Hypertension

REVIEW

Brain Vascular Dysfunction in Mothers and Their Children Exposed to Preeclampsia

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ABSTRACT: Preeclampsia is a maternal syndrome characterized by the new onset of hypertension and proteinuria after 20 weeks of gestation associated with multisystemic complications, including brain alterations. Indeed, brain complications associated with preeclampsia are the leading direct causes of fetal and maternal morbidity and mortality, especially in low- and middle-income countries. In addition to the well-recognized long-term adverse cardiovascular effects of preeclampsia, women who have had preeclampsia have higher risk of stroke, dementia, intracerebral white matter lesions, epilepsy, and perhaps also cognitive decline postpartum. Furthermore, increasing evidence has also associated preeclampsia with similar cognitive and cerebral disorders in the offspring. However, the mechanistic links between these associations remain unresolved. This article summarizes the current knowledge about the cerebrovascular complications elicited by preeclampsia and the potential pathophysiological mechanisms involved, emphasizing the impaired brain vascular function in the mother and their offspring.

Key Words: blood-brain barrier ■ brain ■ cognition ■ preeclampsia ■ pregnancy

Preeclampsia is defined as the presence of de novo hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) after 20 weeks of gestation accompanied by proteinuria or evidence of maternal organ injury.[1,2] This disease has different clinical manifestations, including eclampsia, a severe complication of preeclampsia, which is defined as the new onset of generalized tonic-clonic seizures in pregnancy, often complicated by hypertension and proteinuria.[3,4]

Preeclampsia affects 3% to 5 % of pregnancies and can lead to severe complications affecting multiple organs[5–7] with a risk of long-term morbidity and mortality. Eclampsia incidence varies from 2 to 3/10 000 births in high-income countries to 16 to 69/10 000 births in low- and middle-income countries. Preeclampsia is responsible for >70 000 deaths-annually worldwide,[8] which corresponds to 14 % of all maternal deaths.[9] About 60% to 70% of maternal deaths associated with preeclampsia are due to cerebral complications, including eclampsia, cerebral edema, and ischemic or hemorrhagic stroke.[10] The majority of deaths occur in low- and-middle-income countries.[11]

Preeclampsia is a condition that requires the presence of a placenta to develop.[12,13] Poor placentation is a decisive risk factor for preeclampsia with inhibited trophoblast invasion, which is associated with impaired vascular remodeling of the uterine arteries. The above events lead to hypoxia-reperfusion damage in the placenta, which releases harmful factors into the maternal circulation. The maternal clinical signs of preeclampsia are likely associated with generalized systemic inflammatory response and endothelial dysfunction.[12,14] However, limited information is available regarding a possible connection between a hypoxic placenta and cerebral complications in women with preeclampsia.

Indeed, the pathogenesis of cerebral complications in women with preeclampsia is enigmatic. Therefore, there is an urgent need to elucidate the underlying mechanisms to develop potential treatments and prevent maternal deaths. In addition, the developing fetus is exposed to the above insults with clinical studies that have found that children born from women with preeclampsia exhibit

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Nonstandard Abbreviations and Acronyms

AT1-AA	angiotensin II type I receptor
BBB	blood-brain barrier
CSF	cerebrospinal fluid
MRI	magnetic resonance imaging
NfL	neurofilament light chain
NSE	neuron-specific enolase
oxLDL	oxidized low-density lipoprotein
PREDO	Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction
PRES	posterior reversible encephalopathy syndrome
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
VEGFRs	VEGF receptors

morphological changes in some brain regions and cognitive alterations.[15–17]

This review aims to summarize the current knowledge about the cerebrovascular complications elicited by preeclampsia and the potential pathophysiological mechanisms involved, with particular emphasis on the impaired brain vascular function in the mother and their offspring.

CEREBROVASCULAR COMPLICATIONS IN WOMEN WITH PREECLAMPSIA

Acute Cerebral Complications

Acute cerebral complications during pregnancy or postpartum among women with preeclampsia include overlapping conditions,[18] such as ischemic or hemorrhagic stroke and generalized seizures (eclampsia), with high morbidity and mortality rates.[19] Eclampsia is a condition characterized by the occurrence of ≥1 generalized, tonic-clonic convulsions unrelated to other medical conditions during pregnancy.[3] Eclampsia is associated with massive cerebral edema, white matter hemorrhage, and parenchymal necrosis.[18] Stroke is a rare complication in pregnancy, but women with preeclampsia run a 6-fold increased risk.[20–22] Another cerebral vascular complication, arterial dissection, is generally seen more often in pregnancy, particularly in preeclampsia.[19,23] These events are rare but challenging to predict as there are no predictive tests, and maternal strokes might occur up to a few weeks postpartum (Table).

The underlying causes of eclampsia are debated but are currently considered to involve cerebral edema and neuroinflammation.[3] Cerebral edema seen in preeclampsia follows a particular pattern of neurological symptoms combined with vasogenic edema predominately in the posterior lobes. This condition is called posterior reversible encephalopathy syndrome (PRES). Thus, PRES is characterized by neurological symptoms, including headache, visual disorders, and seizures, with reversible subcortical vasogenic brain edema as observed by magnetic resonance imaging (MRI) or computed tomography.[24] PRES was initially considered an exclusive feature of preeclampsia and eclampsia but can also occur in other diseases. PRES usually resolves when the underlying cause is treated (ie, delivery in the case of preeclampsia). Unfortunately, potential long-term complications of PRES are poorly studied.[25] In addition to PRES, transient cerebral arterial spasm, named reversible cerebral vasoconstriction syndrome, has also been associated with preeclampsia, though primarily based on case series.[26–29] These studies using cerebral angiography and Doppler velocimetry have shown the presence of vasospasm in the brain circulation in the acute phase (Figure 1).[30]

Late Cerebral Complications

The American Heart Association has recognized preeclampsia as a sex-specific risk factor for stroke.[32] In addition, studies have reported a 2- to 4-fold increased risk of cerebrovascular disease and stroke later in life after preeclampsia.[33–36] Also, the risk is even higher in women with onset of preeclampsia before 34 weeks of gestation than those who had preeclampsia after 34 weeks of gestation.[37,38] Moreover, women with a history of preeclampsia also present a higher risk of vascular dementia and epilepsy after pregnancy,[6,39–43] and an increased risk of Alzheimer disease,[21] although heterogeneity in risk estimates in the literature exists. This might be caused by changes in the definition of preeclampsia throughout the years, susceptibility for recall-bias in studies where preeclampsia exposure was self-reported many years after the index pregnancy, and variation in years of follow-up between studies, where the association between preeclampsia and vascular disorders attenuate with age.[44] However, preeclampsia and eclampsia have been reliably associated with long-term neurological impairments.[41,42,45,46]

Nevertheless, MRI studies have shown an increased number of white matter hyperintensities (a marker of cerebral small vessel disease which correlates to impaired cognition and dementia), in women, several years after preeclampsia.[46–48] In addition, in cross-sectional studies, women with prior preeclampsia have shown more temporal and frontal white matter lesions,[39,46,48,49] reduced cortical gray matter volume,[49] and smaller total brain volume[39,50] compared with women who had normotensive pregnancies.

Moreover, cognitive impairment has been observed in women with severe preeclampsia both in the acute phase[51] and months to years postparum.[43,52] A recent

Table. Acute Brain Complications in Preeclampsia, Listed Alphabetically

Acute complication	Time of onset	Pathophysiology
Arterial ischemic stroke	Depend on the underlying mechanism.	It can occur through multiple mechanisms in women with preeclampsia, after cardioembolism and arrhythmias, as a result of hypoperfusion after RCVS, aftervenousthrombosis (particularly in cases of eclampsia or HELLP-syndrome), and after cervical artery dissection.
Cerebral venous sinus thrombosis.	Usually in the puerperium. A very uncommon complication of preeclampsia. Presents with headache and is often mistaken for post-dural puncture headache.	Preeclampsia leads to hypercoagulability, systemic inflammation, platelet activation, and endothelial injury predispose to thrombosis and increase the risk of cerebral venous sinus thrombosis.
Hemorrhagic stroke	Usually in the peripartum and postpartum period.	It can occur spontaneously or secondary to rupture of vascular lesions. Spontaneous hemorrhages without an underlying vascular lesion are more common in women with preeclampsia. They might be due to impaired autoregulation unable to compensate for sudden hypertension in combination with preeclampsia-related coagulopathy.
Intracerebral hemorrhage		
Subarachnoid hemorrhage		
PRES	This condition is a radiological diagnosis. Usually within the postpartum period, but can occur at any time during pregnancy.	Constitute a syndrome of vasogenic edema and BBB breakdown, which affects both cortical and subcortical structures, and all brain regions.
RCVS	Usually within the postpartum period, but can occur at any time during pregnancy.	Transient vasospasm in arteries of the circle of Willis. The condition can be associated with ischemic stroke and nonaneurysmal subarachnoid hemorrhage.

For further information, we recommend checking Miller.[22] BBB indicates blood-brain barrier; HELLP-syndrome, hemolysis, elevated liver enzymes, and low platelet count; PRES, Posterior reversible encephalopathy syndrome; and RCVS, Reversible cerebral vasoconstriction syndrome.

meta-analysis reported a correlation between a history of preeclampsia and subjectively reduced cognition, but results diverged regarding objective neurocognitive tests.[43] Conversely, another study concluded that the increased risk was mainly attributed to the cardiovascular phenotype and not driven by preeclampsia.[53] Thus, results are conflicting and the causal relationship between preeclampsia and cognitive decline is not well established. Further prospective studies are needed.

This evidence suggests that women with preeclampsia might have a continued susceptibility to brain injury persisting years postpartum. However, most data derived from epidemiological studies and other residual confounding factors must be considered.

CEREBRAL ALTERATIONS IN THE OFFSPRING BORN TO WOMEN WITH PREECLAMPSIA

The potentially harmful effects of preeclampsia on the offspring of pregnant women are a matter of concern. In the clinical setting, studies have attempted to correlate the cognitive performance of children born to women with preeclampsia with changes in their brain anatomy[15,17] and neuronal networking.[54] Findings of MRI analyses performed in children born to women with preeclampsia demonstrated a larger size in at least five brain regions compared to those born to normotensive pregnancies.[17] In addition to these structural changes, children born from women with preeclampsia also

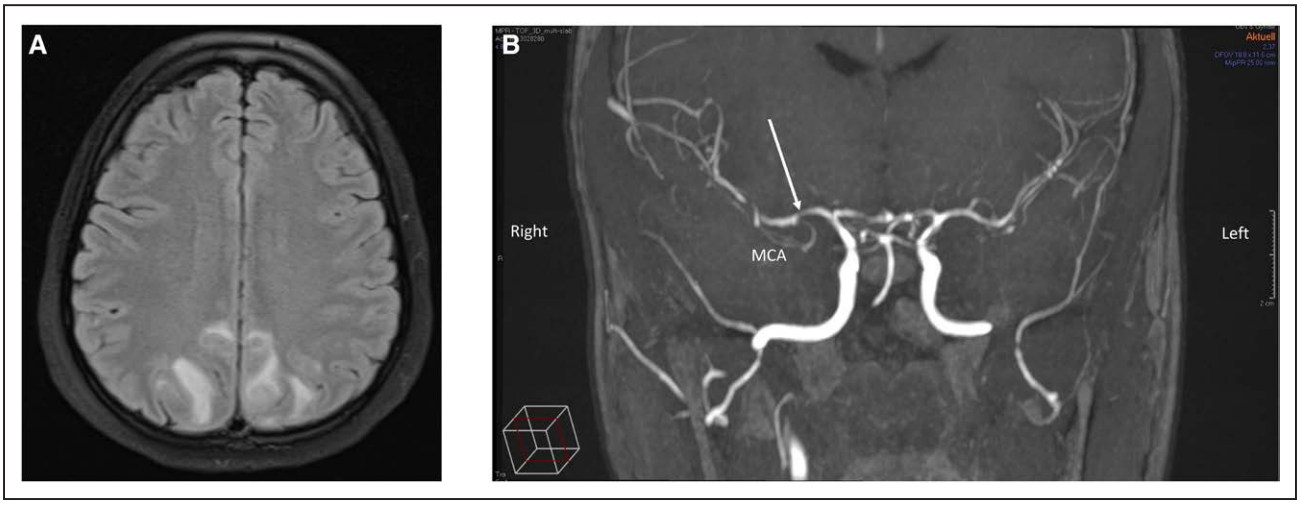

Figure 1. A, Representative image of posterior reversible encephalopathy syndrome (PRES) in the posterior cortical area of the brain in a woman with eclampsia.
B, Representative image of vasoconstriction in the right middle cerebral artery in a woman with eclampsia. Obtained with permission from the PROVE biobank and database.[31]

exhibit higher or lower levels of connectivity in certain critical cognitive areas than matched-control children.[54] Another MRI study[55] reported increased volume in the tract for the superior longitudinal fasciculus and the caudate nucleus in the brains of children born to women with preeclampsia.

Nevertheless, reduced cerebral vessel radii in the occipital and parietal lobes were found in children born to women with preeclampsia compared to matched-control children.[17] The authors proposed that these changes in the brain vasculature of the offspring might have preceded the structural alterations. Although the above reports are relevant due to a well-described matching between case and controls (matching variables included gestational age, children age, gender, maternal parity, and race), we stress that these studies were conducted by the same research group with a limited number of children. Therefore, results must be confirmed in more extensive population studies. Also, we must clarify that these results suggest an association, but not causality.

EVIDENCE OF MENTAL AND COGNITIVE ALTERATIONS IN THE OFFSPRING OF WOMEN WITH PREECLAMPSIA

Studies have attempted to investigate the association between preeclampsia and developmental alterations in the offspring that would, in turn, predispose them to a higher risk of metabolic, neurological, and cardiovascular disorders in adulthood.[15,16,55–66] In the context of brain-related disorders, it appears that children born to women with preeclampsia exhibit an increased risk of developing cerebral palsy, stroke, impaired neurological development, developmental delays at the age of 5 years, poor cognitive development, intellectual disability, anxiety, depressive symptoms, attention-deficit disorder, and hyperactivity in comparison with children born to normotensive women.[67–69]

Despite the apparent association between preeclampsia and the development of brain-related disorders in children, the causality is not clear. However, the above studies present extensive multivariable statistical analyses tending to isolate the potential unique effect of preeclampsia. Adjustment for confounder variables includes analysis considering gestational age, the proportion of appropriateness of fetal growth, maternal smoking, child's sex, the maternal experience of stressful events in pregnancy, maternal sociodemographic information from the prenatal period such as maternal age, maternal education, family income, and the presence of the biological father in the family home, as well as family functioning test.[64] In addition, other confounding variables such as childhood socioeconomic status, child welfare clinic, school records, parity, year of birth, or mother's body mass index have been taken into account.[60,70–72] In agreement with this body of evidence, recent systematic reviews concluded that preeclampsia has independently been associated with neurocognitive and mood disorders in children.[55,73,74]

More recently, the PREDO study (Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction)[68] concluded that maternal preeclampsia and particularly severe preeclampsia are independently associated with a higher risk of mental illness in the offspring. In parallel, another study demonstrated a relationship between preeclampsia and neurodevelopmental disorders in the offspring that could lead to cerebral palsy, epilepsy, attention-deficit/hyperactivity disorder, autism spectrum disorder, and intellectual disability, among others.[69] Since those studies were conducted in a population with a low incidence of preeclampsia (0.8%–1.9%) or included a sample enrichment strategy based on known factors for preeclampsia and growth restriction,[68] the results might not apply to other populations with a higher incidence of preeclampsia.[75]

Most epidemiological studies include behavioral, emotional, and psychosocial developmental disorders in analyzing children born to women with preeclampsia. However, other equally critical cognitive problems that have been associated with preeclampsia, such as language development disorders,[76] have to be considered.[77] For example, a recent study demonstrated that children born to women with preeclampsia exhibited deficits in verbal skills, comprehension, and expressive capacity of narrative discourse.[78]

To summarize, epidemiological analyses and recent systematic reviews indicate that children born to women with preeclampsia have an increased risk of developing brain-related disorders compared to match-controls. Even after adjusting for potential contributions by other maternal health factors (eg, age, prepregnancy body mass index, diabetes status, parity, depression, smoking, and alcohol use), child sex, and gestational age. However, those associations do not represent causality.

PATHOPHYSIOLOGY OF CEREBROVASCULAR ALTERATIONS IN PREECLAMPSIA

The etiology of cerebral complications in preeclampsia and eclampsia in both mothers and their children is unknown. Factors including cerebral vasoconstriction, forced dilatation of cerebral arteries resulting in hyperperfusion, and endothelial dysfunction are suggested to play a role in the maternal side.[6,45,79,80] However, there are concerns about the persistence of endothelial dysfunction present during pregnancy and increased risk of brain injury in women who suffered a pregnancy complicated by preeclampsia.[81] Indeed, it is unclear whether the association of preeclampsia with brain alterations

in the mother might constitute a result of long-lasting consequences of an insult received during pregnancy or if preeclampsia somehow reprograms endothelial cells, causing increased susceptibility. Alternatively, even if preeclampsia and brain alterations may be separated, conditions present in women with a shared risk profile with preeclampsia being merely a stress test.

In the case of cerebral complications in the offspring born from a woman who developed preeclampsia, the pathophysiology is even less clear, and currently, just a few studies have investigated the potential underlying mechanisms.

In the following sections, we will discuss the information on the role of vascular alterations in the pathophysiology of brain complications observed in mothers and their children exposed to preeclampsia.

CEREBRAL BLOOD FLOW REGULATION AT THE MATERNAL SIDE

This review will focus on what is known about cerebral autoregulation in preeclampsia. For an extensive review of cerebral autoregulation, we refer to the excellent review by Claessen et al.[82] Control of cerebral blood flow involves a spectrum of overlapping regulatory mechanisms to facilitate optimal oxygen and nutrient delivery to individual cells in the brain.[82] Those mechanisms are divided into four distinct components: autoregulation, chemoregulation, neuronal regulation, and endothelium-dependent regulation. One component of the autoregulation is called static cerebral autoregulation. This mechanism keeps the cerebral blood flow constant despite blood pressure changes occurring slowly over time.[83] The range in between where the autoregulatory capacity maintains cerebral blood flow at a reasonably constant level is debated and relies on older data from different individuals but is considered to function between a mean arterial pressure of 50 and 150 mm Hg.[81] Supporting data for a plateau of constant cerebral blood flow within a certain range of mean arterial pressure has also been shown in animal studies.[82,83]

Severely elevated blood pressure, seen during severe preeclampsia and eclampsia, increases the potential risk for edema, high intracranial pressure, and other neurological complications when the autoregulatory capacity is lost and cerebral blood flow increases proportionally to the mean arterial pressure.[84] However, severe hypertension alone may not be the only cause of cerebral edema in preeclampsia since cerebral complications also affect women with preeclampsia with mild hypertension or before the onset of hypertension.[85]

The ability of cerebral arterioles to constrict or dilate and maintain cerebral blood flow constant over seconds to minutes in response to sudden fluctuations in mean arterial pressure but within the normal variation (also within normal blood pressure range) is called dynamic cerebral autoregulation.[86] A cross-sectional study investigating dynamic cerebral autoregulation in preeclampsia and healthy pregnancies found that the autoregulatory index, a measurement of the continuous dynamic cerebral autoregulation, was poorer in women with preeclampsia and that it did not directly correlate with the level of blood pressure.[85] Furthermore, another study demonstrated that women with eclampsia showed an even poorer autoregulatory index, which may represent a less effective dynamic cerebral autoregulation compared to both preeclampsia and normotensive pregnancies.[87] This impaired dynamic cerebral autoregulation might cause a delay in the immediate response of cerebral vessels to subtle changes in systemic blood pressure, thereby leading to hyperperfusion and cerebral edema or vasoconstriction and cytotoxic edema also in women with preeclampsia with normal blood pressure.[85,88]

In postmenopausal women with a history of preeclampsia, the cerebral blood velocity has been shown to be increased in response to a sympatico-excitatory stimulus compared with women with normal pregnancies.[89] This response might result from impaired autoregulation of the cerebral microvasculature under high-pressure conditions in women with prior preeclampsia. Likewise, postmenopausal women with a history of preeclampsia had a reduced cerebral blood velocity response to a vasodilatory chemical stimulus (hypercapnia), which suggests a remainder/preexistent cerebral vessel dysfunction.[90]

PREECLAMPSIA AND ALTERATIONS IN THE BLOOD-BRAIN BARRIER AT THE MATERNAL SIDE

Evidence from preclinical and clinical studies has suggested that cerebral complications in preeclampsia may involve alterations in the functionality of the blood-brain barrier (BBB)[90] (Figure 2).

Clinical Studies

Since preeclampsia is a condition only observed in humans, the study of cerebrovascular alterations at the BBB level in women with preeclampsia or women with a history of preeclampsia is challenging and limited to clinical trials involving imaging techniques and biomarkers. Studies have evaluated the accuracy of the more selective brain- or BBB injury biomarkers, including S100B,[91] NSE (neuron-specific enolase),[92,93] NfL (neurofilament light chain),[94] and isoforms of tau protein.[95] Women with preeclampsia exhibit increased circulating concentrations of the above proteins, and even women without overt clinical neurological complications might experience brain- or BBB injury. Although there are some alternative sources to these proteins, their transport from

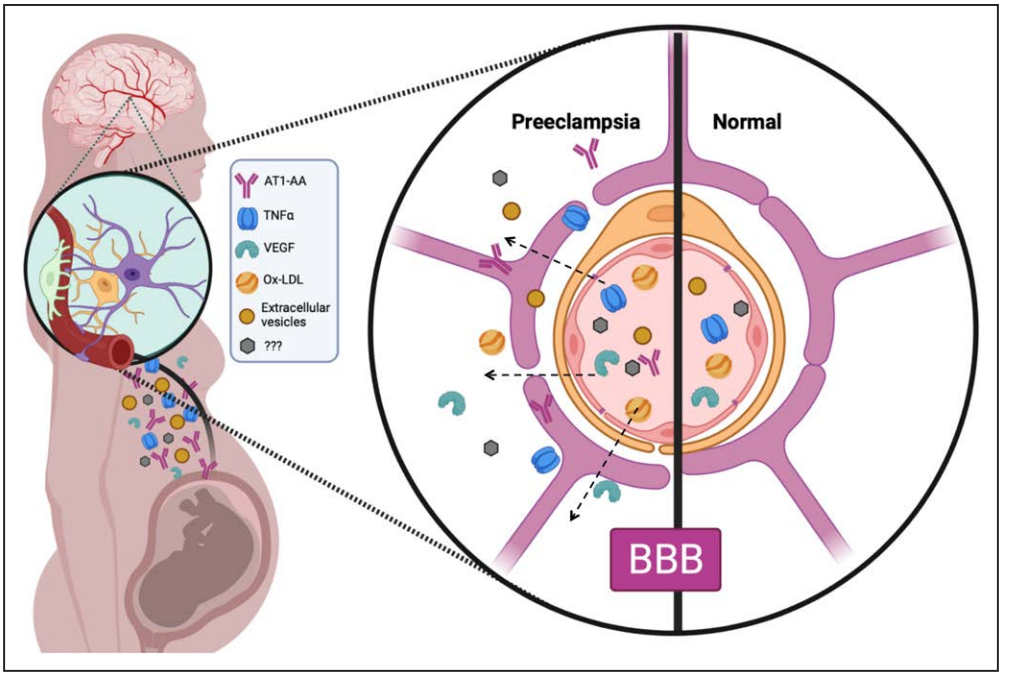

Figure 2. Disruption of the blood-brain barrier (BBB) in women with preeclampsia.
Potentially, harmful circulating factors, including VEGF (vascular endothelial growth factor), sFLT-1, TNF (tumor necrosis factor)-a, oxLDL (oxidized low-density lipoprotein), AT1-AA (angiotensin II type I receptor), or placental extracellular vesicles have been involved in the disruption of the BBB in preeclampsia. It is unclear whether a combination between them or other not-yet described harmful molecules (???) are also participating. Figure created using BioRender.

the CNS to the systemic circulation is unknown. Results from another cross-sectional study supported the neuronal origin of NfL, demonstrating increased cerebrospinal fluid (CSF) and plasma concentrations of NfL in preeclampsia.[96] However, the authors could not demonstrate an injured BBB by differences in CSF/plasma albumin quotient. Interestingly, the increased plasma S100B and NSE concentrations may persist in women with a history of preeclampsia one year postpartum.[93] Another study with women with severe disease including a large group of women with eclampsia demonstrated increased plasma concentrations of tau and GFAP (glial acidic fibrillary protein) in women with preeclampsia. Concentrations were particularly increased in women with eclampsia and hemolysis, elevated liver enzymes, and low platelet count syndrome, and these correlated to number of neurological complications.[97]

A few studies have investigated both neuroinflammation and BBB integrity in preeclampsia.[98,99] One study assessed the concentrations of C5a, C5b-9, TNF (tumor necrosis factor)-α, and IL (interleukin)-6 in CSF and the CSF-plasma albumin ratio in preeclampsia cases with or without severe features compared to hypertensive disease without proteinuria and normotensive controls. No difference was found between groups for any inflammatory markers or the CSF-plasma albumin ratio. The other study of a population with more severe disease, including eclampsia, could demonstrate an increased neuroinflammatory activity in eclampsia and preeclampsia by increased CSF concentrations of IL-6, IL-8, and TNF-α and in addition, signs of an impaired BBB by increased CSF-plasma albumin ratios.[99]

Preclinical Studies

Cellular and molecular events associated with the alterations in BBB functionality exhibited in preeclampsia rely on in vitro and rodent-based in vivo models.[100–103] In terms of in vivo studies, the induction of a hypertensive state in pregnant rodents can be achieved through different treatments.[104,105] The reduced uterine placental perfusion model (RUPP)[106] is most employed. However, the outcome largely depends on the hypertension model used. We refer to excellent reports published in the field[30,102,107–109] in which disruption of the BBB was generated in vivo or ex vivo using pressurized brain blood vessels.

In addition, a feature of the RUPP model is related to its effects postpartum since it replicates the cerebrovascular complications after delivery, observed in clinical studies.[93] A report demonstrated that RUPP-rats showed increased water content in the posterior cortex after 2 months postpartum, suggesting persistent vasogenic edema.[109] Furthermore, this outcome was accompanied by a reduction in the protein expression of the tight junction protein occludin in the same region, suggesting impairment in the barrier properties of the BBB.

In terms of in vitro studies, to provide more physiological relevance in the human scenario, we employed the human-derived brain endothelial cell line d3, obtained

from the healthy brain endothelium of a female epileptic patient.[110] Exposure of cell monolayers to plasma from women with preeclampsia increased the permeability to fluorescein isothiocyanate (FITC)–dextran 70 kDa. In addition, it reduced the transendothelial electrical resistance, as a sign of disruption of the BBB, with no changes in the mRNA expression of the tight junction proteins occludin and zonula occludens-1.[110] Significantly, reduction in the transendothelial electrical resistance value was associated with higher plasma concentrations of the NfL detected in the same plasma of women with preeclampsia. This finding indicates that NfL could be a promising biomarker for BBB alterations in preeclampsia.[111]

PROPOSED MECHANISMS OF ENDOTHELIAL DYSFUNCTION AT THE MATERNAL BBB: ROLE OF THE PLACENTA

As preclinical studies have been pivotal in demonstrating that the serum or plasma from preeclampsia can disrupt the BBB and impair the cerebral blood flow autoregulation, the current evidence suggests that circulating factors, likely released from the placenta, may cause these alterations. This evidence has been summarized in recent reviews,[19,45,88] and in Figure 2. Although little information is available about the potential circulating mediators, several candidates have been studied, including VEGF (vascular endothelial growth factor),[100,112] TNF-α,[101,113] oxLDL (oxidized low-density lipoprotein),[114,115] AT1-AA (angiotensin II type I receptor),[116] and placental extracellular vesicles.[117,118] Over the following sections, these underlying factors are discussed.

Vascular Endothelial Growth Factor

VEGF is considered a key regulator of blood vessel formation in health and disease. The biological functions of the VEGFs are mediated by a family of cognate protein tyrosine kinase receptors (VEGFRs [VEGF receptors]),[119] identified as VEGFR1, VEGFR2, and VEGFR3. Also, VEGF binds to the VEGFR1 decoy receptor (or sFlt-1), a soluble splice variant of VEGFR1 lacking the intracellular tyrosine kinase domain. Several studies have shown that women with preeclampsia demonstrate higher circulating sFlt-1 concentrations than normotensive pregnant controls.[120,121] sFlt-1 is not specific to pregnancy but is secreted into the maternal circulation in increased concentrations by trophoblast, most probably secondary to placental hypoxia.[122,123]

In preeclampsia, VEGF bioavailability is decreased compared to normal pregnancy due to high circulating levels of sFlt-1[119, 120]. The overexpression[124] and exogenous administration[125] of sFlt-1/sEng (ie, soluble endoglin) in adult and pregnant mice, respectively, increased BBB permeability. Interestingly, the sole overexpression of sFlt-1 in adult mice did not increase BBB permeability,[124] suggesting that the neutralization of VEGF signaling is part of a more complex mechanism responsible for the cerebrovascular complications of preeclampsia. However, this outcome contrasts with observations reported by Cross et al,[126] including a group of nonpregnant women receiving the VEGF inhibitor bevacizumab, who exhibited a reversible preeclampsia-like syndrome with cerebrovascular dysfunction.[126]

Another member of the VEGF family is PlGF (placental growth factor), which presence is required for an adequate fetal brain vessel formation and function.[127–129] Circulating concentrations of PlGF are reduced in women with preeclampsia.[121] However, whether this reduction observed in preeclampsia impairs the BBB is unclear.

In animal brain endothelial cells, VEGFR2, rather than VEGFR1, regulates the BBB permeability.[130] A study[131] using cerebral veins of pregnant rats showed that plasma from late-pregnant rats, but not those from nonpregnant rats, increased the BBB permeability, associated with activation of both VEGFR1 and VEGFR2. Using a similar approach, it was shown that plasma from women with preeclampsia increased BBB permeability, an effect that was abrogated upon inhibition of VEGFRs, most likely VEGFR2.[99]

The observed disruption of the BBB after exposure of cell monolayers to plasma from women with preeclampsia was associated with high mRNA levels and differential tyrosine phosphorylation of VEGFR2 in the human brain endothelial cell line.[112] We measured the phosphorylation of Y951 and Y1175 tyrosine residues, linked with cell permeability[132] and cell proliferation,[133] respectively, and found that the phosphorylation of Y951 was higher in cells exposed to plasma from women with preeclampsia than those exposed to plasma from normal pregnancy or nonpregnant women. Conversely, phosphorylation of Y1175 was reduced in cells exposed to plasma from normal pregnancy and preeclampsia compared to nonpregnant women.[112] Blockage of VEGFR2 revert in vitro markers of the BBB disruption generated by plasma of women with preeclampsia.[134] These results not only confirm in a human setting the participation of VEGFR2 in the damage of the BBB after exposition to plasma of women with preeclampsia observed in a rodent model.[100] However, it also revealed the complexity in the activation of VEGFR2 and the specific underlying pathways leading to cellular outcomes, such as cell permeability.

Tumor Necrosis Factor-α

The proinflammatory cytokine TNF-α might also link placental ischemia and cerebrovascular dysfunction. TNF-α is an essential mediator of the innate and acquired immune response.[135] In addition, this cytokine impacts endothelial cells by increasing vascular permeability

and induces apoptosis of trophoblastic cells in placental explants.[136]

Normal pregnancy is associated with a subclinical inflammation with elevated levels of proinflammatory cytokines.[137,138] Moreover, this proinflammatory phenotype is exacerbated in the context of preeclampsia, as studies on women with preeclampsia have correspondingly shown increased levels of TNF-α in plasma and serum from 28 weeks of gestation until birth[139] and in one study also in CSF.[99]

Regarding the potential cerebrovascular alterations elicited by TNF-α, a study demonstrated that RUPP-rats showed increased placental and systemic levels of TNF-α and brain water content compared to normal pregnant rats.[113] Furthermore, it was shown that pregnant rats treated with TNF-α exhibited a similar outcome. The above effects observed in both RUPP and TNF-treated pregnant dams were counteracted by treatment with the TNF-α inhibitor etanercept.

oxLDL and AT1-AA

A group of studies has addressed the role of oxLDL in BBB dysfunction in rodent models of preeclampsia.[114,115] In cerebral veins isolated from nonpregnant dams, treatment with plasma from women with early-onset preeclampsia increased their permeability over the vascular wall compared with the effect observed with plasma from late-onset preeclampsia and normal pregnancies.[115] However, the blockade of LOX-1 (lectin-like oxidized low-density lipoprotein receptor-1), an oxLDL scavenger receptor, reversed the increase in BBB permeability. Furthermore, in pregnant rats fed with a high-cholesterol diet, using a model of preeclampsia, blockade of LOX-1 counteracted the oxLDL-mediated increase in BBB permeability.[115] A later study showed that treatment of isolated rat cerebral veins with $MgSO_4$ attenuated the increase of BBB permeability elicited by the exposure to rat serum supplemented with oxLDL on BBB.[114]

Women with preeclampsia exhibit high levels of agonistic autoantibodies for the AT1-AA.[140] This has been suggested to contribute to the development of cerebrovascular dysfunction in models of placental ischemia. In pregnant rats subjected to RUPP, the treatment with the AT1 antagonist losartan reverted the impairments in cerebral blood flow autoregulation.[141] A later study showed that the AT1-AA antagonist n7AAc apart from attenuating the negative effects on cerebral blood flow autoregulation, decreased BBB permeability, cerebral edema, and oxidative stress in RUPP dams.[116]

Extracellular Vesicles

Preeclampsia has been linked to impaired placental invasion of the maternal vascular bed.[142] This stress damages placental cells in contact with maternal circulation (ie, trophoblast), leading to detachment and release of cell fragments, microparticles, and small extracellular vesicles (sEVs, including a wide range of sizes, such as exosomes) into the maternal circulation.[122] In addition, increasing evidence has associated the release of sEVs and placental-derived extracellular vesicles (PDsEVs) with maternal endothelial dysfunction in preeclampsia.[143–146]

Little information is available regarding sEVs and disruption of the BBB in preeclampsia. Han et al.,[118] used PDsEVs isolated from injured murine placentae and injected them in pregnant mice to generate a preeclampsia-like syndrome. These PDsEVs disrupted the integrity of a cultured mouse brain endothelial cell line (bEnd.3) and generated a reduction in the cerebral blood flow in nonpregnant mice.

In the setting of human studies, exposure to plasma and plasma-derived sEVs from women with preeclampsia increased the permeability and reduced the transendothelial electrical resistance in human-derived brain endothelial cell line/D3 brain endothelial cells. A similar outcome was observed using hypoxic PDsEVs (isolated from placentas of normal pregnant women exposed to hypoxia, 1% O_2, 18 hours), which also increased the permeability to Evan blue in the brain C57BL6 nonpregnant mice. Thus, plasma-sEVs from women with preeclampsia or hypoxic placentae can disrupt the BBB.[117] However, the underlying mechanisms and the consequences of this disruption are unknown.

Since sEVs are carriers of harmful molecules,[147–149] including VEGF, TNF-α, or modified lipids (ie, oxo-LDL), microRNAs, among other crucial signaling components,[150,151] it is possible that disruption of the BBB generated by PDsEVs may have profound consequences not only for acute cerebral complications in women with preeclampsia but also on long-term due to potential reprogramming of brain endothelial cells.

CEREBRAL BLOOD FLOW REGULATION AT THE FETAL SIDE

Less is known about cerebral blood flow regulation in the offspring of women with preeclampsia. Nevertheless, in severe cases of preeclampsia, the fetus redistributes its cardiac output to maximize oxygen and nutrient supply to the brain, a phenomenon called fetal brain sparing or preferential cerebral perfusion in response to placental insufficiency.[152] This redistribution of fetal blood flow to the brain is a compensatory mechanism protecting the fetus from potential damage.

Currently, it is unclear whether the redistribution of the blood flow towards the brain in those fetuses remains after birth. A recent publication indicates that children born from women with preeclampsia exhibited

an overall tendency toward impaired cerebral autoregulation within the first 5 days after birth. Furthermore, this tendency disappeared after multivariate analysis adjusting for confounders, such as fetal brain sparing.[153] These results suggest that impaired autoregulation might extend after birth in children born from women with preeclampsia. However, many confounding factors, including preterm birth, use of hypertensive drugs, intrauterine growth restriction, and magnesium sulfate, among others, make this assumption challenging to sustain.

The middle cerebral artery (MCA) pulsatility index and MCA/uterine artery or MCA/umbilical artery pulsatility index ratios are used in the prediction of adverse perinatal outcomes in complicated pregnancies, such as preeclampsia. These variables might also characterize the MCA impaired function in fetuses of women with preeclampsia. In several studies, a significantly lower MCA pulsatility index and MCA/umbilical artery pulsatility index ratios were found in fetuses from women with severe preeclampsia compared with normotensive pregnancies.[154,155] Whether MCA might indicate functional impairment of the whole cerebral vasculature in the offspring or if it is only associated with this macrovascular artery is not fully understood.

Animal studies have reinforced the biological significance of the findings of alterations in the MCA function. Offspring born from dams fed with a high-cholesterol diet (used as a preeclampsia-like model), present structural and functional defects in the MCA.[156] Vascular characteristics and reactivity of the MCA were evaluated on postnatal days 16 (P16), 23 (P23), and 30 (P30). In early postnatal life, MCAs from offspring of preeclampsia were stiffer than in pups from normal pregnancies, and their stress-strain patterns were relatively similar at P16 and P23. However, by P30, this relationship reversed, and MCAs from pups from normal pregnancies became stiffer, whereas MCAs from pups from preeclampsia became more compliant. These findings indicate differential maturation in the stiffness of MCA between pups born from normal pregnancy and preeclampsia. However, underlying mechanisms and functional consequences for the brain functioning in the setting of preeclampsia are still unknown.

Based on this evidence, we could assume that placental hypoxia/reperfusion leads to alterations in the blood flow reaching the fetal brain due to a strategic prioritization of blood flow to vital organs. Whether these changes remain after birth is unclear. Notwithstanding these findings, we clarify that fetal brain blood flow alterations are not exclusive to preeclampsia. They have also been observed in women with pregnancies considered at high risk for fetal compromise, including, intrauterine growth restriction, post-term pregnancies, previous pregnancy loss, women with hypertension, diabetes, or other maternal pathology.[157]

PREECLAMPSIA AND ALTERATIONS IN THE BBB AT THE FETAL SIDE

Another question that remains unanswered is whether preeclampsia produces alterations in the BBB at the fetal side and if this could be related to the alteration in vascular functionality. As far as we know, there are no studies in this field. However, it has been reported that maternal obesity (ie, sometimes presented as a model of preeclampsia), during pregnancy can compromise the BBB formation in the fetus,[158] in particular in the arcuate nucleus (a structure that regulates body weight in response to blood-borne signals of energy balance), in the offspring.

PROPOSED CONSEQUENCES OF CEREBRAL VASCULAR ALTERATIONS IN THE OFFSPRING BORN FROM WOMEN WITH PREECLAMPSIA

As described throughout this review, little is known about how preeclampsia may impair the neurodevelopment in the offspring. Current hypotheses include that the neurological and cognitive impairments exhibited by the offspring might be driven by neuroinflammation or impaired cerebrovascular function (Figure 3).

A study demonstrated that the brain of fetuses extracted from RUPP model showed increased levels of proinflammatory cytokines, chemokines, higher incidence of microbleeds, and reduced microglial density in the subventricular zone, either excreted from the fetal brain or originating from maternal blood.[159]

In another study, pregnant rats were treated with an inhibitor of nitric oxide synthase, the N-nitro-L-methylarginine, at different gestational ages to induce an early and late-onset preeclampsia-like state.[160] Under the above conditions, the cortical and cerebellar expression of 2 markers of neuroinflammation, was assessed in both mother and pups. The results showed that in pups, the expression of the 2 markers (IBA1 and EAAT) was increased and decreased, respectively, at postnatal days 1 and 60. The authors suggested that the reduced expression of EAAT under a neuroinflammatory insult could lead to increased concentrations of cortical and cerebellar glutamate, resulting in excitotoxicity.

Brain cortex and the hippocampus are particularly susceptible to hypoxia-induced injury in the newborns, which seems to be the case in preeclampsia.[161] Why brain hypoxia after birth may be present in children born to women with preeclampsia is unknown. MRI studies have shown reduced blood perfusion in both occipital and parietal areas in the brain of children born to women with preeclampsia.[17]

Hypoxia in the brain of offspring born to preeclampsia (using an N-nitro-L-methylarginine model) at the

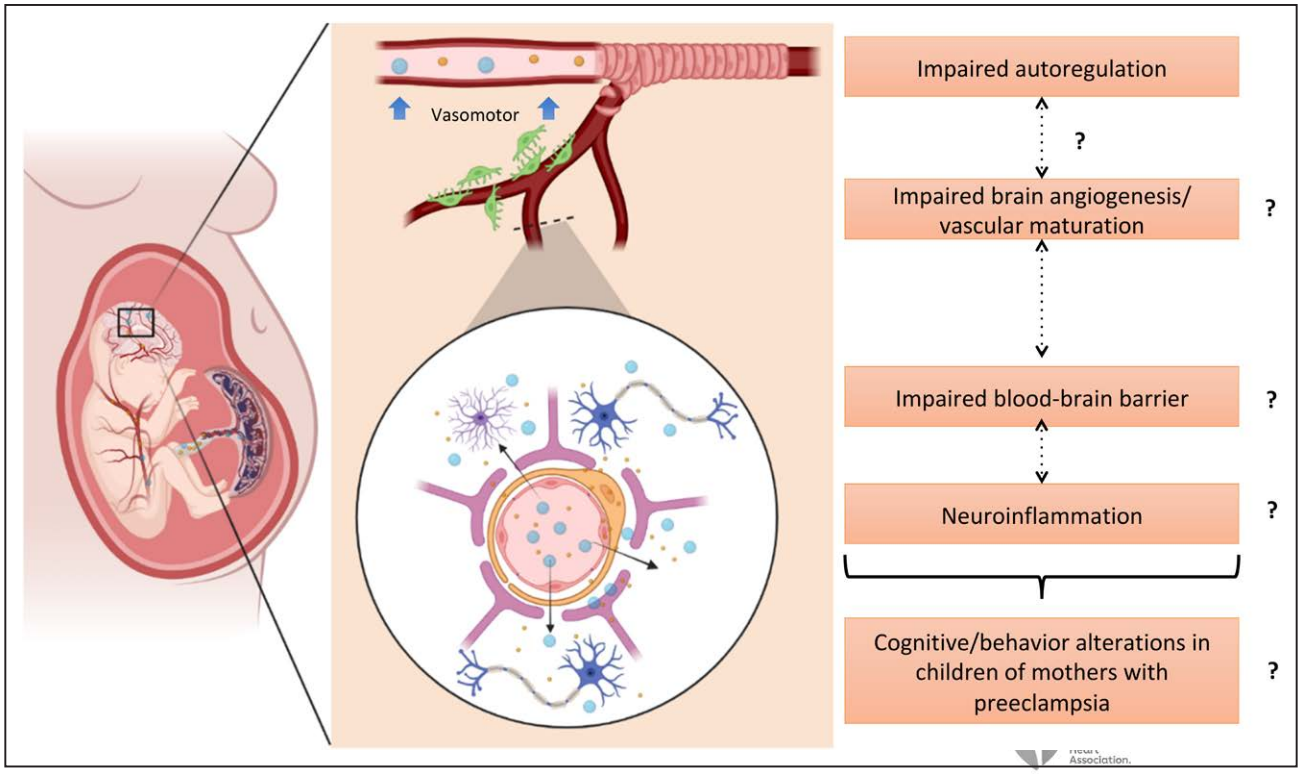

Figure 3. Neurological and cognitive impairments exhibited in children of women with preeclampsia might involve impaired cerebrovascular function.

Similar to maternal circulation, placental-derived potential harmful factors can reach the fetal central nervous system. Brain vascular alterations in offspring from preeclampsia may include high vascular resistance (ie, impaired autoregulation?), impaired brain angiogenesis (?), disruption of the fetal blood-brain barrier (?), which may lead to neuroinflammation and cerebral cells activation (ie, microglia, astrocytes, pericytes, among others). Figure created using BioRender.

postnatal stage was also demonstrated in an animal study by Tachibana et al,[162] who described that cells positive for HIF-2α (ie, hypoxic cells; hypoxia-inducible factor 2α), were highly abundant in regions that include white matter, the dentate gyrus, and cornu ammonis of the fetal hippocampus indicating that these areas received less blood perfusion. Using a similar model but in rats, it has been shown that male offspring born to N-nitro-L-methylarginine rats exhibited a dramatically reduced number of proliferating cells in the hippocampus compared to controls.[163] These are indirect evidence of impaired brain perfusion in selected brain areas in offspring born to preeclampsia, but again, underlying mechanisms are unknown.

CONCLUDING REMARKS

The findings from preclinical and clinical studies are consistent in demonstrating that preeclampsia is associated with cerebrovascular alterations in the mother. The underlying causes of the acute clinical complications, such as stroke, eclampsia, and cerebral edema most probably involve increased blood pressure, coagulation disorders, cerebral blood flow alterations, and BBB disruption, resulting in cerebral edema, increased neuroinflammation, seizures, and death.

As the impact of preeclampsia on the offspring has just begun to be assessed, more studies are required to determine the extent of cerebrovascular and neurological dysfunction that a child could suffer after being born from a pregnancy complicated by preeclampsia. However, growing evidence supports the association between maternal hypertension in pregnancy and alterations in developmental cognition in the offspring. In addition, it remains unknown if the brain alterations in the offspring are direct consequences from an unfavorable milieu caused by preeclampsia or if the drivers are rather preterm birth or intrauterine growth restriction which are both commonly observed in preeclampsia.

Future multidisciplinary studies to elucidate how preeclampsia impairs brain vascular function and disrupts the BBB in both mother and fetus. This effort will offer the potential of significant improvements in understanding and mitigating preeclampsia-induced brain sequelae in both mother and their children.

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Acknowledgments

The authors would like to thank the researchers belonging to Vascular Physiology Laboratory and GRIVAS health for their valuable input. Also, to Dr Hiten Mistry for his valuable editorial assistance. Funding. This study was funded by Fondecyt 1200250 (Chile), STINT for collaboration Chile and Sweden (Saving maternal brains; MG2019-8462); The Swedish Research Council (Saving maternal brains; 2020-01640); The Swedish Brain Foundation (Saving maternal brains; FO2019-0128). C. Escudero conceptualized the article. C. Escudero and L. Bergman critically analyzed the available literature and edited the article. E. Kupka, J. Acurio, and D. Lopez prepared the draft of the article. B. Ibañez, H. Sandoval, and F. Troncoso prepare tables and figures. P. Torres-Vergara and A.K. Wikström critically edited the article. All coauthors approved the final version of this article.

Sources of Funding

None.

Disclosures

None.

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