whitney test was used to analyze the significance of the difference of variables with irregular distribution between the two observed groups, and an independent t-test was used for variables with a normal distribution. The correlation was tested using the Spearman test. The significance was set at p <0.05.

4. RESULTS

The average age of the subjects in the control group was 30.30 \pm 3.73 years (range 22-38 years), and of the women in the investigated group was 31.70 \pm 4.42 years (range 22-40 years). There was no statistical difference between women's age in the control and investigated groups (F=2.343; p=0.130), along with difference in the parity of the pregnant women in the control and investigated groups (χ^2 =0.001; p=0.590). Analysis of risk

factors for preeclampsia of subjects in the investigated group are shown in Table 1. Comparison of gestational age at birth, Apgar scores at 1 and 5 minutes and birth weight of newborns in control and investigated group of examinees are shown in the Table 2, and the differences were tested using ANOVA test. As expected more women in the investigated group delivered by Cesarean section (17 out of 40 or 42.5%) while in the control group more women delivered vaginally (27 out of 40 or 67.5%). The difference was statistically significant ($\chi^2=3.955$; $p=0.048$). The average body mass index (BMI) in the control group at the beginning of the research was 23.9 ± 5.21 kg/m², and in the investigated group it was 26.23 ± 4.15 kg/m². At the end of the research the average BMI in the control group was 27.63 ± 6.16 kg/m², and in the investigated group 31.47 ± 4.31 kg/m². The ANOVA test showed a statistically significant difference in BMI between the control and the investigated group at the beginning ($F=4.90$; $p=0.03$) and at the end of the research ($F=10.446$; $p=0.002$). There was a statistically significant difference between the average systolic blood pressure during pregnancy in comparison with the investigated group ($F=45.673$; $p=0.001$). The women in the control group had an average systolic blood pressure of

Risk factor from the history	Description	Number	Percentage	p*
Smoking	Yes	10	25.0%	0.001
	No	30	75.0%	
BMI	Malnutrition	0	0%	0.001
	Normal body weight	0	0%	
	Overweight	15	37.5%	
	Obesity	25	62.5%	
Preeclampsia in a previous pregnancy	Yes	5	12.5%	0.001
	No	35	87.5%	

Table 1. The frequency of risk factors for preeclampsia in women of the investigated group. *Chi square test; BMI Body Mass Index; p probability

113.29 ± 10.97 mmHg, while the systolic blood pressure of investigated group (130.87 ± 12.25 mmHg) was significantly higher than the control group. The average of diastolic blood pressure of the control group (72.18 ± 5.78 mmHg) during pregnancy in comparison with the investigated group (82.95 ± 7.19 mmHg) was significantly low-

Parameter	Examined group	Mean	SD	SEM	95% CI	Range		ANOVA	
						Minimum	Maximum	F	p
Gestational age at birth (weeks)	Control	39.05	1.58	0.25	38.54-39.56	35.00	42.00	25.867	0.001
	Investigated	36.40	2.89	0.46	35.48-37.32	28.00	40.00		
APGAR 1	Control	9.55	0.78	0.12	9.30-9.80	6.00	10.00	24.772	0.001
	Investigated	8.23	1.48	0.24	7.75-8.71	4.00	10.00		
APGAR 2	Control	9.80	0.61	0.10	9.61	9.99	7.00	11.764	0.001
	Investigated	8.77	1.80	0.29	8.19	9.35	10.00		
Birth weight (g)	Control	3,425	548.47	18.89	3,178-3,799	2,900	4,100	31.454	0.001
	Investigated	2,589	909.38	17.85	2,178-2,887	1,810	3,050		

Table 2. Comparison of gestational age at birth, Apgar scores at 1 and 5 minutes and birth weight of newborns in control and investigated group of examinees. Statistically significant levels are in bold font; SD Standard deviation; SEM Standard Error of Mean; CI Confidence Interval; p= probability value

Parameter	Group of subjects	Mean	SD	SEM	95% CI	Range		ANOVA	
						Minimum	Maximum	F	p
Urea mmol/L	Control	2.74	0.45	0.07	2.60 - 2.89	1.80	3.73	7.508	0.008
	Investigated	3.15	0.82	0.13	2.89 - 3.41	2.05	6.00		
Creatinine □mol/L	Control	55.83	5.97	0.96	53.90 - 57.77	41.75	67.75	2.909	0.092
	Investigated	58.43	7.48	1.18	56.04 - 60.83	32.00	84.75		
Uric acid □mol/L	Control	208.18	30.00	4.80	198.45 - 217.90	151.50	275.00	12.991	0.001
	Investigated	239.79	49.77	7.87	223.87 - 255.70	149.00	341.00		
AST IU/L	Control	25.82	3.58	0.85	21.32 - 29.90	12.50	39.00	0.918	0.711
	Investigated	29.79	9.77	0.87	20.87 - 38.70	10.00	44.00		
ALT IU/L	Control	35.83	9.97	2.96	23.90 - 47.77	17.08	47.75	7.11	0.201
	Investigated	38.43	7.88	3.18	26.04 - 45.83	22.09	54.75		
LDH IU/L	Control	274.1	45.1	7.15	260.5 - 419.5	102	373	7.508	0.008
	Investigated	315.5	85.2	12.3	289.0 - 374	205	600		

Table 3. Comparison of the average levels of blood urea, creatinine, uric acid, AST, ALT and LDH in the control and investigated group using ANOVA test in the control and investigated group of examinees

Group	Model	Beta In	t	p	Partial Correlation	Collinearity Statistics	
						Tolerance	
Test	1	Parity	-0.057	-0.311	0.758	-0.060	0.973
		Initial BMI	-0.134	-0.746	0.462	-0.142	1.000
		Final BMI	-0.090	-0.498	0.622	-0.095	1.000
		Systolic blood pressure	0.596	4.059	0.000	0.616	0.948
		Diastolic blood pressure	0.569	3.809	0.001	0.591	0.958
		Notch	0.266	1.436	0.163	0.266	0.892
	2	Initial BMI	-0.131	-0.666	0.511	-0.129	0.862
		Final BMI	-0.081	-0.425	0.674	-0.083	0.935
		Systolic blood pressure	0.663	4.473	0.000	0.659	0.875
		Diastolic blood pressure	0.584	3.859	0.001	0.603	0.945
		Notch	0.314	1.604	0.121	0.300	0.807
		3	Systolic blood pressure	0.664	4.201	0.000	0.651
Diastolic blood pressure	0.586		3.721	0.001	0.605	0.922	
4	Notch sign in uterine arteries	0.324	1.558	0.132	0.303	0.758	
	Notch sign in uterine arteries	0.348	2.221	0.037	0.428	0.736	

Table 4. Linear regression of parity, body mass index, systolic and diastolic blood pressure and notch sign in uterine arteries as possible predictors for preeclampsia. BMI Body Mass Index; p probability

er (F=54.559; p=0.001). The difference of urea, uric acid and LDH in the serum of the control and investigated group was statistically significant, while the differences were not statistically significant for creatinine, AST and ALT (Table 3). The Wilcoxon non-parametric paired test revealed that changes of the concentration of blood urea of control and investigated group at all assessment periods of investigation were not statistically significant. Initial creatinine levels in the control group (55.92±5.97), and at the end of the research (53.88±10.12) there was a decrease by -2.05 µmol/L (data not shown), while in the investigated group there was statistically significant increase of creatinine levels by 7.19 µmol/L (data not shown) at the end of the research in comparison with the initial levels (p=0.001). The Wilcoxon non-parametric paired test revealed that the average creatinine levels were significantly different in all assessment periods in the control and investigated group (Z=-3.075; p=0.002). The difference between the first and the second assessment period there was a statistically significant increase of 2.01 µmol/L (Z=-2.785; p=0.005), as well as between the second and third assessment period (1.58 µmol/L ; Z=-3.717; p=0.001), and the third and fourth assessment period (3.60 µmol/L; Z=-5.115; p=0.001), and between the initial and final assessment period (7.19 µmol/L; Z=-5.115; p=0.001).

In comparison with the initial uric acid levels in the control group (204.72±34.0 µmol/L), and at the end of the research (221.18±47.62 µmol/L) there was an increase by 16.46 µmol/L (data not shown), and in the investigated group there was statistically significant increase of uric acid levels by 214.45 µmol/L (data not shown) at the end of the research in comparison with the initial levels (p=0.001). The difference between the third and fourth assessment period of uric acid concentration in the control group was significantly increased (17.1

µmol/L; Z=-1.995; p=0.001), while for the rest of comparisons the difference was not statistically significant. The comparison between the initial and final assessment period there was statistically significant increase of uric acid levels in the control group (16.46 µmol/L; Z=-1.988; p=0.001). The concentration of uric acid at the initial and final assessment periods of investigated group was also statistically significant (Z=-7.502; p=0.001).

In comparison with the initial AST levels in the control group (17.72±4.00 IU/L), and at the end of the research (38.18±7.62 IU/L) there was an increase by 20.46 IU/L which was statistically significant, and in the investigated group there was statistically significant increase of AST levels by 19.45 IU/L at the end of the research in comparison with the initial levels.

The Wilcoxon non-parametric paired test applied to the average values of AST over all assessment periods within the control and investigated group showed a statistically significant difference in the control group between the first and second measurement (Z=-3.141, p=0.011) and between the third and fourth measurement (Z=-5.552, p=0.001). The difference between the initial AST values in the control group, and at the end of the research there was a statistically significant increased level of AST values by 20.46 (Z=-7.993, p=0.031). In the investigated group, a statistically significant difference was noticed in AST values between the second and third measurements (Z=-5.399, p=0.001). The difference between the initial AST values in the investigated group, and AST values at the end of the research there was statistically significant increased level of AST by 19.45 (Z=-7.682, p=0.001).

In comparison with the initial ALT levels in the control group (25.92±9.97 IU/L), and at the end of the research (41.87±4.12 IU/L) there was an increase by 15.95 IU/L which was statistically significant, and in the investigated

group there was statistically significant increase of ALT levels by 7.19 IU/L at the end of the research in comparison with the initial levels. A statistically significant difference was found in the control group between the first and second assessment ($Z=-3.075$; $p=0.002$) and between the first and last assessment ($Z=-2.748$; $p=0.011$). In the investigated group, there was a statistically significant increase from the first to the last assessment by 7.19 IU/L ($Z=-3.255$; $p=0.003$), while all other comparisons of ALT levels in different assessment periods were not statistically significant. In comparison with the initial LDH levels in the control group (283 ± 16.3 IU/L), and at the end of the research (371 ± 15.3 IU/L) there was an increase by 88 IU/L which was statistically significant, and in the investigated group there was statistically significant increase of LDH levels by 174 IU/L at the end of the research in comparison with the initial levels. Statistically significant difference of LDH levels in the control group was found between the third and fourth assessment period ($Z=-4.561$, $p=0.045$) and at the end of the research in comparison with the initial levels ($Z=-4.963$, $p=0.013$). In the investigated group, a statistically significant difference of LDH level was statistically significant between the first and the second assessment ($Z=-2.985$, $p=0.044$), and between the second and the third assessment ($Z=-4.219$, $p=0.001$), as well as between the third and the last assessment ($Z=-4.009$, $p=0.001$). The initial level of LDH compared with the level at the end of research of the investigated group was statistically significant ($Z=-10.404$, $p=0.001$). The blood flow in uterine arteries of the control group was within the physiological range throughout the entire research. In the investigated group pathological flow in uterine arteries was found in 18 to 26 out of 40 women, while in 6 to 8 out of 40 the notch sign was found, which was not statistically significant by ANOVA test. The difference between the average levels of pathological blood flow on the side of the placenta in women without and with preeclampsia was not statistically significant. The blood flow in uterine arteries of the control group was within the physiological range throughout the entire research. In the investigated group pathological flow in uterine arteries was found in 20 to 22 out of 40 women, while in 9 to 13 out of 40 the notch sign was found, which was not statistically significant by ANOVA test. The difference between the average levels of pathological blood flow on the side opposite to the placenta in women without and with preeclampsia was not statistically significant. Of the total number of subjects in the investigated group who did not have preeclampsia ($n=11$), during the analysis of flow, in one of the notch was present, while it was absent in 10. Of the 29 women with the diagnosis of preeclampsia, the notch was present in 14, which was statistically significant ($\chi^2=5.094$; $p=0.023$ with Yates correction). The presence of a notch sign during assessment of blood flow in uterine arteries in subjects in the investigated group with the diagnosis of preeclampsia had the specificity of 47.62%, and sensitivity of 88.89%. The prevalence of the disease in subjects with a notch sign during assessment of blood flow in uterine arteries was 70%, respectively. The pos-

itive predictive value of a notch sign during assessment of blood flow in uterine arteries as a marker for diagnosis of preeclampsia in the second trimester of pregnancy was 90.91%, and its negative. Linear regression of variables which may be predictive for preeclampsia is shown in the Table 4. It was found that systolic and diastolic blood pressure are dependent variables which are predicting preeclampsia, whilst a notch sign in uterine arteries was designated as an independent variable predicting preeclampsia, ($B=0.348$; $t=2.221$; $p=0.037$).

5. DISCUSSION

Early diagnosis of preeclampsia remains one of the main aims of antenatal care (7,8). An important issue is an improvement of prediction models for preeclampsia in order to identify high-risk pregnant women, and appropriate follow-up of the fetus who can be severely affected (8,9). Many studies that have analyzed the effect of preeclampsia on the overall status of fetuses imply that they are at high risk due to hypoxia caused by preeclampsia. The basic laboratory diagnostics, with a clinical and gynecological examination, together with anamnestic data can be of great importance to assess the risk, but also to categorize the patients in relation to the risk of preeclampsia (11-17).

Preeclampsia and data from the history

Our study showed that the occurrence of preeclampsia is influenced by the patient's smoking habits, body mass index (BMI), preeclampsia in a previous pregnancy, as well as systolic blood pressure. Studies in developed countries showed that a high body mass index (BMI) before pregnancy increases the risk of preeclampsia (18), which was the case in our investigation as well. In research conducted by Mrema et al. in Tanzania from 2010 to 2013, of the 17,738 women, 6.6% had a low BMI, 62.1% a normal BMI, 24.0% women were overweight and 7.3% were obese (18). In relation to the total number of subjects, 582 subjects (3.3%) had preeclampsia of whom there were 31% (181 subjects) of overweight and 10.6% (62 subjects) of obese women (18). The aim of the study by Yusrawati et al. was to assess whether nutrition and BMI are risk factors for preeclampsia (19). The prevalence of abnormal BMI was higher in women with preeclampsia, 19 (27.1%) in comparison with 12 (17.1%) in the control group, which correlates with the results of our research (19). The results of the research by Nzele D. et al., which indicate higher systolic and diastolic blood pressure in pregnant women with preeclampsia in comparison with the control group of healthy pregnant women, are in concordance with the results of the present research (20). In the study by Baschat et al. blood pressure in women with normal pregnancies and those with preeclampsia was analyzed. They showed that women with preeclampsia had higher blood pressure at the beginning of pregnancy in comparison with healthy pregnant women, and that trend continued, which is comparable with the results of the present research (21). In our research, linear regression showed that systolic and diastolic blood pressure were dependent variables indicating the presence of preeclampsia. By analyzing

the risk factors for preeclampsia, it was revealed that smoking was a risk factor present in 25% of subjects in the investigated group, but there were significantly more subjects who did not smoke ($p=0.001$), which supports the data from the literature that moderate smoking during pregnancy protects from the development of preeclampsia (22).

In the research by Guida et al. which involved 293 patients with preeclampsia, it was shown that 205 (70%) of the women had a premature birth, and in 80% of cases they delivered by Caesarean section (23), while in our study 44.8% out of 29 patients with preeclampsia had a premature birth, and 58.6% of them delivered by Caesarean section.

Preeclampsia and biochemical blood test

Our research showed that the average values of urea, uric acid and LDH differ between the investigated groups, while the difference was not statistically significant between average values of AST, ALT and creatinine between the groups. A statistically significant difference was found of the average concentration of urea during pregnancy between the control and the investigated groups. In the research by Aslan Cetin et al. conducted on 79 pregnant women, of whom 27 had a normal pregnancy, 30 had early-onset and 22 late-onset preeclampsia, the average urea and creatinine levels were significantly higher in the pregnant women with preeclampsia than in the control group, which was also the case in our research (12). In comparison to this research, somewhat higher mean values of uric acid were recorded in pregnant women with preeclampsia in the research by Gao et al. (14). The research conducted by Heilmann et al. included 52 patients with preeclampsia and 40 healthy pregnant women as the control group. Most of the subjects with preeclampsia had significantly higher hematocrit and uric acid levels, and aggregation of red blood cells, which is in concordance with the results of our research (15).

Assessment of blood flow in uterine arteries and notch sign in preeclampsia

Our research has shown that pathological flows in the uterine arteries significantly correlate with the occurrence of preeclampsia, with a predominant correlation of flow on the placental side in comparison with the side opposite to the placenta. The presence of the notch sign in the Doppler record showed high sensitivity as a marker of preeclampsia. All patients with bilateral notch sign developed preeclampsia. In a study conducted by Lopez-Mendez et al., a total of 102 women were recruited and divided into two groups: 65 formed the investigated group (38 mild and 27 severe preeclampsia) and 37 were the control group (24). There were no differences in risk factors such as the personal or familial history of preeclampsia and parity between the groups (24). Considering the Doppler US findings, from individual parameters evaluated in the uterine artery, a notch sign showed to be the most meaningful (although not the most frequent) individual finding, due to the fact that its presence was restricted to the investigated group. Albaiges et al. conducted research involving subjects in the 23rd

week of pregnancy using a color Doppler of the uterine arteries and the presence of a notch sign as a predictive test for preeclampsia (25). The results reported a detection rate of 90% for patients who developed preeclampsia and 70% for fetuses with intrauterine growth restriction. In addition, in 80% of preeclamptic pregnancies fetal deaths occurred, and in 50% of them placental abruption was identified (25). They further elaborated that women with pathological blood flow and bilateral notch sign were at the highest risk to develop preeclampsia which was 40%, while the risk for intrauterine growth restriction for the fetus was 45% (25). The relative risk for development of adverse outcomes before 34 weeks of gestation and fetal death in this group ranged from 50 to 100 % (25). Nagar et al. conducted a study to determine the role of color Doppler in predicting high-risk pregnancies and their outcome (26). Of 500 patients, 110 had abnormal Doppler, of which 70 had abnormal Doppler blood flow in uterine arteries, and 50 patients had abnormal umbilical artery blood flow (26). In the group of 70 patients with abnormal Doppler findings in uterine arteries, 20 patients developed preeclampsia, 10 pregnancy-induced hypertension, and 25 fetuses were diagnosed with intrauterine growth restriction (26). The ratio of systolic and diastolic (S/D) blood pressure and the presence of a notch sign showed a sensitivity of 60% and positive predictive value of 33.3% and 37.5% (26). In 50 patients with pathological blood flow in the umbilical artery, 10 developed preeclampsia, 15 pregnancy-induced hypertension, and in 15 fetuses intrauterine growth restriction was noted (26). The S/D ratio had the highest positive predictive value, and 40% sensitivity for all cases (26). The specificity of all Doppler indexes was 91-96% (26). Preeclampsia developed in 15 out of 20 patients with positive notch sign (26). All 10 cases with abnormal Doppler blood flow both in the uterine and umbilical arteries developed preeclampsia and intrauterine growth restriction of the fetus (26). Uyar et al. concluded that the presence of a notch sign and pathological blood flow in the uterine arteries in the second trimester of pregnancy can be considered as acceptable method for the prediction of preeclampsia (27), which was one of the results of our study.

In the research by Pongrojpraw et al. the sensitivity of pathological blood flow in the uterine arteries and the presence of a notch sign as a test for diagnosis of preeclampsia was 59.25%, and specificity of 66.67% (28).

6. CONCLUSION

According to our investigation, the following parameters from the history were considered as a risk-factors for preeclampsia: non-smoking, obesity, excess body weight, and previous pregnancy with preeclampsia. From the laboratory tests the following parameters were considered as the risk factors for preeclampsia: increasing levels of urea, uric acid, and LDH. From an analysis of the arterial resistance index in the uterine arteries in the control and investigated groups, we conclude that physiological flows both on the side of the placenta and on the side opposite to the placenta were indicators of the

physiological (normal) course of the pregnancy, whilst pathological flows were linked to the development of an impaired course of pregnancy. Notch sign was considered to be a very strong predictor of preeclampsia, especially if present bilaterally. Doppler sonography in the second trimester of pregnancy is a good predictor for early diagnosis of preeclampsia.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms
- **Author's Contribution:** EM and AK gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Both authors had role in drafting the work and revising it critically for important intellectual content. Both authors gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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