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Article

OBESITY-RELATED PRE-ECLAMPSIA - FETUS AND NEWBORN OUTCOMES (literature review)

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Abstract. The paperdeals with the studying the epidemiology of risk factors of preeclampsia, including the delayed risk of preeclampsia associated with obesity. Obesity- is a serious risk factor for preeclampsia. Throughout the world, hypertensive disorders in pregnancy and related complications are among the main causes of maternal and their fetuses/newbornsmorbidity and mortality. Fetal and neonatal outcomes associated with eclampsia and its complications are significant, including neonatal mortality and serious long-term neonatal morbidity.

Key words. pregnancy; preeclampsia; obesity.

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For many years, PE remains one of the serious multisystem pathological complications of pregnancy, the frequency of which has no tendency to decrease. Still Hippocrates in the IY century BC He described the disease of pregnant women, the symptoms of which aligned with epilepsy. Only in 1827, R. Bright suggested that eclampsia (translated from Greek "lightning", "outbreak") is a kidney disease based on the definition of albuminuria. In 1843, J. Lever describes edema and headache for eclampsia. A. Delore in 1884 put forward an infectious theory and even identified the so -called Bacillus Eclampsae. In 1886, E. Leyden, the term "nephropathy" was introduced, and in 1908 S. D. Minov "Preeclampsia". In 1905, J. de Lee suggested that eclampsia is the result of toxins, and W. Zangemeister described the classic triad: arterial hypertension, swelling, proteinuria, which is the basis for the diagnosis and assessment of the severity of PE [1,2].

Hypertensive disorders during pregnancy, including preeclampsia (PE), represent a wide range of conditions that are associated with significant incidence and mortality of mothers and their and fruits/newborns. According to various authors, the incidence of PE is from 3 to 10% of all pregnancies. All over the world, PE and related complications are one of the main causes of maternal mortality. Currently, there is a tendency to reduce maternal mortality due to preeclampsia in developed countries, however, the maternal incidence remains high and is the main factor that contributes to hospitalization in the intensive care unit during pregnancy [3].

Approximately 12-25% of the fetal growth restrictions and small for this gestational age of the fetus, as well as from 15 to 20% of all premature births are associated with preeclampsia. Contenting complications associated with PE are significant, including the mortality rate of newborn and serious long -term neonatal incidence. Despite the tangible successes of medicine, the only well -known pathogenetic treatment of preeclampsia is the completion of pregnancy regardless of the gestational age [3,4]. The purpose of this publication is to discuss the epidemiology of risk factors PE, including the delayed risk of PE associated with obesity.

Obesity is a rapidly increasing risk factor for preeclampsia, which dictates the need to understand the pathogenetic mechanisms that contribute to the increase and implement this risk.

Preeclampsia is a syndrome specific for pregnancy, in which many organs are affected, characterized by the development of hypertension and proteinuria, mainly detected from 20 or more weeks of pregnancy. According to various estimates, PE complicates from 2 to 8% of all pregnancies. Although the exact reason is unknown, the pathophysiological processes underlying this disorder are described in two stages. The first stage is characterized by reduced placental perfusion, possibly associated with abnormal placenta, violation of trophoblast invasion and inadequate remodeling of the spiral arteries of the uterus. The second stage refers to maternal systemic manifestations with inflammatory, metabolic and thrombotic answers, which are reduced to a change in vascular function, which can lead to a violation of the activities of several organs [5,6].

The exact classification of various hypertensive disorders during pregnancy remained complex due to the changing nomenclature, as well as geographical variations in accepted diagnostic criteria. For example, such terms as "toxemia" and "hypertension

caused by pregnancy" are now considered outdated.

In addition, discussions continued on various diagnostic PE criteria in different regions of the world. This applies to the degree of hypertension, the presence/absence of proteinuria and the classification of the severity of the disease. These inconsistencies led to problems when comparing and generalizing epidemiological and other results of major studies [6].

The classification system, based on the report of the "working group by high arterial pressure during pregnancy", is most often used in the United States, which defines four main categories: gestational hypertension, preeclampsia/eclampsia, chronic hypertension and mesmeric hypertension of preeclampsia. Preeclampsia is defined as the first detected prolonged blood pressure (> 140 mm Hg Sistolic or> 90 mm Hg of HG diastolic at least 2 dimensions with an interval of 4-6 hours and proteinuria (at least 1+ or at least 1+ or > 300 mg in a 24-hour urine collection after 20 weeks of pregnancy [7].

The preeclampsia is considered severe if, in addition to the defining criteria for blood pressure and proteinuria, any of the following is present:

- blood pressure from 160 mm Hg. and higher
- systolic and/or diastolic from 110 mm Hg. and more.
- The excretion of five or more grams of protein with daily urine.
- neurological disorders (visual changes, headache, convulsions, coma). Pulmonary edema.
- liver dysfunction (increased liver transaminase or epigastric pain.
- impaired renal function, oliguria or increased concentration of creatinine in blood serum> 1.2 in women without indicating in a history of kidney disease.
- thrombocytopenia.
- placental detachment, restriction of the fetal growth or oligohydramnion.

Eclapsia refers to seizures that occur only in women with PE, and cannot be classified as other reasons.

Hellp syndrome is determined by the presence of hemolysis, increased liver transaminase and low platelets. Hellp is not necessarily manifested in the presence of hypertension or proteinuria, but it is believed that it is associated with preeclampsia.

Diagnosis of preeclampsia can be especially complicated in women with previously existing hypertension and/or chronic kidney disease, since both an increase in blood pressure and excretion of protein in urine increase to the end of pregnancy.

Thus, the diagnosis is based on a sudden increase in blood pressure or proteinuria and/or confirmation of a violation of the function of parenchymal organs [1,2].

The main reason for the critical assessments of various classification systems boils down to the fact that none of them has been independently appreciated in terms of the ability to identify those women who are at risk of adverse pregnancy outcomes. But recent studies were aimed at developing clinically significant definitions based on the forecast data of adverse outcomes [8–11].

A systematic review of the World Health Organization shows that hypertensive disorders in the structure of maternal mortality account for 16% of all maternal deaths in developed countries, 9% in Africa and Asia and up to 26% in Latin America and the Caribbean basin [12]. In regions with the highest MS, most deaths are associated with eclampsia, but not with preeclampsia. Based on the research data of the national study of the register of prescribed patients in the United States, the level of preeclampsia during childbirth and childbirth increased by 25% from 1987 to 2004, while the eclapsia indicator reduced I went out by 22%, although this indicator is not significant [4]. Severe complications of pre-eclampsia and eclampsia include renal failure, stroke, cardiac dysfunction or respiratory failure/arrest, coagulopathy, and liver failure. In a study of hospitals operated by Health Care America Corporation, preeclampsia was the second leading cause of pregnancy-related intensive care admissions after obstetric bleeding [3].

Fetal and neonatal outcomes associated with preeclampsia vary worldwide. Approximately 12 to 25% of fetal and small-for-gestational age growth restriction and 15 to 20% of all preterm births are associated with preeclampsia.

The associated complications in preterm infants are significant, including neonatal mortality and serious long-term neonatal morbidity. A quarter of stillbirths and neonatal deaths in developing countries are due to preeclampsia/eclampsia. Infant mortality due to preeclampsia is three times higher in low-resource health facilities than in high-income countries, largely due to a lack of facilities and capacity to provide neonatal intensive care [4].

A number of studies have reported a 7–20% chance of recurrence of preeclampsia in a subsequent pregnancy [12]. This risk is further increased if a woman has had preeclampsia complicated by two previous pregnancies, as well as if she developed preeclampsia at an earlier gestational age. Estimates of recurrence of preeclampsia vary greatly depending on the quality of the diagnostic criteria used. In an Icelandic study using strict diagnostic criteria for preeclampsia and other hypertension disorders, the likelihood of recurrent preeclampsia or superimposed preeclampsia in a second pregnancy was 13% [12]. Dr. Leon Chesley and his collaborators demonstrated that women whose even single pregnancies were complicated by eclampsia had a mortality risk that was two to five times higher over the next 35 years compared to those whose pregnancies were not complicated by preeclampsia. Other studies have also demonstrated an association between preeclampsia and cardiovascular disease and related mortality. The risk of cardiovascular disease was increased 8-fold in Scandinavian women who developed preeclampsia severe enough to require early delivery.

In a cohort of women who give birth in Jerusalem, the risk of mortality at 24-36 years of follow-up is twice as high in women with prior preeclampsia compared with women who have not been diagnosed [13]. Mortality was largely related to cardiovascular causes. These results were also confirmed in other populations [13]. Metabolic syndrome-hypertension, dyslipidaemia, insulin resistance, endothelial dysfunction, and vascular abnormalities have been observed months to years after preeclampsia, which also supported the concept of a link between preeclampsia and cardiovascular disease later on [13]. Whether these common risk factors lead to preeclampsia and then cardiovascular disease, or whether preeclampsia itself may contribute to this long-term risk remains unresolved. Based on these data, preeclampsia should be considered as a cardiovascular risk factor, and women with a history of preeclampsia should have ongoing, close surveillance to prevent and/or detect future cardiovascular disease. The epidemiology of preeclampsia reflects a wide range of risk factors, as well as the complexity and heterogeneity of the disease. Risk factors can be classified according to specific pregnancy characteristics and history. The increase in the frequency of preeclampsia may be associated with a higher prevalence of predisposing diseases such as chronic hypertension, diabetes mellitus, obesity, infertility, as well as the use of artificial reproductive technologies with a concomitant increase in multi-embryonic pregnancy [13].

According to a systematic review of controlled trials, first pregnancy is a significant risk factor, nearly tripling the risk of developing preeclampsia compared to repeat pregnancies. An estimated two-thirds of cases occur in first pregnancies after the first trimester. The relationship between first gestation and preeclampsia suggests an immunological mechanism that allows subsequent pregnancies to protect the mother's body from paternal antigens. In support of this concept, there is evidence that previous reproductive losses, prolonged sexual activity before pregnancy, or prolonged cohabitation before pregnancy are among the factors that reduce the risk of preeclampsia. On the contrary, the risk of preeclampsia increases with the use of barrier contraceptives, changing the future father, fertilization with donor spermatozoa. But even during a subsequent pregnancy, a change in sexual partner also increases the risk of preeclampsia [3].

Excessive volume of the placenta, as well as hydatidiform mole, multiple gestations are also associated with the development of preeclampsia. Early development of this complication may have more serious clinical manifestations [3,14].

The extreme age limits of childbearing age are also associated with preeclampsia. However, once a parity adjustment occurs in the young age group for recurrent pregnancies (because most first pregnancies occur at a younger age), the association between younger age and preeclampsia is lost. Multiple studies demonstrate a higher prevalence of preeclampsia in older women, regardless of parity; however, many do not control pre-existing medical health problems. After controlling for baseline differences, women aged 40 years and older had a two-fold risk of developing preeclampsia: an odds ratio of 1.68, (1.23-2.29) among primigravidas and 1.96, (1.34-2.87) among frequently pregnant women [13,14]. The connection between the African-American and American race and preeclampsia is explained by the higher prevalence in this group of chronic hypertension, often not diagnosed. Although some studies demonstrate a higher risk of preeclampsia among African American women, 32-34 large prospective research, which controlled the Association of the identified preeclampsia with other risk factors, did not find a significant connection between preeclampsia and African-American race. Heavier forms of preeclampsia can be associated with the negligent race of the mother [16].

Many risk factors for maternal mortality from preeclampsia are similar to the factors of cardiovascular diseases. The previous chronic hypertension, diabetes, obesity of vascular disorders, chronic kidney pathology, autoimmune states are associated with the risk of preeclampsia, and the degree of risk is seriously tied with the seriousness of the underlying chronic disease. Women with chronic hypertension have a risk of preeclampsia by10-25% more compared to the general population [7]. This risk is increased to 31% in women with long-term hypertension-from 4 and sick. With a diagnosis of gestational diabetes, the total risk of developing preeclampsia is approximately 21%. At the same time, the risk of 11-12% with diabetes lasting less than 10 years increases to 36-54% among women with longer diabetes leading to impaired microcirculatory homeostasis. In case of low kidney diseases (creatinine is a serum of 1.5 mg/DL), the risk of preeclampsia is estimated at 20-25%, but in more than 50% in pregnant women with severe renal failure.

Preeclampsia is more common in women with autoimmune states, such as systemic red lupus and antiphospholipid syndrome [7]. Family history according to preeclampsia is supposed to the risk of this formidable complication of pregnancy. Paradoxically, smoking cigarette is associated with a decrease in the risk of preeclampsia, possibly due to the modulation of angiogenic factors [14]. Obesity - an increased cetla index (BMI, kg/m2) is also associated with preeclampsia. Given the obesity epidemic in the United States and the world, this is one of the most significant and potentially variable risk factors for preeclampsia. In the United States, the proportion of women with overweight or obesity has increased by about 60% over the past thirty years [17]. The World Health Organization evaluates the prevalence of women with obesity and overweight (body mass index> 25 kg/m2) - in the United States of 77%, 73% in Mexico, 37% - in France, 32% - in China, 18% - 18% In India and 69% - in South Africa with wide variations on each continent [18]. The high prevalence of obesity and the predictable increase have significant consequences for pregnancy, since obesity is associated with infertility, spontaneous miscarriage, malformations of the fetus, thromboembolic complications, gestational diabetes, stillbirth, premature births, cesa -cross -section, macrosomia of the fetus and hypertension disorders [19]. Obesity increases the overall risk of preeclampsia by about 2-3 times [20]. The risk of preeclampsia is gradually increasing with an increase in BMI, even within the normal range. It is important to note that not only the late or light forms of preeclampsia are increasing, but also the early and severe preeclampsia, which are associated with greater perinatal incidence and mortality. Increased risk is present in both European and African-American women [21]. The connection between the risk of preeclampsia and obesity is also demonstrated in different populations around the world. The advanced concept that obesity can play a causal role is based on the fact that weight loss reduces the risk of preeclampsia. Some studies show that an excessive increase in the mass of mothers is associated with the risk of preeclampsia, although they can be refuted by the fact of fluid retention in interstation and cavities for preeclampsia, which contributes to weight growth. Although weight loss is not recommended during pregnancy, obesity refers to potential variable risk factors for preeclampsia [15]. Weight loss before pregnancy is recommended for women with overweight and obesity, which can help reduce the risk of adverse outcomes. According to American researchers, in a number of regions 30% the risk of preeclampsia is due to obesity. Obesity is a risk factor for both relatively preeclampsia and cardiovascular diseases [22]. In connection with the above, it is important to study the general mechanisms of the development of obesity and PE, which will ensure a deeper understanding of the pathophysiology of preeclampsia, potential areas for further research and possible goals of therapy.

According to estimates, insulin resistance is present in two -thirds of obese people. It is also a risk factor for cardiovascular diseases and type 2 diabetes [23]. Insulin resistance is more often found in preeclampsia and can persist until the age of seventeen after a pre-sequet of pregnancy, which increases the risk of cardiovascular diseases. Metabolic syndrome (obesity, hypertension, insulin resistance, impaired glucose tolerance and dyslipidemia) is also more often observed among women with a history of preeclampsia [23,24]. Regarding the metabolic syndrome, it was suggested that obesity contributes to hypertension in connection with many common pathogenetic mechanisms, including reducing the access of nitrogen oxide due to oxidative stress, an increase in sympathetic tone and ongotensinogen with fatty tissue. Dyslipidemia and an increase in the number of free fatty acids released from adipocytes also allegedly contribute to oxidative stress and insulin resistance [24].

Inflammation is a common pathogenetic mechanism of obesity, cardiovascular diseases and preeclampsia. Fat tissue generates several inflammatory mediators, which can disrupt the function of the endothelium and are more actively produced in obese people. C-reactive protein (CRP) is an inflammatory mediator produced by the liver, as well as adipocytes, its blood content is higher in obesity, it is associated with cardiovascular incidence. The circulating CRP rises at an early stage of pregnancy before the development of preeclampsia and, apparently, has a stronger connection with preeclampsia among women with obesity [25]. Inter-Lykin-6 is another powerful inflammatory mediator, which can lead to vascular damage and is associated with obesity, resistance to insulin and later-with cardiovascular disease. The concentration of the circulating CRP is also higher for preeclampsia associated with obesity, which indicates the potential connection of these pathologies [25]. The factor of tumor necrosis - alpha (TNF -A) is also produced by fat tissue and is associated with insulin resistance, endothelial damage and oxidative stress. Circulating concentrations increase both with the progressive severity of obesity and with preeclampsia [26]. Nevertheless, studies show that the TNF-A content is not higher in pregnant women with obesity compared to not suffering obesity [6,26]. As one of the important mechanisms of preeclampsia, oxidative stress is postulated, leading to a change in the function of the endothelium and the occurrence of vascular dysfunction. Obesity is also associated with oxidative stress, possibly secondary in relation to inflammation and free fatty acids, as well as to a lower concentration of circulating antioxidants [6,24]. Thus, oxidative stress can be a factor that contributes to the development of preeclampsia in fat women.

Leptin and adipiponectin - two substances produced by adipose tissue affect metabolism and are associated with cardiovascular diseases. Obesity is characterized by an increased level of leptin and a reduced concentration of adippipinectin [27]. Circulating leptin increases with preeclampsia and correlates with maternal BMI [27]. It should be noted that leptin is also produced by a placenta, probably representing the main source of circulating concentrations during pregnancy. Adiponectin has effects sensitive to insulin, its content decreases with obesity, and correctly correlates with cardiovascular risk. There is still no consensus regarding the concentration of adipiponectin of pre -extraclampsia, since the studies had conflicting reports about higher and low concentrations [2,28].

Based on the mechanism of action and associations with cardiovascular diseases and obesity, these adipokins can matter in the mechanism of development of preeclampsia, especially among women with obesity or inclination to it.

The balance of circulating angiogenic factors changes in pregnant women with the risk of preeclampsia in comparison with normal pregnancy [2]. The levels of the placental growth factor (PGF) and the vascular endothelial growth factor (VEGF) are lower in women with preeclampsia. This is probably due to a higher concentration of the circulating soluble SFLT- an anti-egogenous factor that binds and inactivates PGF and VEGF [29]. Some studies showed that the levels of SFLT-1 and PGF are reduced in pregnant women with obesity, while in other studies it is stated that higher BMI is associated with higher SFLT-1 concentrations and a higher SFLT-1/PGF ratio indicating the predominance anti -angiogenic effects in the early stages of pregnancy [29]. Although the research results are not consistent with each other, an altered angiogenic environment with obesity can cause the development of preeclampsia. Features of lifestyle, such as diet, sleep disturbance and physical activity also have a close causal connection with obesity and cardiovascular diseases. Many of these factors are associated with preeclampsia, thus increasing the likelihood of the presence of some general pathogenetic mechanisms of obesity and preeclampsia, which contribute to an increase in preeclampsia. Violation of the synthesis of nitrogen oxide (NO) and bioavailability leading to vascular dysfunction - the general key mechanism of the pathogenesis of obesity and cardiovascular diseases [30]. Asymmetric dimethylarginin (ADMA) is a competitive agonist L-Arginin, the precursor of the synthesis of nitrogen oxide. ADMA functions as an inhibitor of nitrogen oxide synthesis, leads to a decrease in the formation of NO and an increase in the formation of superoxide. Increased adma concentrations are associated with inflammation, insulin resistance, dyslipidemia, obesity and cardiovascular diseases. Interestingly, the circulating adma, as shown, decreases with weight loss [30]. In several studies, higher concentrations of ADMA were demonstrated with preeclampsia and even before its development [10]. In a number of clinical studies, L-Arginine was used to cancel some effects of ADMA. It was safely used during pregnancy. One randomized controlled study showed that the frequency of preeclampsia was reduced with the introduction of a combination of arginine

and antioxidant therapy in a high -risk group compared to placebo or antioxidants [31]. Further research will be useful for clarifying the effects of L-arginine at the degree of risk of preeclampsia and in women with obesity. Thus, the best understanding of the relationship between obesity, preeclampsia and cardiovascular diseases can also shed light on the general mechanisms of pathogenesis and offer adequate treatment.

A wide range of risk factors for the development of preeclampsia emphasizes the heterogeneity of this syndrome. Obesity - a growing problem around the world - is a serious factor in the risk of preeclampsia, and the realized risk of PE of fat women can subsequently lead to cardiovascular complications and mortality from cardiac pathology. Further study of the mechanisms underlying these connections will develop recommendations to reduce these potential risks.

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