OBSTETRICS AND GYNAECOLOGY

PATHOGENETIC MECHANISMS OF BLOOD-BRAIN BARRIER DYSFUNCTION IN PREECLAMPSIA

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RESUME

Hypertensive disorders during pregnancy are the most difficult and unresolved problems of modern obstetrics. Today, their frequency ranges from 12 to 40 % and has no downward trend. About 60–70 % of maternal deaths in hypertensive disorders occur due to cerebral complications, due to the development of eclampsia, cerebral edema and stroke. Underestimating the severity of the condition, inadequate treatment and delayed delivery are the main causes of maternal morbidity and mortality. Despite significant advances in understanding the main stages of the pathogenesis of preeclampsia, the mechanisms of damage to cerebral vascular endothelial cells, as well as the features of local paracrine and autocrine regulation of cerebrovascular blood flow in proinflammatory and hypoxic conditions remain relevant for further study. This literature review is devoted to the study of the main mechanisms of disruption and/or damage to the blood-brain barrier in preeclampsia. A systematic analysis of modern Russian and foreign literature was carried out using the information databases eLibrary, Scopus, PubMed, MEDLINE and Cochrane Library for the period from January 2010 to December 2024. Information is provided on the role of vascular endothelial growth factor and its receptor system in increasing transcellular transport, as well as close contact proteins in enhancing the paracellular pathway. The mechanisms of impaired autoregulation of cerebral blood flow leading to the development of vasogenic cerebral edema in preeclampsia and eclampsia are described. Understanding the key links in the pathogenesis of damage to the blood-brain barrier in preeclampsia will allow us to further identify reliable and accessible early predictors of the development of cerebral dysfunction in this complication of pregnancy.

Keywords: *preeclampsia, eclampsia, hypertensive disorders during pregnancy, blood-brain barrier, cerebrovascular complications, biomarkers of cerebral dysfunction*

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ПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ ДИСФУНКЦИИ ГЕМАТОЭНЦЕФАЛИЧЕСКОГО БАРЬЕРА ПРИ ПРЕЭКЛАМПСИИ

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РЕЗЮМЕ

Гипертензивные расстройства во время беременности относятся к наиболее сложным и нерешенным проблемам современного акушерства. На сегодняшний день их частота составляет от 12 до 40 % и не имеет тенденции к снижению. Около 60–70 % материнских смертей при гипертензивных расстройствах происходят из-за церебральных осложнений, вследствие развития эклампсии, отека головного мозга и инсульта. Недооценка степени тяжести состояния, неадекватное лечение и запоздалое родоразрешение являются основной причиной материнской заболеваемости и смертности. Несмотря на значительные успехи в понимании основных этапов патогенеза преэклампсии, механизмы повреждения эндотелиальных клеток сосудов головного мозга, а также особенности локальной паракринной и аутокринной регуляции цереброваскулярного кровотока в провоспалительных и гипоксических условиях, остаются актуальными для дальнейшего изучения. Данный литературный обзор посвящен изучению основных механизмов нарушения и/или повреждения гематоэнцефалического барьера при преэклампсии. Проведен систематический анализ современной отечественной и зарубежной литературы с использованием информационных баз eLibrary, Scopus, PubMed, MEDLINE и Cochrane Library за период с января 2010 г. по декабрь 2024 г. Представлена информация о роли фактора роста эндотелия сосудов и системы его рецепторов в увеличении трансклеточного транспорта, а также белков плотных контактов в усилении паракле точного пути. Описаны механизмы нарушения ауторегуляции мозгового кровотока, ведущие к развитию вазогенного отека головного мозга при преэклампсии и эклампсии. Понимание ключевых звеньев патогенеза повреждения гематоэнцефалического барьера при преэклампсии позволит в дальнейшем определить надежные и доступные ранние предикторы развития церебральной дисфункции при данном осложнении беременности.

Ключевые слова: *преэклампсия, эклампсия, гипертензивные расстройства во время беременности, гематоэнцефалический барьер, цереброваскулярные осложнения, биомаркеры церебральной дисфункции*

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INTRODUCTION

According to modern concepts, preeclampsia is defined as a complication of pregnancy, childbirth and the postpartum period, characterized by an increase in blood pressure after the 20th week of pregnancy (≥ 140 and/or ≥ 90 mm Hg) in combination with proteinuria (protein loss > 0.3 g/day or > 0.3 g/l in 2 portions of urine taken at an interval of 6 hours) and/or at least one other parameter indicating the development of multiple organ failure [1]. Without proper treatment, preeclampsia is associated with severe cerebrovascular complications, including eclampsia (seizures), hemorrhagic and ischemic stroke, posterior reversible encephalopathy syndrome (PRES), and reversible cerebral vasoconstriction syndrome (RCVS) [2, 3, 4]. Magnetic resonance imaging (MRI) has shown that 70–100 % of patients with severe preeclampsia have cerebral edema with evidence of increased intracranial pressure [5]. Cerebrovascular changes are the direct cause of approximately 70 % of maternal deaths [2, 6, 7].

The two-stage concept of preeclampsia development suggests that impaired placentation causes chronic placental ischemia and oxidative stress, which leads to the release of antiangiogenic factors, free radicals, and oxidized lipids into the maternal circulation, contributing to the development of generalized endothelial dysfunction [8, 9]. The results of preclinical and clinical studies have shown that in preeclampsia there is an imbalance between pro- and antiangiogenic factors, characterized by an increase in circulating soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) levels, with a simultaneous decrease in the concentration of placental growth factor (PlGF) and transforming growth factor β1 (TGF-β1) [10].

According to the proposed model of preeclampsia pathogenesis, cerebrovascular complications are one of the possible manifestations of multisystemic endothelial damage [2, 6, 7]. However, this concept does not fully reflect the pathogenesis of central nervous system dysfunction, as in approximately one third of women, eclampsia may develop against the background of moderate levels of arterial hypertension and in the absence of proteinuria, and cerebral complications may occur after childbirth [8, 11].

In a study conducted by Too G. et al. in 2018, it was reported that the risk of stroke within 60 days after delivery for women who experienced hypertensive disorders during pregnancy was 41.7 % [12]. The exact prevalence of posterior reversible encephalopathy syndrome is not fully understood. However, a retrospective study conducted by Liman T.G. et al. in 2012 showed that PRES was present in more than 90 % of women with eclampsia and approximately 20 % of those with preeclampsia [13]. Eclampsia remains a serious complication of pregnancy, and reliable biomarkers or clinical indicators for predicting the development of seizures do not currently exist [14].

A long-term consequence of preeclampsia and eclampsia is damage to the white matter of the brain, which can be observed on magnetic resonance imaging several years after delivery, which significantly increases the risk of future cognitive impairment and dementia [15, 16]. Despite significant progress in understanding the key stages of preeclampsia pathogenesis, the mechanisms underlying damage to cerebral endothelial cells and the characteristics of local paracrine and autocrine regulation of cerebal blood flow under proinflammatory and hypoxic conditions remain relevant for further study [2, 6, 7].

Assessment of blood-brain barrier permeability in hypertensive disorders during pregnancy

The blood–brain barrier (BBB) is a neurovascular unit that separates brain tissue from the systemic circulation. Components of the neurovascular unit include endothelial cells, pericytes, perivascular nerves, smooth muscle cells, astrocytes, and adjacent neurons [17]. Cerebral endothelial cells have distinct characteristics compared to those in peripheral organs due to their lack of fenestrations. Instead, they are connected to one another through a dense network of tight junctions, which have high electrical resistance and regulate the transport of water-soluble substances, such as nutrients, metabolites, and gases, across the barrier. The BBB serves as a protective barrier that prevents the brain from neurotoxins, neurotransmitters, and macromolecules [18].

BBB disruption plays a central role in the pathogenesis of cerebral complications in women with preeclampsia [6, 18, 19]. Cerebral edema, often observed in severe preeclampsia and eclampsia, is likely due to dysfunction of endothelial cells of the cerebral microcirculation, which leads to increased permeability and fluid perfusion into the brain parenchyma [14]. Increased BBB permeability in preeclampsia may be attributed to a variety of pathogenetic mechanisms: increased transcellular transport without changing the mechanical properties of the BBB (implemented through VEGF and its receptor system); enhanced paracellular pathway (changes in the expression/function of tight junction proteins (TJs)); increased microvascular pressure leading to the formation of vasogenic cerebral edema (impaired cerebral blood flow autoregulation) [6, 18]. Figure 1 schematically illustrates the main pathophysiological mechanisms of increased BBB permeability.

To characterize the pathogenetic mechanisms involved in the development of cerebrovascular complications of preeclampsia, several researchers have developed experimental animal models [20, 21]. Most studies aimed at investigating changes in BBB functionality in humans are primarily conducted using MRI of the brain [22] and assessing the levels of circulating markers of neuroinflammation, neurodegeneration, and endothelial dysfunction in various biological fluids (blood, cerebrospinal fluid, urine, tears) [19, 23, 24].

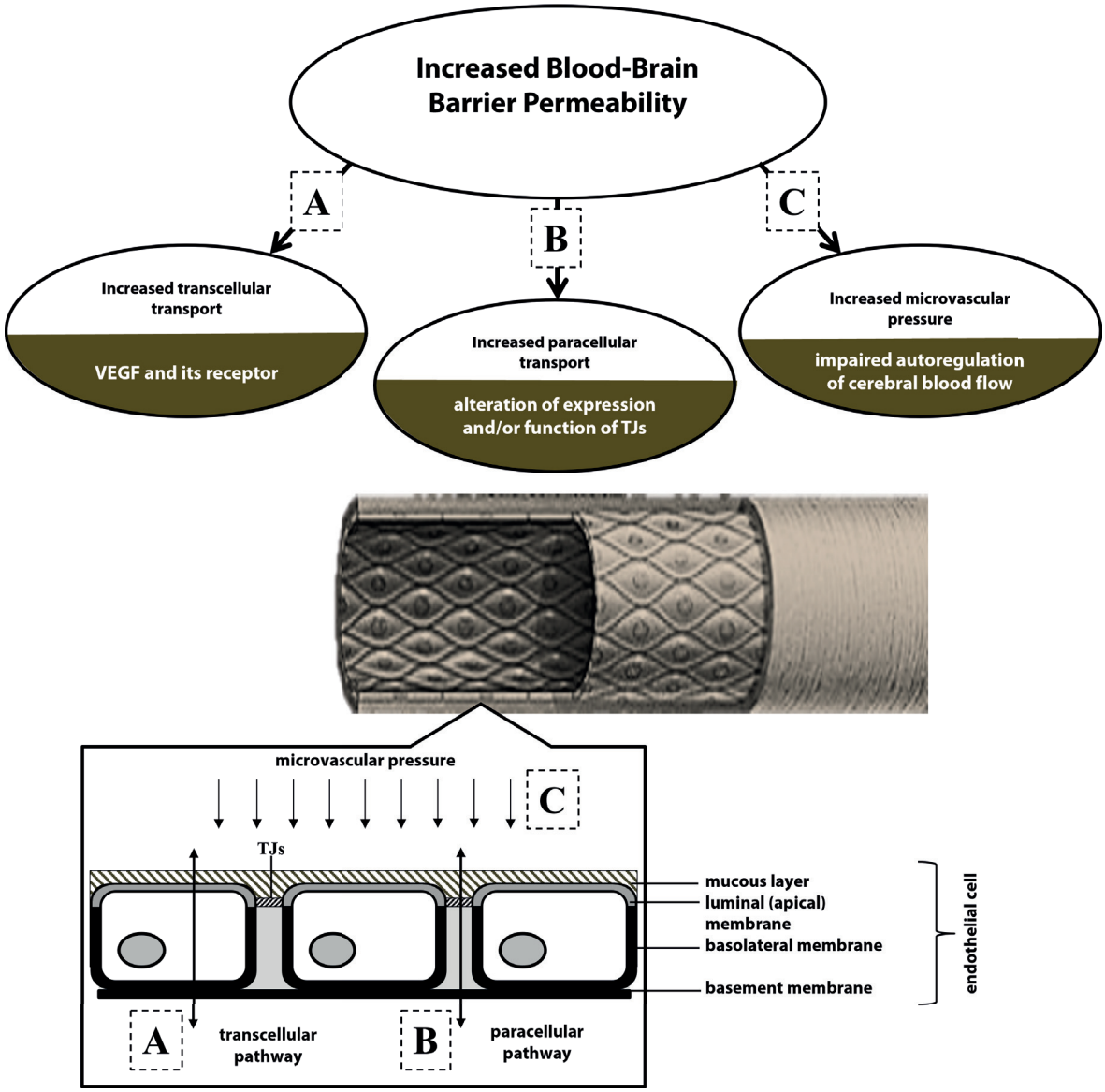

FIG. 1.
The main pathophysiological mechanisms of increased permeability of the blood-brain barrier

It has been established that the levels of neurospecific markers may indicate brain injury prior to the onset of overt neurological symptoms [24].

The results of the studies reviewed are contradictory regarding the disruption of BBB integrity in preeclampsia. In the study conducted by Burwick R.M. et al. in 2019, the levels of albumin, complement proteins C5a, C5b-9, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were measured in paired blood and cerebrospinal fluid samples in patients with preeclampsia, during which no signs of BBB damage and neuroinflammation were observed [19].

According to other data collected by Johnson A.C. et al. (2014) in a study on a rat model of severe preeclampsia, it has been shown that the administration of magnesium sulfate ($MgSO_4$) increased the seizure threshold while maintaining the integrity of the blood-brain barrier. To simulate severe preeclampsia, placental ischemia (decreased uteroplacental perfusion pressure) was created in combination with a high-cholesterol diet. The rats developed arterial hypertension, oxidative stress, endothelial dysfunction, fetal growth retardation, and placental hypoplasia. The seizure threshold was determined by measuring the amount

of pentylenetetrazol (PTZ). Rats that were not administered $MgSO_4$ were more sensitive to PTZ, with a seizure threshold that was 65 % lower than that of the control group ($p < 0.05$). BBB permeability to sodium fluorescein, measured *in vivo*, revealed an increase in rats that had not received $MgSO_4$ treatment, compared to controls ($p < 0.05$) [21].

Calcium-binding protein S100B is a biomarker of BBB activation/damage [23, 24]. This protein affects the proliferation, differentiation, and growth of endothelial cells in the cerebral circulation, as well as calcium homeostasis and intracellular enzymatic activity. A dose-dependent effect of S100B has been demonstrated. At low concentrations, when there is increased BBB permeability without damage to the central nervous system, this cerebral marker has a neuroprotective effect. High concentrations of S100B have been found to be associated with neurotoxicity, inflammation, activation of microglia and astroglia, and increased expression of proinflammatory mediators [25].

The research group led by Friis T. et al. (2022) analyzed the concentration of neuroinflammatory and neurodegenerative markers, including neurofilament light chain (NfL), tau protein (Tau), neuron-specific enolase (NSE), and S100B, in the blood plasma samples of patients with preeclampsia, pregnant women with a normal pregnancy, and non-pregnant women. Plasma concentrations of NfL, Tau, NSE, and S100B were higher ($p < 0.05$) in women with preeclampsia compared to patients in other study groups. The researchers created an *in vitro* BBB model including human cerebral vascular endothelial cells (hCMEC/D3). Increased plasma NfL levels were associated with decreased transendothelial electrical resistance ($p = 0.002$), used in an *in vitro* model to assess BBB integrity [24].

Research aimed at exploring markers of neuroinflammation and neurodenaturation in preeclampsia requires further investigation. We believe that studying the levels of these markers may allow for an indirect assessment of BBB permeability and potentially help develop screening tests to identify individuals at high risk of severe cerebral complications and optimize management and treatment strategies for these patients.

The pathogenic role of VEGF in the cerebrovascular complications of preeclampsia

The VEGF protein family is classified as angiogenic factors that regulate vascular permeability, endothelial cell viability, and participate in vasculogenesis and vasorelaxation by stimulating the synthesis of nitric oxide (NO), including in the cerebral circulatory system. These homodimeric proteins are present in five different isoforms: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF [26]. PlGF regulates angiogenesis via its signaling pathways or by enhancing VEGF-mediated activity. For the development of normal pregnancy, the levels of VEGF and PlGF within the bloodstream rise, but the mechanisms through which the brain and BBB adapt to these changes are unknown [27].

Human vascular endothelial growth factor receptors (VEGFRs) are transmembrane tyrosine kinase structures that include VEGFR1 or Fms-like tyrosine kinase-1 (Flt-1), VEGFR2 or kinase insert domain receptor (KDR), and VEGFR3 or Flt-3 [26]. VEGFR-mediated VEGF signaling to induce vascular permeability has been well studied in peripheral tissues. VEGF has affinity for both Flt-1 and VEGFR2, whereas PlGF binds only to Flt-1 [18].

VEGFR2 has been shown to be expressed in endothelial cells and in the trophoblast layer of the human placenta. This receptor has a more potent tyrosine kinase activity than VEGFR1. VEGFR1 has been found to induce a transient opening of endothelial intercellular junctions, while VEGFR2 seems to act as a major regulator of cellular permeability [27].

Chronic placental ischemia leads to an increase in the level of hypoxia-inducible factor-1-alpha (HIF-1α). HIF-1α has been shown to be oxygen-sensitive and it is rapidly inactivated and degraded under normoxia, while its degradation is inhibited under hypoxic conditions [28]. When HIF-1α binds to HIF-1β, active HIF-1 is formed, which is transferred to the cell nucleus to regulate the expression of various genes, such as sFlt1 and sEng [29].

Several weeks prior to the preeclampsia onset, the placenta overproduces sFlt-1, which is accompanied by an increase in its concentration in the maternal serum [9, 18]. sFlt-1 has been identified as a truncated splice variant of VEGFR-1 and consists of six extracellular IgG-like domains with a unique C-terminus, lacking transmembrane and intracellular domains. *In vivo*, it has been reported that sFlt-1 exists as several isoforms with varying molecular weights between 100 and 145 kDa [18]. sFlt-1 has been found to act as a VEGFR1 decoy receptor, binding both VEGF and PlGF and reducing the levels of their active circulating forms. It also forms a heterodimer with VEGFR2, inhibiting the activation of this receptor [30]. Therefore, it can be proposed that in preeclampsia, sFlt-1 functions as an antagonist of VEGFR2 signaling, balancing the effects of VEGF-mediated signaling by regulating BBB permeability (Fig. 2) [18, 30].

The VEGFR2-mediated signaling pathway that induces BBB permeability has not yet been fully understood. In an *in vitro* experiment, Torres-Vergara P. et al. (2022) used human brain endothelial cells as a BBB model, which were subjected to treatment with plasma derived from women with preeclampsia. The study found that VEGFR2 is involved in BBB disruption by increasing apoptosis and permeability of cerebral endothelial cells. Activation of this receptor occurs due to increased phosphorylation at tyrosine 951 (pY951), and inhibition at tyrosine 1175 (pY1175) [27].

According to a study conducted by Troncoso F. et al. in 2023, infants who experienced preeclampsia during their intrauterine development demonstrate reduced angiogenesis in the brain nuclei. This is associated

with lower circulating VEGF/PlGF/VEGFR2 protein levels, impaired brain endothelial migration, and dysfunctional assembly of F-actin filaments. These changes may predispose to structural and functional alterations in long-term brain development [31].

It has been found that the sFlt1 level in the first trimester is not clearly associated with the development of preeclampsia [32]. According to the study conducted by Nzelu D. et al. in 2020, women with chronic arterial hypertension in the first trimester showed reduced concentrations of PlGF and sFlt-1. Furthermore, these markers had low predictive value for the development of preeclampsia (ROC-AUC = 0.567 [95% CI 0.537–0.615] and 0.546 [95% CI 0.507–0.585], respectively) [10]. The results of first trimester preeclampsia screening based on an algorithm that combines PlGF level assessment with maternal clinical factors, mean arterial pressure, and uterine artery pulsatility index provide consistent and promising results in predicting preeclampsia [33]. Moreover, the assessment of the sFlt1/PlGF ratio in pregnant women also has diagnostic value [34].

It is important to emphasize that sFlt-1 is not the sole factor responsible for the antiangiogenic imbalance in preeclampsia. The role of Endoglin (Eng), which is a TGF-β1 co-receptor, is currently under investigation. The extracellular domain of Eng inhibits TGF-β1 binding to the cell surface, thereby reducing the effect of NO [27]. It has been found that TGF-β1 modulates VEGFR2 signalling in endothelial cells [35].

In a model of HELLP syndrome induced by the daily administration of exogenous sFlt-1 and sEng to pregnant mice, a regional increase in BBB permeability at the posterior cortex was observed [36]. Because the administration of exogenous sFlt-1/sEng leads to the development of a HELLP-like syndrome, other models based on reduced uteroplacental perfusion may be more appropriate for studying cerebrovascular complications associated with preeclampsia. In such models, increased sFlt-1/sEng levels and BBB permeability were detected; however, the mechanism through which these antiangiogenic factors influence the development of cerebrovascular complications remains to be determined [37, 38]. Therefore, we consider further research into sEng as a potential predictor of cerebral complications associated with preeclampsia to be promising.

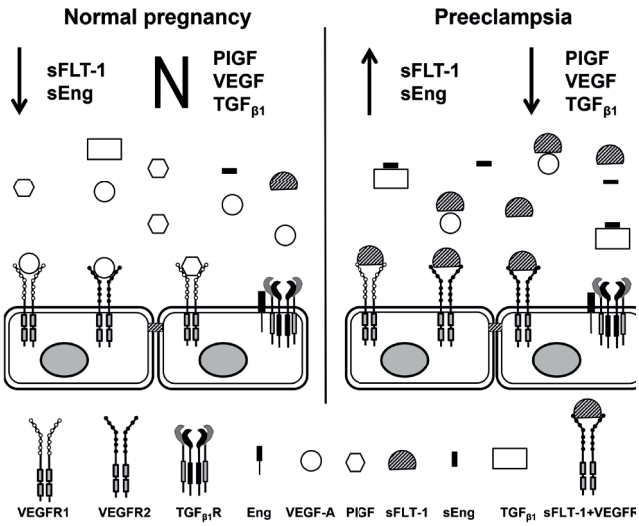

FIG. 2.
The scheme of pro- and antiangiogenic factors interaction in preeclampsia and normal pregnancy

The pathogenetic role of endothelial damage markers and tight junction proteins in the development of cerebrovascular complications of preeclampsia

A key role in the development of preeclampsia is played by endothelial dysfunction, which increases the production of vasoconstrictors – endothelin-1 (EDN-1), sFlt1 and sEng, leading to their imbalance with the vasodilator NO [39, 40]. This imbalance has a negative impact on the brain and eyes in preeclampsia and manifests in the disorder of local hemodynamics, the formation of vasospasm and vascular thrombosis with the development of hypovolemia and tissue ischemia, increasing in severity with disease progression [8, 9, 39].

Pregnancy is associated with significant physiological adaptive changes in the maternal cardiovascular system. NO has been shown to be a soluble gaseous mediator that performs a wide range of physiological functions, including maintaining vascular homeostasis and modulating vascular tone [41]. Reactive oxygen species can influence the maintenance of vascular tone by reducing NO production. According to Matsubara K. et al. (2015), endothelial NO synthase (eNOS), which is constitutively expressed in the vascular endothelium and regulates vascular tone through NO synthesis, is suppressed by excessive production of oxidative stress factors [42]. Inhibition of endothelial NO synthesis leads to dysregulation of vascular tone, platelet and leukocyte adhesion [41]. eNOS and its associated NO synthesis have been linked to maternal endothelial dysfunction, but the precise pathogenesis remains uncertain. Women with severe preeclampsia have lower circulating eNOS levels, which is largely associated with decreased PlGF levels, while women with moderate preeclampsia show a slight increase in these parameters [43]. These findings may indicate that although compensatory increases in eNOS and PlGF levels are observed in moderate preeclampsia, these mechanisms are not activated in severe cases of this disease.

Generalized endothelial dysfunction caused by placental antiangiogenic factors is considered to be the ultimate link in the pathogenesis of preeclampsia [8, 9]. Markers of endothelial damage

and dysfunction include serum concentrations of endothelial activating factors, such as vascular cellular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule type-1 (ICAM-1) and selectins, especially E-selectin; serum levels of endothelial glycocalyx (EG) degradation markers, such as hyaluronan (HA) and syndecan-1 (SDC-1); EDN-1 concentration; levels of circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPCs) [44, 45]. Anti-endothelial cell antibodies (AECA) are groups of immunoglobulins IgG, IgM, and IgA produced secondarily in response to endothelial cell injury. The appearance of AECA is related to the severity of proteinuria, and the cytotoxicity to endothelial cells by AECA-positive sera may contribute to the development of endothelial damage in preeclampsia. The IgG-AECA subclass in preeclampsia increases EDN-1 release from endothelial cells, which may affect local vascular tone, including in the brain [46].

It has been found that VCAM-1 and ICAM-1 are among the important factors in the development of local inflammatory changes that promote leukocyte migration and their adhesion to the endothelium [45, 47]. It has been observed that VEGF is involved in increasing the expression of these adhesion molecules on endothelial cells, both *in vivo* and *in vitro*. Adhesion of leukocytes to the vascular endothelium and an increase in leukostasis followed by capillary occlusion and endothelial cell apoptosis lead to increased permeability and destruction of the BBB [39]. Plasma levels of ICAM-1 and VCAM-1 increase in preeclampsia and may be used as laboratory markers for the development of this condition [45, 47, 48].

The key components of intercellular proteins TJs are transmembrane proteins: occludin (Ocln), claudin (Cldn), tricellulin, and junctional adhesion molecules (JAMs), which form complex threads and control the permeability characteristics of paracellular transport [49, 50, 51]. These proteins are involved in the regulation of proliferation, differentiation, and polarization of epithelial cells. Tight junction proteins prevent the tissue fluid diffusion through the epithelium and regulate the permeability of ions, small hydrophilic molecules, and even macromolecules, thereby maintaining the difference in the composition of the apical and basolateral membranes [52].

To regulate cell adhesion, paracellular transport, and surface-to-internal signaling, TJs are associated with cytoplasmic adapter, scaffold, cytoskeletal, and signaling proteins that form a structural link to the actin cytoskeleton. The best-studied cytoplasmic adapter protein, Zonula occludens (ZO-1), has several domains: the PDZ domain (PSD-95/Discs large/ZO-1 homologous) interacts with Cldn and other adapter proteins, ZO-2 and ZO-3, the GUK domain (Guanylate kinase homology) interacts with Ocln, and the SH3 domain interacts with signaling proteins [51].

Reduced TJs expression leads to increased BBB permeability and the development of vasogenic cerebral edema with an increase in fluid volume in the extracellular space. Cldn has been shown to increase transendothelial electrical resistance of the BBB, primarily by reducing cation permeability through it [53]. Initially, several Cldn (-1, -3, -5, and -12) were thought to be expressed in the BBB, but more recent studies indicate that only Cldn-5 is the dominant component of the cell membrane, with limited expression and the contribution of other Cldn to maintaining BBB homeostasis and integrity [54]. Results from Greene C. et al. (2022) show that chronic suppression of Cldn-5 in the central nervous system caused spontaneous seizures in mice with severe neuroinflammation. Epilepsy alters the integrity of the BBB by modulating Cldn-5, which promotes a local inflammatory response, activation of cell adhesion molecules, and immune cell infiltration of the brain parenchyma [54]. We consider further research into the Cldn-5 role in the development of seizures in eclampsia to be promising.

Additionally, the 65 kDa transmembrane protein Ocln is of significant research interest, as it is considered a marker of BBB integrity [49, 55]. According to current data, Ocln comprises two extracellular domains and one intracellular domain. The first extracellular domain (ECL1) has a very high concentration of tyrosine and glycine residues. The tyrosine residues are involved in forming hydrophobic interactions and H-bonds, while glycine residues provide flexibility. The second extracellular domain (ECL2) is sensitive to hypoxia, is rich in tyrosine residues, and contains two cysteines that form disulfide bridges in an oxidizing environment. Compared to ECL1, ECL2 is the main binding domain that interacts with other tight junctions and regulates their function. The intracellular C-terminal domain of Ocln is rich in serine, threonine, and tyrosine residues and directly binds to ZO-1 and the actin cytoskeleton [55]. Ocln expression is regulated by signaling pathways such as nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), protein kinase C (PKC), RhoK, and ERK1/2. Factors regulating the functions of Ocln protein in maintaining BBB permeability include matrix metalloproteinases 2 and 9 (MMP-2, -9), as well as various proinflammatory cytokines [55].

BBB permeability is associated with Ocln phosphorylation, including VEGF-induced phosphorylation, at serine/threonine or tyrosine [55]. The results obtained by Ni Y. et al. (2017) demonstrated that TNF-α induces Ocln phosphorylation in a human cerebral endothelial cell line (hCMEC/D3) by transiently stimulating the p38MAPK and ERK1/2 pathways, leading to increased BBB permeability and disruption [56]. The study conducted by Zhang Y. et al. (2019) demonstrated that TNF-α suppresses Ocln expression by activating the HIF-1α/VEGF/VEGFR-2/ERK signaling pathway [57]. MMP-9 and IL-1β-induced expression in pericytes suppressed Ocln expression in a BBB model and led to increased BBB permeability. This process was regulated by the NOTCH3/NF-κB signaling

pathway [58]. A study conducted by Kanayasu-Toyoda T. et al. (2018) reported the role of Cldn and Ocln in neovascularization and angiogenesis. The deficiency of these transmembrane proteins has been associated with inhibition of brain endothelial cell proliferation, which can lead to long-term microvascular impairment and the development of neurological dysfunction [59].

An experimental study conducted by Clayton A.M. et al. (2019) on preeclampsia models in rats subjected to placental ischemia showed the presence of edema in the posterior part of the brain 2 months after birth. A decrease in Ocln expression, an increase in the levels of anti-inflammatory cytokines IL-4 and IL-10, and a simultaneous significant increase in pro-inflammatory cytokines IL-17, IL-1α, IL-1β, leptin, and MIP-2 (CXCL2) were detected in this area of the brain [60]. However, the obtained results did not allow us to determine the primary mechanisms in the development of cerebral edema. Thus, a decrease in Cldn-1 expression leads to a decrease in transendothelial electrical resistance with an increase in the fluid volume in the extracellular space and the development of vasogenic cerebral edema. Neuroinflammation processes are accompanied by increased fluid transport into the cell through water channels, which leads to cell swelling and the potential development of cytotoxic cerebral edema [60].

The modulation of paracellular transport through targeting TJs has been proposed as a potential drug delivery system for treating brain diseases; however, this approach has several limitations and is still under development. Further preclinical studies will help to evaluate the potential of tight junction proteins as a therapeutic target for cerebrovascular conditions with impaired BBB integrity, including hypertension-related disorders during pregnancy [51, 61].

The pathogenetic mechanisms of impaired autoregulation of cerebral circulation in preeclampsia

The high metabolic demands of the brain require a relatively constant cerebral blood flow. Its autoregulation is accomplished through myogenic, neurogenic, metabolic, and endothelial control. Myogenic control involves changes in vessel diameter due to contraction of smooth muscle cells in response to increased blood pressure. Neurogenic control is performed by perivascular nerves [62]. Metabolic control is initiated in response to changes in carbon dioxide and oxygen levels and is closely linked to neuronal activity, a process known as functional hyperemia or neurovascular coupling. Endothelial control is realized through the production of vasoactive factors that regulate vascular tone and should normally be in mutual balance [45, 63]. Figure 3 illustrates the mechanisms of cerebral blood flow autoregulation.

The regulation of cerebral blood flow is essential for meeting the metabolic demands of the brain and ensuring normal brain function. In situations

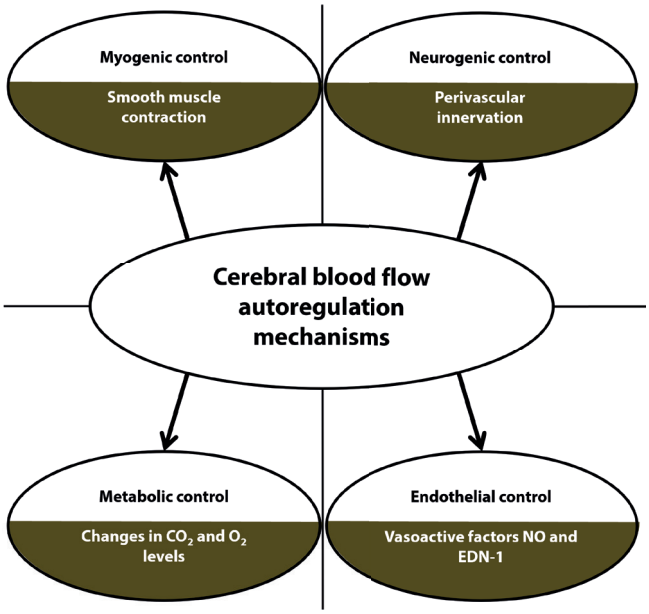

FIG. 3.
Mechanisms of autoregulation of cerebral blood flow

where blood flow to the brain is insufficient, such as in cases of ischemic stroke or hypovolemia due to hemorrhage, ischemic brain injury may occur. Conversely, hyperperfusion due to decreased cerebrovascular resistance may lead to disruption of the blood-brain barrier and vasogenic edema, which is often observed in severe preeclampsia and eclampsia [2-4]. One of the primary mechanisms that regulate cerebral blood flow involves changes in cerebrovascular resistance, which is inversely proportional to the diameter of the blood vessels. Normally, cerebral blood flow is maintained at approximately 50 ml/100 g of brain tissue per minute with a cerebral perfusion pressure of approximately 60–160 mmHg [63, 64]. When cerebral perfusion pressure deviates from the specified reference values, the autoregulation of cerebral blood flow becomes impaired, and the flow becomes linearly dependent on the mean arterial pressure. In cases of acute arterial hypertension, which can occur in severe preeclampsia among other conditions, increased intravascular pressure may overcome the myogenic vasoconstriction of arteries and arterioles, leading to a loss of their ability to maintain vascular resistance [14]. The resulting loss of autoregulation and hyperperfusion can lead to damage to the vascular endothelium, resulting in the development of vasogenic cerebral edema [64].

Transcranial Doppler sonography is used to assess changes in cerebral blood flow velocity, as well

as to calculate cerebrovascular resistance and cerebral perfusion pressure in women with preeclampsia and eclampsia [3, 4]. It has been found that in both women with preeclampsia and women with systemic hypertension, the cerebral perfusion pressure is significantly higher compared to pregnant women with normal blood pressure. Moreover, the cerebrovascular resistance index also increases, indicating the preservation of cerebral blood flow autoregulation. In addition, it has been demonstrated that cerebral blood flow velocity increases in preeclamptic patients compared to those with normal pregnancies [64]. A number of studies have reported a decrease in cerebrovascular resistance in combination with signs of cerebral edema, as indicated by computed tomography and/or MRI data [2, 6, 7]. These data suggest that in most women with preeclampsia there is adequate autoregulation of cerebral blood flow. However, in cases where there is decreased cardiovascular regulation and an autoregulatory breakthrough, excessive perfusion injury, cerebral edema, and neurological symptoms are observed [6, 65].

In a study conducted by van Veen T.R. et al. (2013), cerebral blood flow velocity was measured using transcranial Doppler ultrasonography in pregnant women with gestational hypertension, chronic hypertension, and preeclampsia. No statistically significant relationship was found between the autoregulation index and blood pressure, which, according to the authors, indicates the development of an autoregulatory breakthrough and hyperperfusion without excessive hypertension [66]. A decrease in cerebrovascular resistance in cases of preeclampsia may potentially expose the maternal brain to a significant increase in cerebral perfusion pressure due to the lack of hypertensive adaptation of cerebral arteries. In non-pregnant women, chronic hypertension results in a compensatory decrease in the diameter of the arterial lumen, which increases cerebrovascular resistance and shifts the autoregulation curve towards higher blood pressure values [39, 63, 67].

During normal pregnancy, the maternal vascular resistance reduces, leading to a slight decrease in blood pressure [39]. However, in women with preeclampsia, these adaptive mechanisms do not function sufficiently. Although the exact mechanism of these disturbances remains unclear, it is believed that altered MMP production and/or activity play an important role in the inappropriate vascular remodeling process [32, 39, 68]. These zinc-dependent proteases are produced as precursors that are cleaved into active forms with variable tissue expression, distribution, and substrate specificity. MMP activity is regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs) and altered MMP/TIMP ratios [68, 69]. MMPs have been demonstrated to degrade extracellular matrix proteins, including collagen and elastin [70]. During normal pregnancy, MMPs are involved in the remodeling of uterine and vascular tissue [70, 71]. Changes in the expression/activity of MMP-2 and MMP-9 may lead to decreased vasodilation and increased vasoconstriction with the development of hypertensive disorders during pregnancy [71, 72]. In the study conducted by Timokhina E. et al. (2021), threshold values of MMP-2 and MMP-9 were established to predict the development of preeclampsia in the first trimester [69]. The study conducted by Rao R.S. et al. (2023) revealed significantly increased expression of the EDN-1 and MMP-9 genes in patients with preeclampsia [73]. Understanding the role of MMPs in the remodeling and functioning of the vascular system in pregnant women can help develop new approaches to the prediction and treatment of preeclampsia [68, 69, 73]. Figure 4 illustrates a schematic representation of cerebrovascular changes associated with arterial hypertension, normal pregnancy, and hypertensive disorders during pregnancy. As arterial hypertension progresses, the wall thickness of cerebral vessels increases, and the lumen diameter decreases. During pregnancy, adaptive external (muscular) remodeling occurs, which leads to a slight expansion of the vascular lumen. In chronic arterial hypertension against the background of pregnancy, internal (endothelial) remodeling of cerebral vessels occurs. Preeclampsia is a condition characterized by abnormal internal (endothelial) remodeling in response to increased blood pressure, which probably contributes to increased hydrostatic pressure, which can damage microvessels, and lead to disruption of the BBB, microbleeding, an increase in glial cell numbers and chronic neuroinflammation and neuronal damage (Fig. 4) [63, 74].

CONCLUSION

Women with a history of preeclampsia and/or eclampsia are at an increased risk of developing neurological disorders, including cognitive decline and dementia, which may occur months or even years after delivery. Preclinical and clinical studies have demonstrated that impaired blood-brain barrier permeability plays a key role in the development of central nervous system dysfunction in preeclampsia. The main mechanisms inducing neuroinflammation and neurodegeneration include increased transcellular (mediated by vascular endothelial growth factor and its receptor system) and paracellular (associated with altered expression and function of tight junction proteins) transport, as well as impaired cerebral blood flow autoregulation. These mechanisms lead to impaired cerebral blood flow autoregulation, resulting in hyperperfusion and the development of vasogenic cerebral edema. Although significant progress has been made in understanding the key aspects of preeclampsia pathogenesis, the mechanisms that cause brain endothelial cell damage, as well as the local paracrine and autocrine regulation of cerebral blood flow,

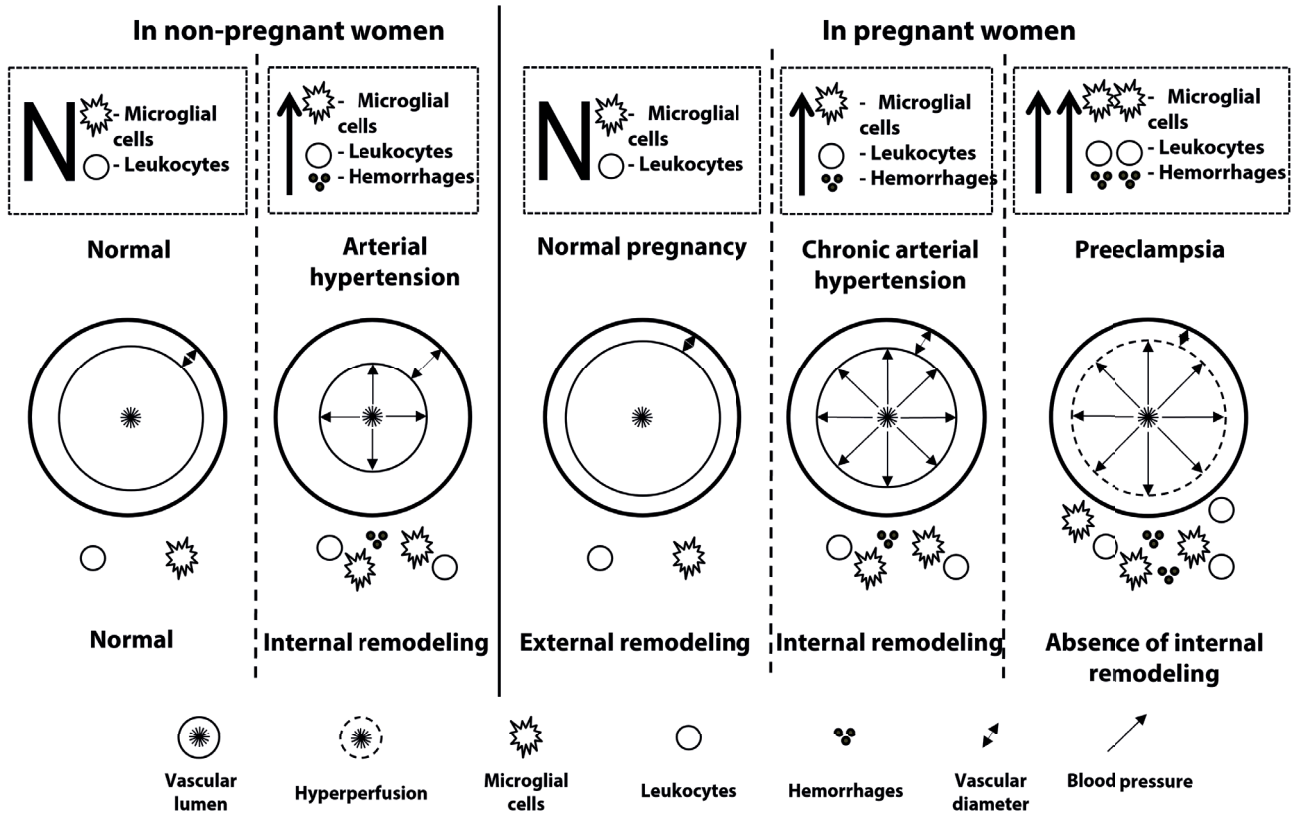

FIG.4.
Cerebrovascular changes associated with arterial hypertension, pregnancy and preeclampsia

continue to be highly relevant for future research. Understanding the key factor for the development of new approaches to the diagnosis and treatment of cerebrovascular complications associated with preeclampsia. This could significantly improve outcomes for both mothers and their newborns.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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