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Uric Acid Values Along with Doppler Sonography Findings as a Tool for Preeclampsia Screening

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ABSTRACT

Introduction: Preeclampsia is defined as hypertension (systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg) after week 20 of gestation with one or more of the following symptoms: proteinuria, organ dysfunction (including renal, hepatologic, hematologic or neurological complications) and in case of stagnation of fetal development. So far, there are no valid clinical tools or tests that can tell with sufficient sensitivity and specificity in early pregnancy which pregnant woman will develop preeclampsia or have unwanted outcomes. **Aim:** To present the properties of biochemical parameter, uric acid, in patients with signs of preclampsia, which was confirmed by Doppler sonography. **Methods:** The study included 60 female subjects in the second trimester of pregnancy who were examined or were hospitalized at the Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo. Pregnant women who had normal Doppler sonography scan of the uterine arteries in the second trimester of pregnancy were included in the control group, while pregnant women with pathologic Doppler sonographic findings in the second trimester of pregnancy were included in the group of pregnant women at risk of preeclampsia, i.e. the study group. **Results:** There is statistically significant difference between the average value of uric acid in the control and in the study group (213.36 ± 28.96 μmol / L vs 249.73 ± 47.06 μmol / L) (F = 12.991; p = 0.001). Applying the Wilcoxon non-parametric paired test to the average uric acid values during all measurements within the control group, no statistically significant difference was found. There was a statistically significant increase in the study group between all measurements, from 18.04 μmol / L between the first and second measurement (Z = -1.955; p = 0.043), 29.10 μmol / L between the second and third measurement (Z = -2.973; p = 0.003), 37.27 μmol / L between the third and fourth measurement (Z = -4.325; p = 0.001) and 109.87 μmol / L at the end of the study in comparison to values from the start of the study (Z = -4.309; p = 0.001). **Conclusion:** Uric acid values should become part of a broad biochemical range in screening and optimizing the treatment of patients diagnosed with early preeclampsia.

Keywords: uric acid, preeclampsia, screening.

1. INTRODUCTION

Preeclampsia is defined as hypertension (systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg) after week 20 of gestation with one or more of the following symptoms: proteinuria, organ dysfunction (including renal, hepatologic, hematologic or neurological complications) and in case of stagnation of fetal development (1). It causes increased maternal morbidity and fetal mortality and morbidity (1). The incidence of cerebrovascular disease after giving birth is increased in women who previously had preeclampsia in pregnancy (2). Preeclampsia is a systemic disease which involves a number of disorders in pregnant woman and within the fetoplacental unit. There are various epidemiological data on the presence of preeclampsia and it is present in 0.5 to 15% of all pregnancies, and symptoms usually occur at the end of second and early third trimester of pregnancy (1). The etiology of preeclampsia is not fully explained. One theory says that there is no physiological change in the uterine spiral arteries in pregnant women with preeclampsia. Psychologically spiral arteries undergo changes to adjust to pregnancy and this adaptation develops during the first and second trimester (1). The pathological process is fully developed when symptoms appear. There is no real therapy yet, and the only recognized "true therapy" of preeclampsia so far is childbirth, where six weeks after birth it is expected that preeclampsia is cured.

However, preterm birth is in many cases associated with considerable mortality and morbidity in preterm infants (1). These children most often require prolonged intensive care, and with the development of complications, lifelong disability also occurs, leading to high health care costs. Early identification of women with risk of preeclampsia is a key goal of antenatal care. In addition to biochemical analysis, Doppler sonography of the uterine arteries plays a major role in the prediction of preeclampsia (2). The incidence of preeclampsia is estimated to be 2% -7% in industrialized western countries, while it has increased to 10% of all pregnancies in developing countries, with an increasing tendency in recent years (3). Preeclampsia may have early or late onset (4). Late-onset preeclampsia (prevalence, 5% of cases) occurs at or after 34 weeks gestation. The condition of early onset (<34 weeks gestation) tends to be more severe (5). So far, there are no valid clinical tools or tests that can tell with sufficient sensitivity and specificity in early pregnancy which pregnant woman will develop preeclampsia or have unwanted outcomes. Examination by Doppler ultrasound in second-trimester, where uterine arteries are evaluated with measuring the increased resistance index and notch detection, have reasonable testing characteristics to identify low- and high-risk women for the development of preeclampsia. However, this first trimester test has low to moderate predictive sensitivity and specificity (6). Untill now, no single biochemical marker has been found whose early detection would indicate a future onset of preeclampsia. The reason for this is probably the fact that this disease is heterogeneous in nature with the influence of numerous pathophysiological processes. Most of the biochemical parameters included in the prediction reflect placental disorders, that is, placental factors, angiogenesis factors, inflammation, endothelial activation, oxidative stress, and platelet activation. Of all the biochemical parameters examined, the highest useful value in the early prediction of preeclampsia is certainly pregnancy related plasma protein A (PAPP-A) and placental growth factor (PIGF) (7). Uric acid is mainly synthesized in the liver, intestines and vascular endothelium as an end product of exogenous purine pool, and endogenously from damaged, dying and dead cells (adenine and guanine are degraded into uric acid) (8).

In pregnancy, uric acid values drop by 25-35% due to estrogen, hypervolemia and increased glomerular filtration (9). Elevated uric acid is associated with hypertension, renal pathology and an unexpected cardiovascular incident in a non pregnant population and with a fatal outcome in hypertensive pregnant women (10).

2. AIM

The aim of this study was to present the properties of biochemical parameter, uric acid, in patients which have been undergone Doppler sonography for preeclampsia detection.

3. METHODS

This prospective study was conducted on subjects of the Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo. The study included 60 female subjects in the second trimester of pregnancy who were examined or were hospitalized at the Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo. Pregnant women who had normal Doppler sonography scan of the uterine arteries in the second trimester of pregnancy were included in the control group, while pregnant women with pathologic Doppler sonographic findings in the second trimester of pregnancy were included in the group of pregnant women at risk of preeclampsia, i.e. the study group. There were 30 patients included in control group and 30 in study group. The study included pregnant women after 20 weeks of gestation when changes in the spiral arteries were complete. This criterion had to be met for both control and study group. Inclusion criteria for control group were as follows: second trimester of pregnancy (after week 20 of gestation), physiological finding of Doppler sonography of the uterine arteries: on the side with the placenta of physiological value (Ri = 0.39-0,52) and on the side without placenta of physiological value (Ri = 0.37 -0.61). Inclusion criteria for study group: second trimester of pregnancy (after week 20 of gestation), pathological findings of Doppler ultrasound of the uterine arteries: on the side with the placenta of pathological value (Ri ≥ 0.53), and on the side without placenta of pathological value (Ri ≥ 0.62), notch sign verified. Exclusion criteria from the study included: anamnestic data on hypertension before the 20th week of gestation, as well as data on essential hypertension, chronic cardiovascular and renal diseases, subjects who continued to control pregnancy in other health care institutions, preterm pregnancy, subjects with diagnosed epilepsy or history of seizures. At the beginning of the study, based on the findings of Doppler ultrasound of the uterine arteries, the subjects were included in the study and were classified into one of two groups. In addition to the ultrasound examination, patients provided a comprehensive history of previous pregnancies, if any, and possibly provided laboratory findings. The IBM statistics SPSS v19.0 statistical package (Chicago, Illionis, USA) was used for data analysis. while the results of all tests at p <0.05 were considered statistically significant. The ANOVA test (with Bonferroni correction) was used to compare parametric variables, while the Wilcoxon signed-rank test was used to compare the difference between two consecutive measurements for nonparametric variables.

4. RESULTS

The average value of uric acid in the control group was 213.36 ± 28.96 μmol / L, and in the subjects in the study group the average value of uric acid was 249.73 ± 47.06 μmol / L. Using the ANOVA test, a statistically significant difference in the average value of uric acid during pregnancy was found between the control and study groups, F = 12.991; p = 0.001.

The average value of uric acid in the control group during the first measurement was 213.53 ± 26.21 μmol / L, and during the second measurement 209.03 ± 34.53 μmol / L. During the third measurement, the average

	N	X	SD	SEM	95% CI		Minimum	Maximum
					Lower	Upper		
Control group	30	213.36	28.96	5.28	202.55	224.18	173.00	275.00
Study group	30	249.73	47.06	8.59	232.15	267.30	177.00	341.00
F=12.991; p=0.001								

Table 1. Average values of uric acid during pregnancy in control and study group (X- average, SD -standard deviation, SEM—standard error of the mean (μmol / L)).

	Groups	X	N	SD	SEM
Control	First measurement	213.53	30	26.21	4.78
	Second measurement	209.03	30	34.53	6.30
	Third measurement	208.43	30	36.58	6.68
	Last measurement	222.20	30	51.07	9.32
Study	First measurement	205.86	30	31.39	5.73
	Second measurement	223.90	30	46.29	8.45
	Third measurement	253.00	30	59.81	10.91
	Last measurement	315.73	30	90.99	16.61

Groups		First-Second	Second-Third	Third-Last	First-Last
Control	Z	-1.265b	-.350b	-1.924c	-.638c
	p	.206	.727	.054	.524
Study	Z	-1.955c	-2.973c	-4.325c	-4.309c
	p	.049	.003	.000	.000

Table 2. Change in average uric acid values during all measurements within the groups (X- average, N—number of patient, SD -standard deviation, SEM—standard error of the mean (μmol / L)).

value of uric acid in the control group was 208.43 ± 36.58 μmol / L, and at the end of the study this value was 222.20 ± 51.07 μmol / L. The average value of uric acid in the study group during the first measurement was 205.86 ± 31.39 μmol / L, and during the second measurement 223.90 ± 46.29 μmol / L. During the third measurement, the average value of uric acid in the study group was 253 ± 59.81 μmol / L, and at the end of the study this value was 315.73 ± 90.99 μmol / L.

Applying the Wilcoxon signed-rank test to the average uric acid values during all measurements within the control group, no statistically significant difference was found. There was a statistically significant increase in the study group between all measurements, from 18.04 μmol / L between the first and second measurement (Z = -1.955; p = 0.043), 29.10 μmol / L between the second and third measurement (Z = -2.973; p = 0.003), 37.27 μmol / L between the third and fourth measurement (Z = -4.325; p = 0.001) and 109.87 μmol / L at the end of the study in comparison to values from the start of the study (Z = -4.309; p = 0.001).

5. DISCUSSION

Hyperuricemia is a common finding in preeclamptic pregnancies. The elevation of uric acid in preeclamptic women often precedes hypertension and proteinuria, the clinical manifestations used to diagnose the disorder (10). Impact of uric acid in pregnancy has been tested in numerous studies (10). In this study, the average uric acid value in the control subjects was 213.36 ± 28.96 μmol / L, and in the subjects in the study group the av-

erage uric acid value was 249.73 ± 47.06 μmol / L. In this case, a statistically significant difference in the average value of uric acid during pregnancy was found between the control and study group, p = 0.001.

Analyzing the average uric acid value during all measurements within the control group revealed no statistically significant difference. There was a statistically significant increase in the test group between all measurements, from 18.04 μmol / L between the first and second measurements (p = 0.043), 29.10 μmol / L between the second and third measurements (p = 0.003), 37.27 μmol / L between third and fourth measurements (p = 0.001) and 109.87 μmol / L at the end of the study in comparison to values from the beginning of the study (p = 0.001). Corominas et al. conducted a retrospective study involving 79 healthy pregnant women and 79 pregnant women with preeclampsia and analyzed uric acid, creatinine and urea values. Uric acid values were similar in both groups during the first half of pregnancy. However, at week 20, uric acid increased 1.5 times in pregnant women with preeclampsia without changes in creatinine and urea, which correlates with the results of this study (11). Compared to this study, slightly higher mean uric acid levels in pregnant women with preeclampsia were reported by Gao YF. et al. The average values of uric acid for mild and severe preeclampsia were 359 ± 114 μmol / L and 450 ± 132 μmol / L (12).

In a study conducted by Heilmann et al. which included 52 patients with preeclampsia and 40 healthy pregnant women as a control group most preeclamptic subjects had a significantly increased uric acid, which

correlates with the results of this study (13). Bainbridge et al. claimed that uric acid may play direct roles in the pathological processes of preeclampsia at both placental and maternal vasculature (10). Kang et al. suggested that elevated serum uric acid in pregnancy may not only be a valuable biomarker for preeclampsia but may also have a contributory role in the pathogenesis of fetal disorders (14). Mador et al. suggested that uric acid and its higher values could be the cause or trigger of preeclampsia (15). Mazzali et al. experimentaly confirmed in mice a pathological role of uric acid in development of glomerular and systemic hypertension (16). Roberts et al. sugested that patients who in 10 weeks of gestation have elevated levels of uric acid will have a bigger chance to develop preeclampsia (17). All above, monitoring of uric acid should be part of the daily clinical work of a gynecologist.

6. CONCLUSION

Uric acid values should become part of a broad biochemical range in screening and optimizing the treatment of patients diagnosed with early preeclampsia, together with Doppler sonography.

- **Declaration of patient consent**: The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution**: E.M. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. E.M. had role in drafting the work and revising it critically for important intellectual content. E.M. 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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