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## Diagnostic value of determining the level of purine metabolism intermediates in pregnant women with chronic hypertension and superimposed preeclampsia

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### ABSTRACT

**Introduction:** Chronic hypertension and related cardiovascular diseases are some of the leading causes of maternal and perinatal morbidity and mortality in the world.

**Objectives:** The aim of the study was to evaluate the diagnostic value of purine metabolism products in plasma and blood erythrocytes in pregnant women with chronic hypertension with superimposed preeclampsia.

**Patients and Methods:** Around 139 patients were examined, including 110 pregnant women and 29 healthy non-pregnant women of childbearing age (control group). The content of purine metabolism intermediates was determined; guanine, hypoxanthine (HX), adenine, xanthine (X) and uric acid (UA) - in plasma and erythrocytes. We also determined the level of blood platelets, proteinuria in the general analysis of urine in pregnant women with chronic arterial hypertension, severe preeclampsia, and in pregnant women with chronic hypertension with superimposed preeclampsia.

**Results:** The level of purine catabolism intermediates significantly exceeds in the blood of pregnant women with chronic hypertension and superimposed preeclampsia compared to control group. It was determined that purine intermediates a significant increase in pregnant women with chronic hypertension with superimposed preeclampsia compared to pregnant women with isolated chronic hypertension, pregnant women with severe preeclampsia. An analysis of correlations showed that the increase in purine intermediates in blood in pregnant women with chronic hypertension and superimposed preeclampsia is associated with an increase in proteinuria and thrombocytopenia. It indicates a diagnosis of preeclampsia to chronic hypertension. It can be an additional diagnostic criterion, along with proteinuria and thrombocytopenia.

**Conclusion:** Determination of purine intermediates can be used as an additional diagnostic criterion in pregnancy with chronic hypertension.

### *Implication for health policy/practice/research/medical education:*

Determination of purine metabolites will allow timely prevention of preeclampsia complications. Determination of purine metabolites in pregnant women with chronic hypertension with superimposed preeclampsia is a contribution to fundamental research in pregnancy hypertension. It is an innovative approach to the diagnosis of preeclampsia.

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### Introduction

Chronic hypertension and cardiovascular diseases are some of the leading reasons of maternal and perinatal morbidity and mortality in the world. Chronic hypertension in pregnant women is associated with many severe outcomes,

including preeclampsia, eclampsia, cesarean section, cerebrovascular injury, fetal growth retardation, and premature birth, maternal and also perinatal mortality. In 0.9%–1.5% of pregnant women, it can lead to maternal, intrauterine, and neonatal morbidity and mortality

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(1). Problems of diagnosing and treating hypertension during pregnancy and the latest guidelines for managing chronic hypertension are priorities in obstetrics. The level of chronic hypertension in pregnant women involved by 67% from 2000 to 2009. This increase is mostly associated with widespread obesity and an increase in the age of motherhood (1,2). This trend direction is expected to continue. The American College of Obstetricians and Gynecologists (ACOG) provides a classification for chronic hypertension (3);

- Gestational hypertension - hypertension that occurs after 20 weeks of pregnancy without proteinuria
- Severe preeclampsia - a combination of hypertension and proteinuria (0.3 g/L or more) and/or severe headache, impaired vision, edema of the optic disc, pain in the epigastric region and/or nausea, vomiting, convulse, generalized edema, oliguria (less than 30 mL/h or less than 500 mL of urine in 24 hours), pain on palpation of the liver, platelet count below  $100 \times 10^6/L$ , increased liver enzymes (alanine aminotransferase or aspartate aminotransferase above 70 IU/L), Hemolysis, Elevated Liver enzymes and Low Platelets syndrome (HELLP), arising after 20 weeks of pregnancy
- Chronic hypertension - hypertension that occurred before pregnancy or before 20 weeks of a real pregnancy
- Chronic hypertension with superimposed preeclampsia – accession of preeclampsia in pregnant women who previously had chronic arterial hypertension.

Diagnosis of preeclampsia is not always easily diagnosed and is often a diagnosis of exclusion. A sudden increase in blood pressure or a sudden increase in proteinuria (above the threshold for normal or a clear change from the baseline) leads to an assessment of the possible superimpose preeclampsia and timely adequate management of pregnancy. However, it is often difficult to distinguish between worsening of chronic hypertension and preeclampsia in the presence of chronic hypertension. The abrupt onset of thrombocytopenia can be a diagnostically valuable evidence of the addition of preeclampsia, because unlike increased blood pressure and proteinuria, platelet activation, aggregation and consumption are absent in gestational or chronic hypertension. As in the case of thrombocytopenia, a sudden increase in the level of hepatic enzymes or a sudden development of symptoms characteristic of preeclampsia confirm the addition of preeclampsia. Another way to verify of preeclampsia to chronic hypertension is to increase the level of uric acid, which is the end product of purine catabolism (4). The main purine bases are adenine and guanine. Xanthine and hypoxanthine are metabolic products of adenine and

guanine. Purines exert their effect by activating specific receptors, since purine receptors are widely present in the cells of blood vessels, heart, liver, kidneys and other organs (5). In particular, various types of P2Y receptors are found in a healthy heart and in the development of heart failure (6,7). However, there are many questions about the effect of other intermediates of purine catabolism in the pathogenesis of preeclampsia and chronic arterial hypertension.

### Objectives

The aim of the study was to evaluate the diagnostic value of purine metabolism products in plasma and erythrocytes in pregnant women with chronic hypertension with superimposed preeclampsia.

### Patients and Methods

#### *Study population*

A total of 139 patients were examined, 110 of them were pregnant women hospitalized in the Regional Clinical Hospital, Perinatal Center and 29 patients were healthy non-pregnant women of childbearing age. The criteria for the inclusion of pregnant women in the study was the informed consent of the woman to participate in the study, gestational age 20-42 weeks of gestation, the presence of the studied pregnancy pathology. The exclusion criteria were oncological diseases, HIV infection, tuberculosis, concomitant severe somatic pathology (diabetes mellitus, bronchial asthma, renal, liver failure, all types of collagen vascular diseases and autoimmune diseases), obesity, mental illness and drug addiction.

Pregnant women were divided into three groups and a control group:

- Group 1; 32 pregnant women with severe chronic hypertension (a women with history of chronic hypertension, at a systolic blood pressure (SBP) level of  $\geq 160$  mm Hg and/or diastolic blood pressure (DBP)  $\geq 110$  mm Hg, without proteinuria or thrombocytopenia.
- Group 2; 48 pregnant women with severe preeclampsia (a woman with SBP level of  $\geq 160$  mm Hg and/or DBP  $\geq 110$  mm Hg after 20 gestational weeks and proteinuria 0.3 g/L and more)
- Group 3; 30 pregnant women with chronic hypertension with superimposed preeclampsia (a women with history of chronic hypertension, at SBP level of  $\geq 160$  mm Hg and/or DBP  $\geq 110$  mm Hg with proteinuria or thrombocytopenia).
- Group 4; control group - 29 healthy non-pregnant women of childbearing age.

The diagnosis of severe preeclampsia, chronic severe arterial hypertension, and chronic hypertension with superimposed preeclampsia was made on the basis of the

classification proposed by the protocol of diagnosis and treatment of the Ministry of Health of the Republic of Kazakhstan “Arterial Hypertension in Pregnant Women” No. 36 dated 12/27/2017 (8). At an SBP level of  $\geq 160$  mm Hg and/or DBP  $\geq 110$  mm Hg. Severe preeclampsia was diagnosed in pregnant women on the basis of an increase in SBP  $\geq 160$  mm Hg and/or DBP  $\geq 110$  mm Hg, and proteinuria 0.3 g/L, a single portion of urine or more or 0.3 g or more in daily urine (pregnant women with HELLP syndrome and eclampsia was excluded).

The substrate for the study was blood. Blood sampling was carried out according to general rules on an empty stomach. A blood test was conducted later than an hour after blood sampling. Blood was stabilized with heparin. Red blood cells were separated from plasma by centrifugation. The content of purine metabolism intermediates was determined: guanine, hypoxanthine (HX), adenine, xanthine (X) and uric acid (UA) - in blood plasma, erythrocytes. Purine metabolites were studied by the method of E.V. Oreshnikova et al (9,10). The concentration of the products of the catabolism of purine bases was expressed in units of extinction and UA in  $\mu\text{mol/L}$ . We also determined the level of blood platelets, proteinuria in the general analysis of urine in pregnant women with chronic arterial hypertension, severe preeclampsia, and in pregnant women with preeclampsia against the background of chronic hypertension.

#### Ethical issues

The study was performed in agreement with the principles of the Declaration of Helsinki, 1996 version and its later amendments and also Good Clinical Practice standards. Each patient who took part in the study signed the informed consent form. The study design was approved by the Bioethics Committee of the Karaganda Medical University (No. 33 dated January 3, 2018). All patients'

information remained confidential.

#### Statistical analysis

Statistical analysis of the data was carried out using the software package SPSS version 22.0, taking into account the computational methods recommended for biology and medicine. The analysis of the obtained data included the calculation of the median, upper and lower quartiles. Given the abnormal distribution of the studied parameters, the reliability of the observed differences was determined by the nonparametric method of variance analysis using the Kruskal-Wallis test, with further pairwise determination of the significant differences between the groups using the Mann-Whitney test (Table 1). To identify the relationships between the studied values and establish the strength of these bonds, the Spearman's pair correlation coefficients ( $r$ ) were calculated (Table 3).

#### Results

The results of the study of the content of purine metabolism intermediates in erythrocytes and plasma of pregnant women with various types of hypertension are presented in Tables 1 and 2, respectively. When determining the content of purine metabolism products in erythrocytes in pregnant women with all types of hypertension, statistically significant differences were found with respect to control, to a greater extent in group 3 ( $P = 0.0001$ ). The content of guanine, HX, adenine, UA in the blood erythrocytes of pregnant women with chronic hypertension with superimposed preeclampsia is significantly higher than in pregnant women with chronic arterial hypertension and severe preeclampsia, however, the level of xanthine does not differ among all groups of pregnant women with hypertension.

In blood plasma, the content of purine metabolism products statistically significantly differs relative to the

**Table 1.** The content of metabolites of purine metabolism in red blood cells in pregnant women with various types of hypertension

| Indicator             | 1-Severe chronic hypertension (n=32), (Q25, Q75) | 2-Severe preeclampsia (n=47) (Q25, Q75) | 3-Chronic hypertension with superimposed preeclampsia (n=30) (Q25, Q75) | 4-Control group (n=30) (Q25, Q75) |
|-----------------------|--|---|---|-----------------------------------|
| Guanine (Median)      | 276*# (263; 298)                                 | 422* (384; 459)                         | 544*#(547; 1139)  | 171 (173; 221)                    |
| Hypoxanthine (Median) | 459*# (398; 485)                                 | 381*# (360; 469)                        | 746*# (748; 1284)   | 162 (156; 207)                    |
| Adenine (Median)      | 493# (421; 525)                                  | 357# (339; 449)                         | 683*# (684; 1237)   | 451 (349; 497)                    |
| Xanthine (Median)     | 224 (209; 271)                                   | 207* (195; 250)                         | 284* (327; 984)   | 194 (174; 217)                    |
| Urine acid (Median)   | 104*# (96; 139)                                  | 118* (101; 140)                         | 168*# (179; 289)  | 75 (73; 81)                       |
| X/HX                  | 0.48   | 0.54                                    | 0.38  | 1.19                              |
| UA/HX                 | 0.23   | 0.31                                    | 0.23  | 0.46                              |
| UA/X                  | 0.46   | 0.57                                    | 0.59  | 0.39                              |

\* Statistically significant differences with control according to the Kruskal-Wallis test ( $\leq 0.013$ ).

# Statistically significant differences between group 3 and group 1, 2 according to the Mann-Whitney criterion ( $\leq 0.013$ ).

**Table 2.** The content of metabolites of purine metabolism in plasma in pregnant women with various types of hypertension

| Indicator             | 1-Severe chronic hypertension (n=32), (Q25, Q75) | 2-Severe preeclampsia (n=47) (Q25, Q75) | 3-Chronic hypertension with superimposed preeclampsia (n=30) (Q25, Q75) | 4-Control group (n=30) (Q25, Q75) |
|-----------------------|--|---|---|-----------------------------------|
| Guanine (Median)      | 222# (199; 341)                                  | 284*# (259; 348)                        | 440*# (398; 4711)   | 159 (156; 178)                    |
| Hypoxanthine (Median) | 209# (201; 300)                                  | 261*# (250; 335)                        | 559*# (548; 653)  | 166 (158; 235)                    |
| Adenine (Median)      | 208# (175; 256)                                  | 218*# (207; 286)                        | 384*# (350; 462)  | 135 (135; 153)                    |
| Xanthine (Median)     | 206*# (194; 263)                                 | 207*# (203; 252)                        | 299*# (262; 396)  | 139 (136; 164)                    |
| Urine acid (Median)   | 219*# (184; 240)                                 | 214*# (187; 239)                        | 506*# (449; 522)  | 114 (113; 161)                    |
| X/HX                  | 0.99   | 0.79                                    | 0.40  | 0.84                              |
| UA/HX                 | 1.05   | 0.82                                    | 0.71  | 0.69                              |
| UA/X                  | 1.06   | 1.03                                    | 1.77  | 0.82                              |

\* Statistically significant differences with control according to the Kruskal-Wallis test ( $\leq 0.013$ ).

# Statistically significant differences between group 3 and group 1, 2 according to the Mann-Whitney criterion ( $\leq 0.013$ ).

control. The mostly high level of purine bases and purine intermediates was found in the third group of pregnant women compared with the control, the first and second groups of pregnant women. It was found a trend of increasing of purine metabolism intermediates in the second group relative to the first group.

The calculation of the indices characterizing the activity of xanthine oxidase in red blood cells showed the following findings; in pregnant women with all types of hypertension, there was a tendency toward a decrease in X/HX and UA/HX in erythrocytes, mostly in the 3rd group of pregnant women, relative to the control group, which indicates a certain decrease in xanthine oxidase activity, however, UA/X in red blood cells of the second and third groups pregnant is more elevated. In plasma, the coefficients X/HX, UA/HX, UA/X in all groups of pregnant women are lower than in the control group, which indicates a decrease in xanthine oxidase activity in blood plasma.

Table 3 presents the correlation analysis. Thus, in the third group of pregnant women with chronic arterial hypertension with superimposed preeclampsia, a statistically significant negative correlation between the level of proteinuria and hypoxanthine was determined. A statistically significant positive correlation was also found between proteinuria and xanthine in blood plasma, uric acid in erythrocytes, and blood platelets. At the same time, a statistically significant negative correlation was determined between blood platelets and guanine, plasma hypoxanthine, a positive correlation with proteinuria.

In group 1 of pregnant women with severe chronic hypertension, when determining the correlation between proteinuria and the level of purine intermediates, we found statistically significant positive correlations between the level of proteinuria and xanthine and also with plasma uric acid.

A positive significant correlation was found between platelets and uric acid in pregnant women in the second group with severe preeclampsia.

### Discussion

An analysis of the results allowed us to draw the following conclusions. In pregnant women with chronic hypertension with superimposed preeclampsia, the level of purine catabolism intermediates significantly exceeds the control values, as well as the comparison groups both in red blood cells and in blood plasma. The main trends in the indices characterizing the activity of xanthine oxidase demonstrate a change in its activity in the blood plasma towards an increase, while at the same time its decrease in the blood erythrocytes of pregnant women with all types of hypertension relative to control. This is probably due to the increased release of purines from cells under the conditions of increasing hypoxia, oxidative stress (hypoxanthine is considered as a biochemical marker of hypoxia (9,10,12)) and inhibition of the antioxidant defense of the body under conditions of oxidative stress (11). Additionally, a tendency to an increase in purine metabolites can also be associated with a violation of the reverse transport of purine nucleotides and intermediates of their catabolism into cells, which is caused by impaired capture by their specific receptors on cell membranes. At the same time, xanthine is able to provoke vasoconstriction, which is characteristic of hypertensive conditions. Uric acid and xanthine are inducers of endothelial vessel damage, which contributes to the progression of preeclampsia, further damage to the glomeruli of the kidneys and aggravation during preeclampsia.

An analysis of correlations showed that the increase in purine intermediates in blood plasma in pregnant women with chronic hypertension with superimposed preeclampsia is associated with an increase in proteinuria,

**Table 3.** Results of pair correlation analysis (Spearman r-coefficients) of purine metabolism and protein in OAM, blood platelet count in pregnant women of group 3 (pregnant women with chronic hypertension with superimposed preeclampsia)

|               | Guanine of plasma 3 | Hypoxanthine of plasma 3 | Adenine of plasma 3 | Xanthine of plasma 3 | Urine acid of plasma 3 | Proteinuria 3 | Platelets 3  | Guanine of erythrocytes 3 | Hypoxanthine of erythrocytes 3 | Adenine of erythrocytes 3 | Xanthine of erythrocytes 3 | Urine acid of erythrocytes 3 |
|---------------|---------------------|--------------------------|---------------------|----------------------|------------------------|---------------|--------------|---------------------------|--------------------------------|---------------------------|----------------------------|------------------------------|
| Proteinuria 3 | -0.088              | <u>-0.6**</u>            | -0.1                | <u>0.5**</u>         | -0.2                   | -             | <u>0.5**</u> | 0.3                       | 0.2                            | 0.04                      | 0.2                        | <u>0.4*</u>                  |
| Platelets 3   | <u>-0.4*</u>        | <u>-0.6**</u>            | -0.05               | 0.2                  | -0.18                  | <u>0.5**</u>  | -            | 0.4*                      | 0.2                            | 0.1                       | 0.3                        | 0.2                          |

\*\* The correlation is significant at the level of 0.01 (two-way).

\* The correlation is significant at the level of 0.05 (two-way).

**Table 4.** Results of pair correlation analysis (Spearman's r-coefficients) of purine metabolism and protein in OAM, blood platelet count in pregnant women of group 1 (pregnant women with severe chronic hypertension)

|               | Guanine of plasma 1 | Hypoxanthine of plasma 1 | Adenine of plasma 1 | Xanthine of plasma 1 | Urine acid of plasma 1 | Proteinuria 1 | Platelets 1 | Guanine of erythrocytes 3 | Hypoxanthine of erythrocytes 1 | Adenine of erythrocytes 1 | Xanthine of erythrocytes 1 | Urine acid of erythrocytes 1 |
|---------------|---------------------|--------------------------|---------------------|----------------------|------------------------|---------------|-------------|---------------------------|--------------------------------|---------------------------|----------------------------|------------------------------|
| Proteinuria 1 | 0.2                 | <u>0.3</u>               | 0.2                 | <u>0.4*</u>          | 0.5**                  | -             | <u>0.2</u>  | -0.02                     | 0.18                           | 0.16                      | 0.24                       | <u>0.18</u>                  |
| Platelets 1   | <u>-0.3</u>         | <u>-0.2</u>              | -0.2                | -0.2                 | -0.1                   | <u>0.2</u>    | -           | 0.1                       | 0.1                            | 0.08                      | 0.14                       | 0.13                         |

\*\* The correlation is significant at the level of 0.01 (two-way).

\* The correlation is significant at the level of 0.05 (two-way).

**Table 5.** Results of pair correlation analysis (Spearman's r-coefficients) of purine metabolism and protein indicators in OAM, blood platelet count in pregnant women of group 2 (pregnant women with severe preeclampsia)

|               | Guanine of plasma 2 | Hypoxanthine of plasma 2 | Adenine of plasma 2 | Xanthine of plasma 2 | Urine acid of plasma 2 | Proteinuria 2 | Platelets 2 | Guanine of erythrocytes 2 | Hypoxanthine of erythrocytes 1 | Adenine of erythrocytes 2 | Xanthine of erythrocytes 2 | Urine acid of erythrocytes 2 |
|---------------|---------------------|--------------------------|---------------------|----------------------|------------------------|---------------|-------------|---------------------------|--------------------------------|---------------------------|----------------------------|------------------------------|
| Proteinuria 2 | 0.09                | <u>0.08</u>              | 0.2                 | <u>0.02</u>          | -0.06                  | -             | <u>0.06</u> | -0.06                     | -0.03                          | -0.05                     | 0.03                       | <u>0.09</u>                  |
| Platelets 2   | <u>0.14</u>         | <u>0.16</u>              | 0.16                | 0.24                 | 0.33*                  | <u>0.06</u>   | -           | 0.05                      | 0.05                           | 0.16                      | 0.19                       | 0.09                         |

\*\* The correlation is significant at the level of 0.01 (two-way).

\* The correlation is significant at the level of 0.05 (two-way).



thrombocytopenia and indicates the addition of preeclampsia in pregnant women with chronic hypertension and can be considered as an additional diagnostic criterion, along with proteinuria and thrombocytopenia. In cases of difficulty in diagnosing preeclampsia in pregnant women with chronic hypertension, the determination of purine metabolism intermediates contributes to the correct diagnosis and, mostly importantly, timely treatment. The only etiological method of treating chronic hypertension with superimposed preeclampsia is timely delivery. In cases where the diagnosis is not accurately verified, further prolongation of pregnancy can lead to complications of preeclampsia (eclampsia, HELLP syndrome, placental abruption).

### Conclusion

An increase in the concentration of purine metabolism catabolites is a prognostically unfavorable factor, since purine bases play an important role in the progression of systemic endotheliosis characteristic of preeclampsia. Based on the results obtained, it is possible to propose the determination of the level of purine intermediates in blood plasma as an additional diagnostic tool confirming the layering of preeclampsia in pregnant women with chronic hypertension.

### Limitations of the study

It had some limitations including lack of follow-up of patients, which would demonstrate long-term renal outcomes, but was beyond the objectives of the present study due to the cross-sectional nature of the study.

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### Authors' contribution

DO, OP, ZA, DV and MM conducted the research. DO participated in all steps of creation of article. DV, ZA and MM collected material. OP checked statistical calculations. DO revised and prepared the final manuscript. All authors read and approved the final paper.

### Conflicts of interest

There were no points of conflicts to declare.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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