



THE ROLES OF HYPERHOMOCYSTEINEMIA ON THE DEVELOPMENT OF COMPLICATIONS IN PREECLAMPSIA

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✓ Resume

Preeclampsia is a complex and variable maternal disturbance that ranges from a dramatic onset at early gestation to slowly developing symptoms towards term. Hypertensive complications occur in 12-22% of all pregnancies and a major factor in maternal and neonatal morbidity and mortality.

The purpose of this study was to study the course of pregnancy and assess the state of newborns, from mothers with various severity of preeclampsia, depending on the level of homocysteine. Analyzed the state of 49 pregnant women with preeclampsia and their newborns. The control group was 20 pregnant women without hypertensive disorders. Preeclampsia and the level hyperhomocysteinemia statistically significantly affects not only the health of pregnant women, but also the state of health of the newborn.

Key words: *preeclampsia, endothelial dysfunction, hyperhomocysteinemia*

РОЛЬ ГИПЕРГОМОЦИСТЕИНЕМИИ НА РАЗВИТИЕ ОСЛОЖНЕНИЙ ПРИ ПРЕЭКЛАМПСИИ

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✓ Резюме

Гипертензивные осложнения наблюдаются в 12-22% всех беременностей и являются одним из главных факторов материнской и неонатальной заболеваемости и смертности.

Целью исследования было определение уровня гомоцистеина при гипертензивных состояниях у беременных и оценить влияние гомоцистеина на развитие осложнений при преэклампсии. Проанализировано состояние 49 беременных с преэклампсией и их новорожденных. Группу контроля составили 20 беременных без гипертензивных расстройств. Преэклампсия (ПЭ) и гипергомоцистеинемия статистически значимо влияет не только на здоровье беременной, но и состояние здоровья новорожденного. Чем выше уровень гомоцистеина в крови тем развитие осложнений преэклампсии.

Ключевые слова: *преэклампсия, эндотелиальная дисфункция, гипергомоцистеинемия*

ПРЕЭКЛАМПСИЯ АСОРАТЛАРИ РИВОЖЛАНИШИДА ГИПЕРГОМОЦИСТЕИНЕМИЯНИНГ РОЛИ

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✓ Резюме

Гипертензив бузилишлар барча ҳомиладорликларнинг 12-22% гача учрайди, ҳамда оналар ва болалар касалланиши ва ўлимининг асосий факторларидан бири ҳисобланади.

Таdqиқотдан мақсад гипертензив бузилишлар кузатишган ҳомиладорларда гомоцистеин микдорини аниклаш ва шунга кўра преэклампсия асоратлари ривожланишида гипергомоцистеинемия таъсирини баҳолаш бўлди. Преэклампсия кузатишган 49 нафар ҳомиладор ва уларнинг чакалоклари ҳолати таҳлил қилинди. Назорат гуруҳини гипертензив бузилишлар кузатилмаган 20 нафар соғлом ҳомиладорлар ташкил қилди. Гипергомоцистеинемия нафақат ҳомиладор аёлнинг соғлигига, балки янги туғилган чакалоқнинг соғлигига ҳам таъсир этиши аниқланди.

Калит сўзлари: *преэклампсия, эндотелиал дисфункция, гипергомоцистеинемия*

Relevance

Preeclampsia (PE) is a complex and variable maternal disturbance that ranges from a dramatic onset at early gestation to slowly developing symptoms towards term. Hypertensive disorders during pregnancy, including preeclampsia and eclampsia, are an urgent medical, social and economic problem due to the stable incidence of these gestational complications, the possibility of adverse immediate and long-term outcomes of pregnancy and childbirth for both the mother and the fetus, the difficulty of predicting, the lack of effective prevention and treatment measures [19]. Hypertensive complications are observed in 12-22% of all pregnancies and are one of the main factors of maternal and neonatal morbidity and mortality [1,2,14]. According to the World Health Organization, maternal mortality due to hypertensive complications during pregnancy occurs in 14% in industrialized countries [8,9] and up to 25% in developing countries [4,7], although most deaths due to preeclampsia and eclampsia can be avoided by timely diagnosis and treatment. The outcomes of pregnancy complicated by hypertension in most cases do not cause serious concerns, but sometimes these complications can have tragic consequences for the mother and child (e.g., placental abruption, preterm delivery and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, etc. and for fetus e.g., preterm birth, stillbirth, low birth weight, and small for gestational age, etc.) [5].

The ancient Greeks described symptoms of preeclampsia and eclampsia already, but eclampsia was differentiated from epilepsy first in 1739 by the French obstetrician Sauvages, and later termed Eclampsia parturentium. In 1843, proteinuria was observed, and led to the view that eclampsia depended on uremic poisoning caused by deficient renal excretion. After the detection of eclamptic hypertension at the end of the 19th century, the disease was regarded a manifestation of essential hypertension, brought to light and peculiarly coloured by pregnancy. However, it was recognised that preeclampsia occurred only in the presence of placental tissue, including cases with retained placental tissue and hydatiform mole, where the fetus is absent. Therefore, pathology of the placenta was early suspected as a causative factor. In 1967, Robertson and Brosens described specific structural changes of the uteroplacental unit in preeclampsia, and until recently, unsuccessful placentation has been regarded a necessary factor for preeclampsia to develop [6,13].

Pregnancy complicated by hypertensive disorders includes a spectrum of clinical manifestations from mild to severe forms, the classification of which depends on the severity of hypertension, the presence of clinical signs and symptoms, proteinuria and other laboratory changes. Various hematological changes may occur during the development and progression of preeclampsia [15]. Preeclampsia is a multisystemic syndrome. The a etiology of preeclampsia is still largely unknown, but we know more regarding the pathogenesis. The defects in placentation, which later lead to clinical pre-eclampsia, already emerge in the early weeks of gestation. In preeclampsia, the remodelling of placental spiral arteries is incomplete. The cytotrophoblast invasion of decidua is shallow, limited in the superficial decidua and the myometrial segments of the spiral arteries remain narrow and high-resistance. This first stage in the pathogenesis of pre-eclampsia, poor placentation, is followed by the second stage involving endothelial damage.

In the last two decades, a number of authors have investigated the effect that maternal concentrations of folate, homocysteine, and vitamin B12 may have on the development of preeclampsia [11,12]. Accumulating evidence suggests that hyperhomocysteinemia may be a cause of the endothelial dysfunction provoked by oxidative stress in preeclampsia.

Homocysteine (Hcy) is formed during the metabolism of dietary methionine, found largely in animal protein. Folic acid and vitamin B12 (VitB12) are required for Hcy metabolism; deficiencies in these can result in increased Hcy concentrations [12]. Folate (vitamin B9) is a dietary micronutrient, found in a variety of green leafy vegetables and fruits, which is required during pregnancy to support cell growth and healthy placental development and function. Folate serves as a donor of one-carbon units for the remethylation of homocysteine (Hcy) to methionine and then to S-adenosylmethionine (SAM), the universal methyl donor that affects systemic gene expression and cellular methylation potential (Figure 1). Folate, together with vitamins B12 and B6 as cofactors, is required to maintain Hcy levels within a normal range, because at high concentrations, Hcy is proinflammatory, leads to oxidative stress and has been associated with an increased risk for pregnancy complications. Hyperhomocysteinemia is a risk factor for both cardiovascular disease and vasculopathy [3]. A

mental disorders, HIV infection. All subjects underwent a general clinical examination. The following diagnostic criteria were included in the term hypertensive conditions during pregnancy: Arterial hypertension (mild) - systolic pressure ≥ 140 mm Hg. and/or diastolic pressure ≥ 90 mm Hg. with double measurement with an interval of at least 30 minutes; severe arterial hypertension diastolic pressure ≥ 110 mm Hg. with double measurement with an interval of at least 30 minutes; or systolic pressure ≥ 160 mm Hg. with double measurement with an interval of at least 30 minutes; Proteinuria $\rightarrow$ 0.3 g/day or 0.3 g/l in a double urine test taken 4 hours later [10]. Mild pre-eclampsia - mild arterial hypertension and proteinuria not more than 3 g / l, with or without slight or moderate edema. Severe preeclampsia is severe arterial hypertension with proteinuria, with or without generalized or rapidly increasing edema, or arterial hypertension of any severity with proteinuria with the addition of one of the alarming symptoms [9,17]. Measurement of the level of systolic and diastolic blood pressure was carried out according to the standard method with a sphygmomanometer. After the patient signed a voluntary informed consent to participate in the study, venous blood was taken by the standard method of venipuncture, on an empty stomach.

The determination of the level of homocysteine was carried out by the ELISA method using Homocystein ELISA reagents (EIA 2925). Statistical analysis of data was carried out.

Result and discussion

We examined 69 pregnant women at term (28-36 weeks), which were divided into 3 groups: the first group of pregnant women with mild preeclampsia (n=26), the second group of women with severe preeclampsia (n=23) and the third control group - healthy pregnant women (n=20). The age of women included in the study ranged from 18 to 37 years, the average age was 26.13 ± 3.21 years.

Analysis of general clinical data indicated no differences between groups in terms of age, parity of births in anamnesis, and gestational age ($p > 0.05$). Analysis of the levels of systolic blood pressure and proteinuria revealed significantly distinguishable indicators between the groups ($p < 0.05$).

Table 1. Average age and anthropometric parameters of pregnant women with preeclampsia

groups	Mild PE n=26	Severe preeclampsia n=23	Control group n=20
Average age	29,3 $\pm$ 0,91	26,3 $\pm$ 0,19	27,2 $\pm$ 0,23
Average height sm	157,2 $\pm$ 0,23	158,32 $\pm$ 0,45	161,3 $\pm$ 0,5
Average weight kg	74,3 $\pm$ 0,3	78,5 $\pm$ 0,4	70,5 $\pm$ 0,4

As can be seen from Table 1, the average age of pregnant women examined in all groups of the study was not significantly different from each other ($p > 0.05$). Also, there was no significant difference between the indicators of all the compared groups, and according to the main anthropometric parameters - the height and weight of pregnant women ($p > 0.05$), in comparison with the control group, more body weight and different degrees of obesity were observed in pregnant women with preeclampsia.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The height and pregestational weight of each patient were recorded.

During the study, different levels of obesity and overweight were noted in the main group compared to the comparison group and the control group. In the first group with mild preeclampsia it was equal to 30.1 ± 0.11 kg / m²; in the second group - 33.8 ± 0.40 kg / m²; 26.9 ± 0.42 kg / m² in the control group.

Thus, BMI of pregnant women with severe preeclampsia in the main group was found to have excess body weight and various degrees of obesity in 73%.

Table 2. Somatic diseases observed in examined women

Diseases	Severe preeclampsia n=23		Mild PE n=26		Control group n=20	
	Abs	%	Abs	%	Abs	%
Anemia	19	84,0	19	73	11	56,0
Varicose disease	6	26	6	20,6	3	15,0
Diseases of liver and biliary tract	4	17	3	11,5	2	8,0
Thyroid disease	12	55	15	58,6	9	45,0
UTI	8	35,5	9	34,6	3	12,0
ARI	10	42	8	30,7	5	25,0
Covid 19	9	39,1	7	27,0	3	12,0

It can be seen from Table 2 that in the main group of pregnant women with severe PE, who participated in the investigation, anemia (84%), urinary tract infections(UTI) (35.4%), varicose disease (26%) and acute respiratory infections(ARI) during pregnancy were higher than in the comparison and control group. Diseases of the liver and biliary tract were detected in 17% of women with severe preeclampsia, which is 2 times more than in physiologically developing fetuses (8%). 39.1% of women with severe preeclampsia were infected with covid-19, 27.0% of the mild PE group and this in turn may be caused by complications of hypercoagulability, hyperhomocysteinemia.

The level of homocysteine in the group of healthy pregnant women was 9.76 ± 0.62 mmol/l. The homocysteine index in the group with mild preeclampsia was 17.61 ± 0.65 mmol/l. In the group with severe preeclampsia, the level of homocysteine was significantly distinguishable 23.8 ± 0.33 mmol/l. In pregnant women with severe PE, there was a higher level of Hcy compared with the group with mild PE, while there was an increase in its level with the duration of the disease. In our study, women who subsequently developed severe PE had higher concentrations of Hcy than those in the control group. The logistic regression model demonstrated that Hcy was an independent risk factor for the development of severe PE [18], also showed that maternal and fetal serum Hcy levels were significantly higher in their group with severe PE as compared with their mild PE and control group, suggesting that elevated level of serum Hcy may be associated with the severity of PE.

The results of the analysis showed that the critical values of blood Hcy in the III trimester of pregnancy, associated with complications, such as premature detachment of a normally located placenta 6.1%, placenta previa 4%, perinatal death 8.1%, fetal hypotrophy 12.3%.

An increase in the level of homocysteine in the body is a recognized risk factor for the development of vascular diseases, the features of which resemble vascular changes observed in diseases associated with anomalies of placentation during pregnancy [20]. Since preeclampsia is considered as a systemic vascular disease resulting from endothelial dysfunction [18]. The results of our study indicate higher levels of homocysteine in hypertensive conditions, however, they are reliably distinguishable only in pregnant women with severe preeclampsia. In the group with severe preeclampsia, this figure was 2.2 times higher than in the group with uncomplicated pregnancy.

Preterm birth in pre-eclampsia is usually due to iatrogenic labour, induced labour or caesarean section, because, at present, ending the pregnancy is the only treatment for pre-eclampsia. Preterm birth prolongs newborn hospitalisation and the earlier the delivery the more pervasive the problems. Complications associated with premature birth include respiratory distress, hypoglycaemia, jaundice, feeding difficulties, and more severe in very premature newborns; kernicterus, seizures, periventricular leucomalasia. Preterm delivery, as well as, pre-eclampsia itself, elevates the risk of bronchopulmonary dysplasia and cerebral palsy[17].

The average weight of newborns born from mothers with preeclampsia was 2256.5 ± 2 g, and in the comparison group 2906.3 ± 2.5 . The birth of children weighing less than 1000 g accounted for 6 babies 13%. The average height of newborns in the first group was 43.3 ± 0.4 sm, in the second group in 40.2 ± 0.3 sm in the control group 49.2 ± 0.3 sm (table №3)

Assessment of newborns on the Apgar scale at the first and fifth minutes: in children born from mothers with preeclampsia 5.75 ± 0.18 , 6.31 ± 0.18 , in the control group 7.2 ± 0.07 , 8.4 ± 0.1 . In the first and second groups, the birth rate of newborns on the Apgar scale of 7-8 points was significantly lower than in the comparison group. With hyperhomocysteinemia in pregnant women, severe manifestations of intrauterine fetal hypoxia were more often noted: hypoxic-ischemic encephalopathy,

hyperexcitability syndrome, hypertensive syndrome than in the group with its optimal content ($p<0.05$).

Table №3. Anthropometric indicators of infants of observed pregnancies

Anthropometric indicators	Mild PE n=26	Severe preeclampsia n=23	Control group n=20
The average weight of the baby	2667±2.1	1846±3.2	2906±2.5
Average height	43.3 ± 0.4	40.2 ± 0.3	49.2 ± 0.3

Conclusion

Our study revealed that Hcy is significantly increased in those who developed severe PE. The possible mechanism maybe that homocysteine may cause endothelial dysfunction and, with the progression of pregnancy, this homocysteine-related endothelial injury may aggravate the placental ischemia, thus leading to the development of severe preeclampsia. However, we did not find a relationship between Hcy and gestational hypertension. The possible mechanism should be confirmed in future extensive studies. During pregnancy, there is a significant increase in homocysteine associated with an increase in the severity of hypertension, however, this indicator was significantly higher in severe preeclampsia compared with a normal pregnancy. This indicator can be used as an additional research method in the diagnosis of complications in preeclampsia, along with generally accepted diagnostic criteria. Concerns regarding Hcy are relatively novel in obstetrics. It has been found that alterations in methionine-Hcy metabolism may be related to systematic vascular damage, which can lead to the classic clinical appearance of hypertensive disorders of pregnancy (HDOP). It has also been assumed that higher levels of Hcy may contribute to the development of placental microvascular diseases and preeclampsia, thus affecting the endothelium adversely. Women diagnosed with PE are at a much greater risk of future cardiovascular or cerebrovascular diseases, with an estimated doubling of odds compared with unaffected women [13]. This association indicates that HDOP and cardiovascular diseases may share common risk factors.

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