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Cerebrovascular Dysfunction in Preeclamptic Pregnancies

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Abstract

Preeclampsia is a hypertensive, multi-system disorder of pregnancy that affects several organ systems, including the maternal brain. Cerebrovascular dysfunction during preeclampsia can lead to cerebral edema, seizures, stroke and potentially maternal mortality. This review will discuss the effects of preeclampsia on the cerebrovasculature that may adversely affect the maternal brain, including cerebral blood flow (CBF) autoregulation and blood-brain barrier disruption, and the resultant clinical outcomes including posterior reversible encephalopathy syndrome (PRES) and maternal stroke. Potential long-term cognitive outcomes of preeclampsia and the role of the cerebrovasculature are also reviewed.

Keywords

Preeclampsia; blood-brain barrier; pregnancy; cerebral blood flow; autoregulation

Introduction

Preeclampsia, a pregnancy specific syndrome that complicates 3–5% of all pregnancies, is a condition classified by new onset hypertension (>140/90 mm Hg) and proteinuria or evidence of end-organ damage [1]. Worldwide, hypertensive disorders of pregnancy account for an estimated 62,000–77,000 maternal deaths each year, with increased risk of fatality in the developing world [2,3]. While preeclampsia can affect multiple organ systems due to hypertension and systemic endothelial dysfunction, one of the more delicate maternal systems impacted is the brain. Acute cerebral complications of preeclampsia such as eclampsia (the new onset of seizures in women with preeclampsia), stroke, edema formation, and brain herniation place the mother at significant risk of death and long-term morbidity. In fact, cerebrovascular involvement in conditions such as edema and hemorrhage is a direct cause of death, accounting for ~ 40% of maternal deaths during

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pregnancy [4]. It is not just the acute risk of preeclampsia and eclampsia on the brain that can impact maternal outcome; long-term cognitive changes, lower perceived quality of life, increased lifetime cerebrovascular risk and even persistent white matter lesions within the maternal brain have been reported in mothers with a history of preeclampsia [5–7]. These long-term outcomes highlight that the morbidity and mortality of preeclampsia is not confined exclusively to the gestational period, but can negatively impact the rest of a woman's life. This review will discuss our current understanding of how preeclampsia affects the cerebral circulation in ways that may lead to brain injury in both acute and chronic settings.

Cerebral Blood Flow Autoregulation

The high metabolic needs of the brain require that there is relatively constant cerebral blood flow (CBF) over a wide range of perfusion pressures [8]. In situations where there is insufficient blood flow to the brain, such as in cases of ischemic stroke or hypovolemia due to hemorrhage, ischemic brain injury can occur [9]. Conversely, hyperperfusion due to decreased cerebrovascular resistance (CVR) can lead to blood-brain barrier (BBB) disruption and vasogenic edema with resultant neurologic symptoms, as seen in some cases of preeclampsia or eclampsia [10–13]. One of the primary means by which CBF is regulated is through changes in CVR that is inversely related to the caliber of the vessels supplying the maternal brain [14]. Changes in CVR are proportional to the fourth power of the luminal radius and therefore small changes in diameter of the arteries and arterioles supplying the maternal brain will directly and substantially influence CBF [14]. In healthy adults, global CBF is maintained at approximately 50 mL/100g brain tissue per minute at cerebral perfusion pressures (CPP) between approximately 60–160 mmHg [15,16]. On either end of this limit, CBF autoregulation is lost and CBF becomes directly dependent on mean arterial pressure in a linear fashion [17]. In settings of acute hypertension when arterial pressure may rise above the CBF autoregulatory range, such as in some cases of preeclampsia, the increased intravascular pressures can overcome the myogenic vasoconstriction of arteries and arterioles, causing them to lose their ability to provide vascular resistance [10–12,16]. The resulting loss of autoregulation and hyperperfusion can lead to endothelial damage, edema and risk of brain injury [11–13, 18, 19].

Studies of CBF autoregulation in women with preeclampsia and eclampsia have mostly utilized transcranial Doppler (TCD) to estimate changes in CBF velocity and calculate CVR and CPP. In both women with preeclampsia and systemic hypertension, CPP has been found to be significantly higher than in normotensive pregnant women [20,21]. Additionally, the calculated CVR was increased, indicating that CBF autoregulation was intact [20–22]. Furthermore, CBF velocity has been shown to increase during preeclampsia compared to normal pregnancy [18,21,23]. Belfort et al. demonstrated that although the CBF velocity was elevated in women with preeclampsia, the calculated CVR of the vast majority of women was still normal [20,24]. These results, however, should be interpreted with caution since TCD can only provide relative changes in blood velocity and calculated resistance.

Van Veen et al. stratified a population of hypertensive pregnant women into groups who were gestationally hypertensive, chronic hypertensive or preeclamptic and measured CBF

velocity with TCD [25••]. Though this study had small numbers in some groups, they found that pregnant women with chronic hypertension and preeclampsia had a significantly reduced autoregulatory index compared to normal and gestational hypertension pregnancies, a result that they interpreted as less effective CBF autoregulation [25••]. However, despite a difference between groups, the overall autoregulation was clinically adequate, i.e. the autoregulatory index for all groups was within the normal range. Interestingly, there was no correlation found between the calculated autoregulatory index and blood pressure, which the authors suggest was evidence for the development of autoregulatory breakthrough and hyperperfusion without excessive hypertension [25••].

Despite the fact that the majority of women with preeclampsia have been found to have effective CBF autoregulation, there are studies in which women with preeclampsia or eclampsia have been found to have decreased CVR [18,26,27]. Moreover, decreased CVR was found in combination with evidence of cerebral edema by computed tomography and/or magnetic resonance imaging (MRI) [18]. These data suggest that the majority of women with preeclampsia have adequate CBF autoregulation, but in instances of decreased CVR and autoregulatory breakthrough, over perfusion injury, edema formation and neurological symptoms are found.

Decreased CVR during preeclampsia may potentially expose the maternal brain to significantly elevated CPP due to a lack of hypertensive remodeling of cerebral arteries [20]. Under non-pregnant conditions, chronic hypertension causes the cerebral vasculature to undergo inward remodeling, resulting in narrowing of arterial lumen diameters that increases CVR and protects the downstream microcirculation [28,29]. Hypertensive remodeling of the cerebral circulation also shifts the autoregulatory curve to higher pressures [30]. However, pregnancy has been shown to both prevent and reverse hypertensive inward remodeling in animal models [31,32]. If there is a similar lack of hypertensive remodeling in humans during preeclampsia, the decreased CVR in the face of high CPP could promote BBB disruption and edema formation seen in women with neurological symptoms, including eclampsia.

Blood-Brain Barrier Disruption

The importance of altered cerebral hemodynamics in preeclampsia and eclampsia may be related to decreased CVR and the effect on the BBB. A correlation between increased CBF and BBB permeability has been shown, suggesting that loss of CVR with resultant increased CBF increases BBB permeability [33–35]. The BBB is a highly specialized interface between the circulating blood and the brain, carefully regulating the substances that enter and exit the brain [36]. The cerebral endothelial cells comprising the BBB have unique features compared to vascular endothelium found elsewhere in the body. The BBB is unique due to high electrical resistance tight junctions, low rates of pinocytosis, and a lack of fenestrations that all result in low intrinsic permeability and strict maintenance of the chemical, ionic and metabolic balance required by the brain [37–39]. Disruption of the finely tuned mechanisms of the BBB leads to increased BBB permeability, impaired regulation of flux of molecules across the BBB and vasogenic edema that is potentially injurious to the brain [40].

Evidence for BBB disruption during preeclampsia and eclampsia has been found in both clinical and laboratory settings. Schwartz et al. performed MRI studies on 28 women with preeclampsia with neurologic symptoms or eclampsia and evaluated blood samples for markers of endothelial cell damage [13]. The authors found that brain edema on MRI imaging in preeclamptic and eclamptic women was associated with increased levels of lactate dehydrogenase, which they interpreted as evidence of endothelial cell damage [13]. Additionally, 5 women in this study underwent MRI with gadolinium contrast, which has been used to evaluate permeability of the BBB in conditions such as brain tumors and multiple sclerosis [13,41]. In several of these women, instances of gadolinium enhancement within the brain were found, indicating multifocal areas of BBB disruption in some women with preeclampsia with neurologic symptoms and eclampsia [13]. These data provide direct clinical evidence that preeclampsia and eclampsia can be associated with BBB damage and potentially disruption.

BBB disruption has also been shown in an experimental model of preeclampsia in rats that combined placental ischemia with high fat diet to mimic the clinical findings associated with preeclampsia [42••]. In these animals, increased BBB permeability to small solutes was found [42••]. In addition, animals with experimental preeclampsia had higher seizure susceptibility compared to normotensive pregnant rats [42••]. These data are supported by previous studies that have shown that there are circulating factors present in serum from preeclamptic women that have a detrimental effect on the BBB [43,44••]. In cerebral veins from rats exposed to serum from preeclamptic women, BBB permeability was significantly increased compared to serum from women with normal pregnancies [43]. When plasma obtained from women with early-onset preeclampsia (<34 weeks' gestation) was added to cerebral veins from rats, BBB permeability was significantly increased compared to serum from late-onset preeclamptic women (>34 weeks' gestation) [44••]. These data provide evidence supporting the presence of circulating factors in preeclamptic maternal serum that disrupts the BBB. Additionally, these data also suggest that there may be different etiologies between early-onset and late-onset preeclampsia, especially with regards to the brain. In fact, although eclampsia occurs most often late in gestation, women with early-onset preeclampsia are more likely to die as a result of cerebral complications, further suggesting different disease etiologies between early- and late-onset preeclampsia [4,45].

Posterior Reversible Encephalopathy Syndrome

Eclampsia, the new onset of seizures in women with preeclampsia, is often preceded by neurologic symptoms such as headache, visual changes, nausea and mental status changes [46]. Several theories have been put forth to delineate the pathogenesis of neurologic symptoms associated with eclampsia. One theory arising from early angiographic studies is that cerebral arteries undergo vasospasm in response to acute hypertension, causing regional hypoperfusion, ischemic damage and cytotoxic edema formation [47–50]. The rapidity of resolution of both symptoms and radiologic findings post-partum lends support to the absence of true cerebral ischemia in most eclamptic patients [51]. Alternately, hyperperfusion due to autoregulatory breakthrough with resulting vasogenic edema has also been suggested as a potential etiology [52,53]. In support of this theory, clinical imaging studies of patients with eclampsia, using computed tomography and T₂-weighted magnetic

resonance as well as diffusion-weighted images, have shown cerebral edema formation is more consistent with vasogenic edema than cytotoxic edema [54–61].

One explanation for the etiology of the cerebral edema and neurologic symptoms associated with eclampsia is that it is a form of posterior reversible encephalopathy syndrome (PRES), a variant of hypertensive encephalopathy [18,54,55, 62–64]. PRES is a clinical-radiologic diagnosis associated with neuroimaging findings of cerebral edema without evidence of cerebral infarct and is clinically associated with headache, visual disturbances, encephalopathy and seizures [65]. Not an entity confined to pregnancy, PRES occurs in both males and females, and can be caused by hypertension, allo-immune conditions, organ transplants, chemotherapeutic exposure, and renal failure [47,65]. Like eclampsia, a clear pathologic etiology of PRES has not been well established and is likely multifactorial due to the associated disorders having complex multi-systemic involvement. However, the inclusion of edema in the diagnostic criteria for PRES suggests a causal relationship between edema formation and neurologic symptomatology. The theory that eclampsia and PRES are related is derived from numerous similarities in clinical presentation and radiologic imaging and that both rapidly resolve with treatment of the underlying etiology [27,66]. In addition, PRES is commonly found in women with eclampsia, with recent reports as high as in 98% [67••].

PRES can be caused by an acute elevation in blood pressure that overcomes cerebral artery and arteriole vasoconstriction, resulting in a loss of CBF autoregulation, disruption to the blood-brain barrier (BBB), and vasogenic edema formation [18,54,55,63,64]. Although the majority of patients with PRES are hypertensive, 20–30% are not significantly hypertensive at the time of diagnosis but still have edema formation [47]. Similarly, eclampsia also is associated with ~40–60% of patients without significant hypertension at the time of seizure onset [45,68].

Despite the similarities of eclampsia with PRES, there appear to be some differences between pregnant and non-pregnant cohorts with PRES. Postma et al. found that the obstetric population of women with PRES in the setting of preeclampsia or eclampsia typically had less extreme cerebral edema and had better long-term outcomes than a non-pregnant population with PRES [69•]. Additionally, Liman et al. retrospectively evaluated women with PRES in the setting of preeclampsia or eclampsia and compared their symptomatology and outcomes with individuals with PRES due to other disease etiologies [61]. Interestingly, the authors found that preeclamptic women were significantly more likely to have headache as an initial symptom, compared with altered mental status as seen in other forms of PRES [61]. In addition, preeclamptic patients were also found to have less severe edema formation and were more likely to have complete resolution of the edema on follow-up imaging compared to other etiologies evaluated, including immunosuppression, chemotherapeutics, allo-immune disorders and sepsis [61]. Thus, it is possible that the etiology for PRES in the setting of preeclampsia is not necessarily the same as in other disease states due to the differences in outcome and presentation. Though the exact etiology for both disorders remains elusive, cerebrovascular dysfunction appears to play a key role in their pathogenesis.

White Matter Lesions

Preeclampsia has historically been considered to be a syndrome with symptoms limited to the gestational timeframe. However, there is evidence that long-term changes may occur within the brains of women with a history of preeclampsia. In long-term studies of women with a history of preeclampsia or eclampsia, 34–37% and 41% respectively were found to have white matter lesions (WML) on MRI imaging, a significantly higher rate and volume than women with a history of a normotensive pregnancy (17–21%) [6,70,71•]. WML are radiographic findings of hyperintense regions located within the hemispheric white matter on T2 weighted MRI images of the brain [72]. These lesions are currently thought to be the direct consequence of small vessel disease within the brain [72]. Clinically, WML have been positively associated with cognitive defects and are predictive of cognitive decline and dementia [73–76]. Additionally, studies have found a correlation between increased WML burden within the brain and decline in cognitive performance [77]. The appearance of these lesions may provide a direct connection between small vessel disease within the brain of women with a history of preeclampsia and worsened cognitive outcomes.

Although studies suggest that there is a causative association with a prior history of preeclampsia and subsequent WML on imaging studies, it is possible that the presence of WML are related to the overall cardiovascular phenotype of women that are affected by preeclampsia. This concept is supported by the observation that, in an elderly population, hypertension was associated with increased frequency of WML on MRI imaging [78]. Aukes et al. evaluated the presence and severity of WML in women with a prior history of preeclampsia and the relationship to current cardiovascular risk status and neurologic symptoms during their index pregnancies [6]. In this study, the presence of neurologic symptoms at the time of the index pregnancy was found to not be associated with the subsequent finding of WML within the brain [6]. The authors determined that women that had early-onset preeclampsia (<37 weeks') were significantly more likely to have WML on follow up imaging than women with a history of late-onset preeclampsia (>37 weeks') [6]. Interestingly, women with early-onset preeclampsia were also at significantly higher risk of later developing hypertension and cardiovascular disease than other sub-groups of women with hypertensive disorders of pregnancy [79••]. Though the exact pathogenesis and implications posed by the presence of WML are unclear, the cerebrovasculature appears to be involved with these long-term changes in the brains of previously preeclamptic women.

Cognitive Changes

Some women with a history of preeclampsia and eclampsia report cognitive, emotional, and mood changes in the ensuing years [80]. In addition to the direct emotional impact of preeclampsia and eclampsia, subsequent complaints of cognitive dysfunction such as impaired concentration, memory and ability to attend to tasks are common [5,80]. Several studies utilizing patient self-reports demonstrated that women with a history of preeclamptic or eclamptic pregnancies perceived more cognitive difficulties and worsened quality of life compared to control populations [5,80,81]. However, objective data supporting these findings are limited. Postma et al. objectively assessed cognitive function in patients after eclampsia, finding that there was not a significant difference in sustained attention and

executive functioning between prior eclamptics and matched controls [81]. Similarly, Brusse et al. evaluated maternal cognitive functioning after severe preeclampsia and found that formerly preeclamptic women did not display impaired executive function [82]. This study, however, did find that women with a history of preeclampsia had impaired auditory-verbal memory, with less word learning and recall [82]. Though small, this study thoroughly evaluated numerous neuropsychological tests and addressed the psychological contributions of prior preeclampsia with an evaluation of emotional status [82]. It is important to note that these studies are limited by their retrospective nature, assessing patients only at the intra or post-partum time periods.

Stroke

Stroke in a young population is a rare event, although the long-term morbidity and mortality can be disproportionately high and significantly impacts the lives of whole families [83]. The incidence of stroke in a non-pregnant female population aged 15–44 is ~9 per 100,000 [84]. Pregnancy increases the risk of stroke to an incidence of 10–34/100,000 deliveries [85–87]. The presence of preeclampsia in pregnancy confers a 4–5 fold increased risk of stroke compared to the normotensive pregnant population [87,88]. In the United Kingdom between 1997–2008, 18% of preeclampsia or eclampsia related deaths were considered directly attributable to stroke [89].

Clinically, patients with stroke in the setting of preeclampsia and eclampsia are most likely to present with complaints of severe headache (as high as 96% in one study), and are commonly hypertensive, with a systolic blood pressure typically >150–160 mmHg [90,91]. Martin et al. reviewed the histories of 28 women with severe preeclampsia or eclampsia and stroke, and determined that hemorrhagic stroke was far more common than ischemic stroke in this population, accounting for 89% of preeclampsia related strokes [91]. In the young adult population, ischemic stroke has generally been found to be more common than intracerebral hemorrhage [84,92], indicating that preeclampsia increases the risk of hemorrhagic stroke compared to the non-pregnant population. Although hypertension has been established as a risk factor for preeclampsia related strokes [91,93,94], Martin et al. suggested that it is not the only factor contributing to stroke [91]. These authors pointed out that despite the significantly elevated blood pressures of women in the setting of preeclampsia and eclampsia, cerebral hemorrhage remains rare [91]. Moreover, their evaluation of women with hemolysis, elevated liver enzymes and low platelets (HELLP), a subgroup within the preeclampsia spectrum, suggested that worsening HELLP was more likely to be associated with deteriorating clinical progression [91]. The authors proposed that the worsening characteristics of HELLP are related to endothelial dysfunction and suggest that there is damage to the BBB that increases the risk of stroke in these women [91]. The contribution of altered coagulation in the women HELLP was not evaluated in this study, but abnormalities of both platelets and red blood cells which are found with women with HELLP could potentially increase the risk of stroke in this population. The combination of BBB damage in the setting of hypertension, could contribute to the elevated risk of hemorrhagic stroke especially in women with HELLP [91].

Maternal race also appears to contribute to the increased stroke risk when combined with preeclampsia. Studies have shown that amongst pregnant women of Hispanic and Asian ethnicity, the presence of preeclampsia confers an increased stroke risk [95–98]. In a retrospective case-control study, Tang et al. found that Taiwanese women with preeclampsia had an ~20 fold increased risk of hemorrhagic stroke and ~40 fold increased risk of ischemic stroke compared with a non-hypertensive pregnant cohort, though the overall incidence of stroke within this population remained low with incidence rates 18–19/100,000 deliveries [95].

While the postpartum time period is associated with the highest risk of stroke in the normal pregnant population, this risk is even higher in the preeclamptic population [99]. The postpartum period is notable for significant physiological and endocrine changes, including large decreases in blood volume and rapid changes in hormonal status [99]. It is possible that the potentially disruptive effects of preeclampsia on the cerebral circulation compound the risks inherent within the postpartum time period. Though the risk of stroke is highest in the postpartum period [99], preeclampsia also confers a 1.8 fold increase in the lifetime risk of stroke [7]. Whether this increased risk is a direct result of prior preeclampsia or if it reflects an underlying pre-existing cardiovascular risk phenotype that manifests as stroke later in life is not yet known.

Conclusions

Cerebrovascular dysfunction is central to the acute neurologic risks associated with preeclamptic and eclamptic pregnancies. CBF autoregulation is generally intact during preeclampsia, but if CVR is reduced, the BBB may be damaged, leading to cerebral edema and potentially significant morbidity and mortality. Preeclampsia additionally increases the risk of stroke during both the antepartum and postpartum timeframes. Long-term changes to maternal brains, in the form of WML and cognitive changes, also suggest that the risks of preeclampsia and eclampsia are not necessarily limited to the duration of pregnancy. Understanding the cerebrovascular dysfunction that can occur in preeclampsia may aid in the effective treatment and potential prevention of subsequent adverse outcomes.

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