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PREECLAMPSIA: NEW INFORMATION ABOUT THE PATHOGENESIS, DEFINITIONS AND RECOMMENDATIONS. REVIEW.

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Abstract

Background. Hypertensive disorders of pregnancy - chronic hypertension, gestational hypertension and preeclampsia - are a unique problem, since pathology and its therapeutic treatment simultaneously affect the mother and fetus, sometimes putting their well-being in conflict with each other. Preeclampsia, in particular, is one of the most dangerous complications of pregnancy. Often manifested as first-time hypertension and proteinuria during the third trimester of pregnancy, preeclampsia can rapidly progress to serious complications, including death of both mother and fetus. Although the cause of preeclampsia is still being debated, clinical and pathological studies show that the placenta plays a central role in the pathogenesis of this syndrome.

Aim. To review the scientific literature sources on the pathogenesis and treatment of preeclampsia.

Search strategy. In this review we search full-text publications in English and Russian, which are devoted to the pathogenesis and new recommendations for the treatment of preeclampsia. Next databases were used in the process of literature search: Pubmed, Web of science, Cyberleninka, Google Scholar by keywords. The search period was 2000-2022 years. 1566 publications were identified on this topic. 46 articles corresponded to our research objective. *Inclusion criteria:* Publications of the level of evidence A, B: meta-analyses, systematic reviews, cohort and cross-sectional studies. *Exclusion criteria:* summary reports, newspaper articles and personal messages.

Results and conclusions. Preeclampsia is the leading cause of maternal morbidity and mortality worldwide, the only definitive treatment for which - delivery of the fetus and placenta - leads to significant morbidity and mortality of newborns.

Keywords: *preeclampsia, hypertensive disorders, proteinuria.*

Резюме

ПРЕЭКЛАМПСИЯ: НОВЫЕ СВЕДЕНИЯ О ПАТОГЕНЕЗЕ, ОПРЕДЕЛЕНИЯХ И РЕКОМЕНДАЦИЯХ. ОБЗОР ЛИТЕРАТУРЫ.

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Актуальность. Гипертензивные расстройства беременности - хроническая гипертензия, гестационная гипертензия и преэклампсия - представляют собой уникальную проблему, поскольку патология и ее терапевтическое лечение одновременно влияют на мать иплод, иногда ставя их благополучие в противоречие друг с другом. Преэклампсия, в частности, является одним из самыхопасных осложнений беременности. Часто проявляясь в виде впервые возникшей артериальной гипертензии и протеинурии в течение третьего триместра беременности, преэклампсия может быстро прогрессировать до серьезных осложнений, включая смерть как матери, так и плода. Хотя причина преэклампсии все еще обсуждается, клинические и патологические исследования показывают, что плацента играет центральную роль в патогенезе этого синдрома.

Цель. Провести анализ данных литературы по патогенезу и лечению преэклампсии.

Стратегия поиска. В исследовании изучены полнотекстовые публикации на английском и русском языках, которые посвящены патогенезу и новым рекомендациям по лечению преэклампсии. В процессе поиска литературы использованы следующие поисковые системы: Pubmed, Web of science, Cyberleninka, Google Scholar по ключевым словам. Временной период был обозначен 2000-2022 годами. По данной теме выявлено 1566публикаций. Из них цели нашего исследования соответствовало 46 публикаций. *Критерии включения:* Публикации уровня доказательности А, В: мета-анализы, систематические обзоры, когортные и поперечные исследования. *Критерии исключения:* краткие отчеты, газетные статьи и личные сообщения.

Результаты и выводы. Преэклампсия является ведущей причиной материнской заболеваемости и смертности во всем мире, единственное окончательное лечение которой - родоразрешение плода и плаценты - приводит к значительной заболеваемости и смертности новорожденных.

Ключевые слова: *преэклампсия, гипертензивные расстройства, протеинурия.*

Түйіндеме

ПРЕЭКЛАМПСИЯ: ПАТОГЕНЕЗ, АНЫҚТАМАЛАР МЕН ҰСЫНЫСТАР ТУРАЛЫ ЖАҢА АҚПАРАТ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Жүктіліктің гипертензиялық бұзылыстары-созылмалы гипертензия, гестациялық гипертензия және преэклампсия —бұл ерекше проблема, өйткені патология және оның емі ана мен ұрыққа бір уақытта әсер етеді, кейде олардың әл-ауқатын бір-біріне қайшы келтіреді. Преэклампсия, атап айтқанда, жүктіліктің ең қауіпті асқынуларының бірі болып табылады. Көбінесе жүктіліктің үшінші триместрінде алғаш рет пайда болған артериялық гипертензия және протеинурия түрінде көрінетін преэклампсия ананың да, ұрықтың да өлімін қоса алғанда, ауыр асқынуларға тез жетуі мүмкін. Преэклампсияның себебі әлі де талқыланғанымен, клиникалық және патологиялық зерттеулер плацента осы синдромның патогенезінде басты рөл атқаратынын көрсетеді.

Мақсаты. Преэклампсия патогенезі және емдеу туралы әдебиеттерге талдау жүргізу.

Іздеу стратегиясы. Преэклампсияның патогенезі және емі бойынша жаңа ұсыныстар туралы ағылшын және орыс тілдеріндегі толық мәтінді басылымдар зерттелді. Әдебиеттерді іздеу барысында келесі іздеу жүйелері қолданылды: Pubmed, Web of science, Cyberleninka, Google Scholar кілт сөздер бойынша сараптама жүргізілді. Уақыт кезеңі 2000-2022 жылдармен белгіленді. Осы тақырып бойынша 1566 жарияланым анықталды. Олардың ішінде біздің зерттеуіміздің мақсатына 46 мақала сәйкес келді. *Қосу критерийлері:* А, В дәлелділік деңгейінің жарияланымдары: мета-талдаулар, жүйелі шолулар, когорттық және көлденең зерттеулер. *Шығару критерийлері:* қысқаша есептер, газет мақалалары және жеке хабарламалар.

Нәтижелер мен қорытындылар. Преэклампсия бүкіл әлемде ана ауруы мен өлім — жітімнің жетекші себебі болып табылады, оның жалғыз түпкілікті емі — ұрық пен плацентаның туылуы-жаңа туған нәрестелердің айтарлықтай ауруы мен өліміне әкеледі.

Түйінді сөздер: *преэклампсия, гипертензиялық бұзылыстар, протеинурия.*

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Introduction.

Preeclampsia usually manifests around the 20th week of pregnancy with symptoms of hypertension and proteinuria. Delayed childbearing in developed countries increases the risk factors associated with preeclampsia, which include the elderly age of the mother, obesity and/or vascular diseases. Inadequate prenatal care partly explains the continued high prevalence in developing countries. In this review, we describe representations of the most recent concepts of the pathogenesis of preeclampsia. We also describe in detail the updated definitions, classification scheme and treatment goals for hypertensive pregnancy disorders proposed by obstetric and hypertensive societies around the world. There has been a shift towards considering preeclampsia as a systemic disease with widespread endothelial damage and potential impact on future cardiovascular diseases, rather than as a self-limiting phenomenon. At least now we know that preeclampsia does not end with placental abruption. In conclusion, we summarize the latest strategies for the prevention and treatment of preeclampsia. A deeper understanding of this organization will help in the care of at-risk women before childbirth and for decades after.Preeclampsia is a common disease characteristic of pregnancy, which is manifested by hypertension and various organ disorders, including disorders in the kidneys, liver and lungs. Currently, the only definitive treatment for preeclampsia is termination of pregnancy and delivery of the newborn and placenta. Women with a mild form of preeclampsia in premature pregnancy, as a rule, are shown expectant management to improve the maturity of the fetus, which often requires medical treatment of the mother. In recent decades, there has been increasing evidence that the underlying mechanism of preeclampsia, an endothelial disease, is not limited to pregnancy, but increases the risk of cardiovascular diseases in later life.

Objective. To review the scientific literature sources on the pathogenesis and treatment of preeclampsia.

Search strategy. In this review we search full-text publications in English and Russian, which are devoted to the pathogenesis and new recommendations for the treatment of preeclampsia. Next databases were used in the process of literature search: Pubmed, Web of science, Cyberleninka, Google Scholar by keywords. The search period was 2000-2022 years. 1566 publications were identified on this topic. 46 articles corresponded to our research objective. Inclusion criteria: Publications of the level of evidence A, B: meta-analyses, systematic reviews, cohort and cross-sectional studies. Exclusion criteria: summary reports, newspaper articles and personal messages.

Search results and discussion.

The diagnosis of preeclampsia is made by measuring blood pressure, where the indicators exceed more than 140/90 mmHg and protein excretion in urine exceeding 300 mg/day. However, in the absence of significant proteinuria and high blood pressure, in the presence of any damage to the end organs, such as impaired liver function, thrombocytopenia, renal failure, pulmonary edema or cerebral circulatory disorders, it is sufficient to make a diagnosis. Both mothers suffering from preeclampsia and their children may develop long-term complications. Preeclampsia is observed worldwide in 3-5% of all pregnancies [5]. According to the World Health Organization, hypertension during pregnancy is the leading

cause of maternal mortality, accounting for 16% in industrialized countries and up to 25% in developing countries. Symptoms occur before or during pregnancy or even after childbirth. Preeclampsia is one of the main causes of premature birth, and if left untreated, it can lead to fatal outcomes for mother and child.

Pathogenesis

The pathogenesis of preeclampsia , as well as a number of pregnancy complications,is associated with endothelial dysfunction. the pathogenesis of preeclampsia is associated with a decrease in placenta perfusion due to a violation of cytotrophoblast invasion in the spiral artery of the uterus. In normal conditions, the spiral arteries lose their endothelial and muscular layers during the transformation and move to the sinusoids,which provide blood flow to the nasal space of the placenta,and this adaptation occurs by the 20th week of pregnancy.

In pathological conditions, a decrease in placental perfusion leads to the release of the soluble VEGF receptor-sFlt-1, which neutralizes the circulating endothelial growth factor. As a result of such changes, the blood vessels become unstable to vasopressors. systemic endothelial dysfunction develops. Perfusion of organs and tissues, first of all - the placenta,kidneys, brain and liver, is disrupted.

The pathogenesis of preeclampsia is still being investigated, and significant progress has been made over the past 10 years. Placenta remains the main cause of preeclampsia, as removal of the placenta is necessary to reduce symptoms [40]. Postmortem examination of placentas with progressive preeclampsia often reveals numerous placental infarcts and sclerotic narrowing of arterioles [43]. Studies conducted on animals and humans have shown defective trophoblast invasion with concomitant uteroplacental hypoperfusion, which can lead to preeclampsia [13, 27]. Two models were created: incomplete remodeling of the spiral artery in the uterus, contributing to placental ischemia (stage 1), and the release of antiangiogenic factors from the ischemic placenta into the maternal bloodstream, contributing to endothelial damage (stage 2). During implantation, placental trophoblasts penetrate into the uterus and cause remodeling of the spiral arteries, simultaneously obliterating the middle shell of the spiral arteries of the myometrium; this allows the arteries to adapt to increased blood flow regardless of changes in the vasomotor functions of the mother to nourish the developing fetus [19]. Part of this remodeling requires trophoblasts to adopt the endothelial phenotype and its various adhesion molecules. In case of remodeling disorders, the placenta will be deprived of oxygen, which leads to a state of relative ischemia and increased oxidative stress during states of intermittent perfusion. This abnormal remodeling of the spiral artery was described 50 years ago in pregnant women with arterial hypertension [11]. Since that time, it has been a central pathogenic factor in pregnancies complicated by intrauterine growth retardation, gestational hypertension and preeclampsia [6]. One limitation of this hypothesis is that these results are not specific to preeclampsia and may explain the difference in

manifestations between placental preeclampsia and maternal preeclampsia.

Subtypes of preeclampsia

Back in 1996, scientists Nes and Roberts proposed dividing preeclampsia into placental and maternal, [39] others were divided into early onset (34 weeks of pregnancy) and late onset (34 weeks of pregnancy) [9]. These types have different etiologies and phenotypes. In placental or early preeclampsia, the etiology is abnormal placentation in hypoxia with higher levels of sFlt-1, lower PlGF and a higher ratio of sFlt-1 to PlGF compared to maternal preeclampsia [21, 28]. It has also been shown that uterine Dopplerography has a higher accuracy in identifying patients who will subsequently develop preeclampsia with an early rather than late onset [34–36]. The data obtained confirm the abnormally high impedance of blood flow in the uterine arteries, which was associated with a violation of the physiological transformation of spiral arteries [1, 12]. In late-onset preeclampsia, the problem arises due to the interaction between the presumably normal placenta and maternal factors that suffer from endothelial dysfunction, which makes them susceptible to microvascular damage. These types of classification have prognostic value, since placental or early preeclampsia is associated with a significantly higher risk of complications in mother and child [30, 37]. They also have a greater prevalence of placental lesions, especially between 28 and 32 weeks of pregnancy [29]. Therefore, placental or early preeclampsia is associated with fetal growth restriction and unfavorable outcomes for the mother and newborn [31, 32]. Late preeclampsia is a decompensated reaction to oxidative stress in the placenta caused by a dysfunctional maternal endothelium. Endothelial dysfunction, which is one of the aspects of the systemic inflammatory response of the mother, can lead to generalized vasoconstriction and a decrease in blood flow to various organs, including the heart, kidneys and brain [4]. since the level of pathology is not associated with the placenta, this is usually associated with a lower frequency of fetal involvement and more favorable perinatal outcomes. [42]. Despite the pathophysiological differences between these subtypes of preeclampsia, it should be recognized that the difference is not always clear, since the two subtypes may have a significant overlap, for example, in an elderly woman with vascular diseases who has abnormal placentation. Thus, although subtyping can be useful in understanding and predicting the condition, most patients with preeclampsia have elements of both pathologies.

The placenta plays a crucial role in the development of preeclampsia, since in most cases, the removal of the placenta solves this problem. During a normally developing pregnancy, trophoblasts, which are cells that make up the outer layer of the blastocyst, penetrate into the spiral arteries of the uterus. As part of this process, trophoblasts adopt an endothelial phenotype by expressing adhesion molecules that are found on the surface of endothelial cells. The reconstructed vascular network ensures the proper development of the placenta. in a pregnant woman with preeclampsia the vascular network remains unchanged, and, consequently, the blood flow in the placental bed is aberrant and incompatible with the normal development of the fetus.The hypothesis that defective trophoblastic invasion with concomitant uteroplacental hypoperfusion can lead to preeclampsia, which is confirmed by studies on animals and humans. Pathoanatomic examination of placentas with progressive preeclampsia often reveals numerous placental infarcts and sclerotic narrowing of arterioles. As a rule, in women with preeclampsia, ultrasound evaluation of uteroplacental blood flow decreases, and vascular resistance of the uterus increases. These vascular changes associated with mechanical narrowing of the uterine arteries or aorta, in turn, lead to placental ischemia, hypertension, proteinuria and, variously,

glomerular endotheliosis in several animal species [13, 26]. However, placental ischemia alone, as is observed with restriction of intrauterine growth not enough for the development of preeclampsia.Thus, although uteroplacental ischemia is an important trigger of preeclampsia, in some cases it may be absent, and the mother's response to placental ischemia is variable. Hypoxia causes abnormal placental development as described above; cytotrophoblasts cultured in vitro under hypoxic conditions often cannot fully penetrate into the surface adhesion molecules and change them [43].

In the first trimester of pregnancy, large changes occur in the systemic circulation of a woman. The blood vessels of the kidneys increase in diameter,and this vasodilating reaction leads to an increase in the flow of renal plasma and the glomerular filtration rate [18]. Generalized damage

to the endothelium of the kidneys, liver and brain of the mother at the cellular level occurs after the release of toxic factors from the affected placenta. Many serum markers of endothelial activation and endothelial dysfunction are impaired min women diagnosed with preeclampsia; these markers include Willebrand antigen, cellular fibronectin, soluble tissue factor, soluble E-selectin,platelet growth factor and endothelin.Women with preeclampsia have hypersensitivity to the vasopressors angiotensin II and norepinephrine [18]. Patients with this diagnosis have impaired endothelium-dependent vasorelaxation. Compared with women with normal blood pressure, patients with preeclampsia have problems with hypercoagulation. In fact, activation of coagulation in preeclampsia occurs in the early stages of the disease and often precedes clinical symptoms. It is believed that glomerular endotheliosis, a type of renal thrombotic microangiopathy, is responsible for impaired renal function present in preeclampsia [44]. Preeclampsia is associated with increased fibrin deposition in the renal glomeruli [38]. Pathoanatomic studies of renal tissues in patients with preeclampsia showed the presence of diffuse fibrin deposition. Although the cause of preeclampsia has not yet been determined,it is believed that its manifestations, including endothelial dysfunction, hypertension and proteinuria, are mediated by high circulating concentrations antiangiogenic proteins, such as soluble fms-like tyrosine kinase 1 (sFlt1 or sVEGFR1) [2].

Outcomes for neonate

Hypoperfusion of the placenta can cause fetal growth retardation and lack of water. Children born after pregnancy complicated by preeclampsia have an average of 5% lower birth weight compared to children born after uncomplicated pregnancy. This decrease is even more noticeable in women with pregnancies complicated by early preeclampsia, whose birth weight is on average 23% lower

than expected based on gestational age [33]. In accordance with this, the fetal mortality rate increases; 5.2 per 1000 fetal deaths in women with preeclampsia versus 3.6 per 1000 in women with uncomplicated pregnancy. In women with early preeclampsia, the risk of stillbirth is even seven times higher compared to normotensive pregnancies [15]. Unfavorable intrauterine environment in women with preeclampsia is a significant factor in premature birth, most often iatrogenic [10]. Premature birth is the leading cause of neonatal morbidity and mortality in the world [14]. This is due to higher rates of respiratory distress syndrome in infants, intraventricular hemorrhages, sepsis, bronchopulmonary dysplasia and disability in the development of the nervous system in childhood [41]. In preterm labor, antenatal corticosteroid therapy reduces neonatal morbidity and mortality; in spontaneous preterm labor, as well as in pregnancy complicated by premature hypertensive disorders.

Outcomes for mothers

According to the results of numerous clinical studies of women with preeclampsia, they show an increased risk of developing cardiovascular diseases later in life [3]. A frequently cited meta–analysis of prospective and retrospective cohort studies involving 3,488,160 women showed that the relative risk of hypertension was 3.70 (95% CI 2.70 to 5.05) after 14.1 years of weighted average follow-up and that the relative risk of coronary heart disease and stroke was 2.16 (95% CI 1.86-2.52) after 11.7 years and 1.81 (95% CI 1.45-2.27) after 10.4 years, respectively [5]. Three separate studies conducted in Norway, California and Taiwan have shown that women with preeclampsia have a 12-fold increased risk of developing cardiovascular diseases [23, 26, 30]. Additional adverse outcomes, such as an increased risk of kidney disease, have also been reported [46], metabolic disorders [45] and death. Preeclampsia with early onset led to a higher risk of damage to the end organs from the point of view of the cardiovascular, respiratory, central nervous, renal and hepatic systems compared with late onset [24]. These clinical studies, however, do not determine whether preeclampsia is a cause or a marker of long-term vascular disease.

At a later age after preeclampsia, women are at increased risk of developing cardiovascular diseases In a cohort study based on the Danish registry, 700,000 women were examined with an average follow-up period of 14.6 years [25]. After severe preeclampsia (defined as HR ≥160/110 mmHg or proteinuria 5.0 g/24 h) 6-fold (range: from 5.45 to 6.77) increase in arterial hypertension, 1.7-fold (range: from 1.22 to 2.40) increase in coronary heart disease, 1.9-fold (range: from 1.35 to 2.70) increase thromboembolism and 4-fold (range: from 3.04 to 4.46) type increase There were 2 cases of diabetes mellitus. Bellamy et al. conducted a systematic review with meta-analysis, which involved more than three million women 10-15 years after pregnancy, and found similar results; women with a history of preeclampsia had a 3.7 increased risk of hypertension, a 2.2 increased risk of coronary heart disease, a 1.8 increased risk of stroke and a 1.19 increased risk of venous thromboembolism compared to women without preeclampsia [5]. Two years after delivery, 30% of women who had gestational hypertension or preeclampsia at term had hypertension, and 25% of them had metabolic syndrome [17]. The severity of preeclampsia is associated with the severity of cardiovascular diseases later in life. In women from 3 months to 5 years after pregnancy, 45% who had early-onset preeclampsia had hypertension compared to 25% who had late-onset preeclampsia [45]. In addition to the fact that the risk of cardiovascular diseases increases, also the onset of hypertension occurs at a younger age: 7.7 years earlier in women with hypertensive pregnancy disorder than in women without a history of pregnancy complications [16]. Although there is still insufficient research on whether preeclampsia is a cause of cardiovascular risk or is a marker, this is an opportunity for the prevention of CVD at a relatively young age.

Pre-conception counseling, prevention, treatment and postpartum care for preeclampsia

Care for a woman at risk of developing preeclampsia begins with a consultation before conception, followed by prevention, treatment and appropriate postpartum supervision. A detailed overview of this topic is beyond the scope of this article. However, we would like to highlight a few important points. ACOG recommends that women who have had preeclampsia during a previous pregnancy seek counseling and evaluation before conception. In addition, they recommend that women with a history of chronic hypertension should not use angiotensin converting enzyme inhibitors and angiotensin receptor blockers for those who wish to become pregnant. We agree with counseling on prejudice in high–risk individuals; however, we do not recommend against the use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in women with concomitant diseases such as diabetes, proteinuria or CKD, due to weak signs of congenital malformations in the first trimester [8, 22]. We recommend that you stop taking these medications after confirming pregnancy. Postpartum follow–up, according to ACOG recommendations, includes obtaining a profile of the cardiovascular system, including an annual assessment of blood pressure, lipids, fasting blood glucose and body mass index, in women with a history of premature preeclampsia or recurrent preeclampsia. It is recognized that the evidence underlying these recommendations is small, and therefore health care providers should individualize their decisions based on the value of this information versus convenience and cost.

The only decisive method of treating preeclampsia is the removal of the placenta and, consequently, the fetus. Due to the two conflicting interests of mother and child, timely delivery is one of the main problems of preeclampsia, especially in women with early onset of preeclampsia. Women with preeclampsia are at risk of developing acute renal or hepatic insufficiency, liver rupture, pulmonary edema, brain hemorrhage, disseminated intravascular coagulation and eclampsia progression, while their risk of placental abruption, mortality increases compared to women without preeclampsia. If preeclampsia is diagnosed after 37 weeks of pregnancy, induction of labor is the best choice for the mother and newborn [20]. If mild preeclampsia or hypertension caused by pregnancy occurs at 34-37 weeks of pregnancy, it is necessary to conduct a wait-and-see observation until clinical deterioration is justified; immediate delivery significantly increased the risk

of respiratory distress syndrome of newborns, and adverse outcomes in mothers were not clinically significant [7].

Conclusion. Preeclampsia is a common disease among pregnant women, which has a serious impact on long-term outcomes for both women and their children. Women with a history of preeclampsia are later prone to cardiovascular diseases. This implies the ability to develop and evaluate prevention programs at a relatively young age. The potential impact bof maternal treatment, including medication and the duration of exposure to an unfavorable intrauterine environment, on long-term outcomes for children is unclear and should be evaluated in order to reduce adverse outcomes.Thus, due to our ever-expanding understanding of the pathogenesis of preeclampsia, and now the revised definition of preeclampsia, we hope to more accurately diagnose and treat these patients. In addition, recognizing the long-term effects of this education will hopefully improve our care for these women during pregnancy and for decades after.

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