Neurological lesions of the mother and the fetus in preeclampsia – an overview of the literature

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ABSTRACT

About 3-5% of pregnancies are complicated by preeclampsia (PE), a multisystem disorder of exact unknown etiology, characterized by new-onset hypertension (>140/90 mmHg), proteinuria, and/or evidence of organ dysfunction. Although it is not yet completely understood what causes PE, maternal and placental factors seem to be involved. Endothelial dysfunction, maternal vascular inflammation, and remodeling of spiral arteries during placentation seem to be the underlying mechanisms of this pregnancy-related disease. Acute PE neurological complications, such as eclamptic seizures, cerebral edema, and intracerebral hemorrhage, are responsible for more than 70% of maternal deaths. Furthermore, long-term complications, such as cognitive dysfunction, the elevated lifetime risk of cerebrovascular disease, and persistent white matter lesions increase the rate of PE-related maternal morbidity and mortality. Hypertensive disorders associated with pregnancy affect not only the mother but also the baby by restricting the supply of nutrients and oxygen to the fetus. This has been associated with impaired cognitive development in children, increased lifetime cerebrovascular, cardiovascular, and metabolic risk, low intelligence quotient (IQ) and mental development indices (MDI), and more depression symptoms later in life. This study aims to review the literature and synthesize available information about preeclampsia and its neurological consequences on both the mother and the fetus.

Keywords: preeclampsia, maternal complications, neurologic lesions, fetal neurologic sequelae

INTRODUCTION

Preeclampsia is a multisystem disease that affects 2-5% of pregnancies and contributes significantly to maternal and perinatal morbidity and mortality worldwide [1,2]. It usually appears after the 20th week of gestation [3] and is clinically diagnosed as new-onset hypertension (>140/90 mmHg) [4] and [1]:

- Proteinuria (protein: creatinine ratio ≥ 30 mg/ml, ≥ 300 mg/24 hour, or ≥ +2 dipstick);
- Evidence of other maternal organ dysfunction, such as acute renal insufficiency (creatinine ≥ 1.1 mg/dL), liver dysfunction (elevated liver transaminase blood levels at least twice the normal) with or without epigastric or right upper quadrant abdominal pain, pulmonary edema, acute neurological complications (eclamptic seizures, stroke, altered mental status, severe headaches, cortical blindness, persistent visual scotomata), or hematological complications (thrombocytopenia – platelets < 150.000/μL, disseminated intravascular coagulation, hemolysis);
• Uteroplacental insufficiencies, such as fetal growth restriction, altered Doppler analysis of the umbilical artery wave, or fetal death.

While the exact cause of PE is still unknown, it is clear that it can be caused by both placental and maternal factors, making it a complex disease [5]. Abnormal trophoblast invasion of spiral arteries during placentation causes placental ischemia, releasing placental-derived soluble factors into the maternal circulation [6]. These circulating proinflammatory and antiangiogenic factors appear to cause maternal vascular inflammation and endothelial dysfunction, linked to preeclampsia-related hypertension and proteinuria [2,5,6]. However, not all pre-eclamptic women have placental dysfunction. The physiologic burden of pregnancy, characterized by mild peripheral inflammation, reveals preexisting maternal vascular dysfunction in these cases [5]. The presence of both maternal and placental disease results in the disorder’s most severe and early-onset form [5].

There have been described many maternal risk factors linked to the development of PE, such as advanced maternal age, nulliparity, previous history of PE, family history of PE, use of assisted reproductive technologies, obesity, pre-existing chronic hypertension, renal disease, and autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome [1].

Around the world, about 76,000 women and 500,000 babies die every year because of this disease, with an increased risk for women in low-income countries in developing PE compared to those in developed countries [1]. Over 70% of these fatal cases are attributed to neurological causes, with cerebral edema, intracranial hemorrhage, and eclampsia being the most common [7,8]. The United Kingdom has reported that eclampsia is responsible for 6% of direct maternal deaths [9]. Furthermore, PE accounts for nearly half of all reversible ischemic strokes during pregnancy [7,10].

Unfortunately, PE-related complications do not stop after the baby is born. Several studies have found that mothers with a PE pregnancy have a higher lifetime risk of cardiovascular disease, hypertension, metabolic syndrome, diabetes, and stroke [11-13]. In addition, PE pregnancy babies have an increased lifetime risk of cardiovascular disease and stroke [11,14], but they have also been reported to have cognitive impairments [15-17]. As children, they show deficits in verbal reasoning [11], total intelligence quotient (IQ) score [17,18], and mental development index (MDI) [11,19]. They also have a faster rate of decline in cognitive function as adults and into old age [15,20], as well as more cognitive impairment overall and more depressive symptoms [11].

METHODS

This study aims to review the literature and gather and synthesize available information about preeclampsia and its neurological consequences on the mother and fetal brain development. We have used keywords such as “preeclampsia,” “maternal complications,” “neurologic lesions,” “fetal neurologic sequelae,” and we have searched articles through PubMed, Wiley Library, the International Society for the Study of Hypertension in Pregnancy, the International Federation of Gynecology and Obstetrics, and the Royal College of Obstetricians and Gynaecologists. We identified over 50 articles describing preeclampsia and its short and long-term neurologic lesions on both the mother and the baby.

MATERNAL NEUROLOGICAL LESIONS IN PREECLAMPSIA

Preeclampsia can affect multiple organ systems due to hypertension and systemic endothelial dysfunction, but the brain is one of the most delicate maternal organs. Eclamptic seizures, stroke, edema, and brain herniation are all acute cerebral complications of PE that put the mother at risk of mortality and long-term morbidity. Cerebrovascular involvement in conditions like edema and hemorrhage is a leading cause of death in pregnant women, accounting for nearly 40% of maternal deaths [4,21]. In addition, long-term cognitive changes increased lifetime cerebrovascular risk, and persistent white matter lesions within the maternal brain have all been reported in mothers with a history of PE [4,22,23]. These long-term outcomes show that preeclampsia’s morbidity and mortality are not limited to the gestational period but can have a negative impact on a woman’s entire life.

Healthy gravid females exhibit a reduction in both gray and white matter volumes of the brain while the volume of the lateral ventricles increases [24,25]. These volume changes in the brain and ventricular spaces begin with placental implantation, peak at term, and gradually reverse months later. However, these volumetric changes are even more marked in human PE patients [24,25]. A recent study of a large multiethnic and racially diverse sample found that women with a history of hypertensive pregnancy had smaller brain volumes and higher levels of atrophy decades after the index pregnancy [26].

Cerebral blood flow (CBF) is maintained at 50 mL per 100 g of brain tissue per minute in normotensive individuals, given a cerebral perfusion pressure (CPP) and intracranial pressure in the range of 60 to 150 mmHg [27,29]. When the CPP exceeds 150 mmHg, autoregulation fails, and a “breakthrough” occurs, resulting in hyperperfusion, blood-brain-barrier (BBB) disruption, and vasogenic edema, all of which can contribute to neurological complica-
tions associated with hypertensive encephalopathy and eclampsia [27,29].

Eclampsia, arterial ischemic stroke, reversible cerebral vasocstriction syndrome (RCVS), posterior reversible encephalopathy syndrome (PRES), cerebral artery dissection, cerebral venous sinus thrombosis, subarachnoid hemorrhage (SAH), and intracerebral hemorrhage (ICH) are some of the most severe neurological complications associated with PE [30]. ICH is the most lethal, directly causing up to 70% of PE deaths [31]. Older age, non-white race, heart disease, chronic hypertension, infections, prothrombotic and hypercoagulable states, and migraine history are all risk factors for neurovascular complications of PE [32].

The majority of secondary headache disorders in pregnancy are caused by PE and related conditions. PE headaches are frequently progressive and bilateral, throbbing, refractory to treatment, and exacerbated by physical activity. Patients may experience visual changes such as blury vision and scotomas, which can be misdiagnosed as migraine aura symptoms [30-33].

PRES is a clinical-neuroradiological syndrome frequently associated with preeclampsia and eclampsia and is characterized by primarily parietooccipital white matter lesions indicative of vasogenic edema and other neurological symptoms [30-34]. In 2/3 of patients with PRES and eclampsia, headache is the most frequent neurological symptom, characterized by bilateral occipital location, insidious onset, and a dull quality [30-35].

RCVS is more prevalent in the perinatal period and manifests as an intense, scattered headache with a rapid onset (thunderclap) that is recurring over 1–2 weeks. Neuroimaging reveals segmental cerebral vasocostriction that begins at the periphery and continues to evolve to the central blood vessels before spontaneously resolving after 3 months, although it can be negative at the onset of a headache [30,33,34].

While hemorrhagic strokes caused by vascular lesions such as arteriovenous malformations and cerebral aneurysms have been reported in association with PE [36,37], there is frequently no underlying vascular lesion to account for the bleed [38]. Maternal stroke caused by PE has a high morbidity and mortality rate. Unlike the general population, where 87% of strokes are ischemic [39], half of the strokes associated with hypertensive disorders of pregnancy are hemorrhagic, and 13% are fatal [32]. Stroke has been linked to a 100-fold increase in mortality in pregnant women with hypertensive disorders [40].

Patients with stroke in the setting of PE and eclampsia are more likely to complain of severe headache (up to 96% in one study) and are frequently hypertensive, with a systolic blood pressure of >150–160 mmHg [41,42]. Although hypertension has been identified as a risk factor for preeclampsia-related strokes, Martin et al. asserted that it is not the only factor [4,42]. According to these authors, cerebral hemorrhage is uncommon despite significantly elevated blood pressures in women with PE and eclampsia [42]. Furthermore, they found that worsening HELLP was more likely to be associated with worsening clinical progression in women with hemolysis, elevated liver enzymes, and low platelets (HELLP), a subgroup within the PE spectrum [4,42].

PE is also linked to maternal cognitive dysfunction [43,45], with the severity of the damage directly linked to the total number of eclamptic seizures [45]. According to a pilot study, these formerly PE women’s self-reported deficits included auditory-verbal memory deficits, learning problems, and slow recall, unrelated to depression or anxiety [44]. A long-term follow-up study, however, found no evidence of neurocognitive dysfunction, but the researchers did conclude that this increase in self-reported deficits is a predictor of cognitive impairment and/or dementia later in life [43]. After controlling for cardiovascular disease and known cardiovascular disease risk factors, a more recent study concluded that hypertensive pregnancy disorders might be independent risk factors for cognitive decline [3,26].

NEUROLOGICAL LESIONS OF THE OFFSPRING IN PREECLAMPSIA

During development, the fetal brain goes through many changes to build the structural, vascular, and neurological anatomy to support future autonomic and cognitive functions. Because the brain requires oxygen and nutrients from circulation, fetal cerebral circulation develops simultaneously with brain neural development, and the two tissues share many molecular pathways [46,47].

PE is known to affect placental vascularity, restricting the supply of nutrients and oxygen to the fetus. In experimental models of PE and perinatal asphyxia, low oxygen levels have been shown to cause a rise in neuronal apoptosis [48,49]. Hypoxia can induce tissue inflammatory responses in addition to the vulnerability of neurons to low oxygen levels [49,50]. Hypoxia also promotes the production of reactive oxygen species and oxidative stress, both of which can contribute to neuronal apoptosis. Hypoxia’s effect on neuronal apoptosis, inflammation, and oxidative stress is likely to harm brain development.

Prenatal hypoxia has been linked to impaired cognitive development in children, while PE, in particular, has a negative impact on several aspects of cognitive function in early childhood, including the ability of analytical thinking and cognitive control of behavior [48,51,52]. It has also been demonstrated that children born to mothers who had PE had more depression symptoms later in life, suggesting that PE may have long-term effects on the brain [49,52].
Some studies have looked at brain structure to see if there is a connection between PE and neurological function. According to preliminary research, the structure and connectivity of limbic system components, an area of the brain linked to mood, behavior, and cognition, differs in children from preeclamptic pregnancies [49,52]. Although the underlying causes of PE are unknown, evidence suggests that the condition impacts maternal and fetal health, as well as long-term development [49].

The off springs of PE pregnancies have an increased lifetime risk of various health problems, including cardiovascular, endocrine, and neurological problems [46]. They usually have a body mass index (BMI) of 0.6 kg/m² higher than children born to uncomplicated pregnancies. They can also present a 2.5 mmHg higher systolic and 1.4 mmHg higher diastolic blood pressure [53]. In adulthood, these pressure increases translate to a roughly 2-fold increased risk of stroke [14].

Children from PE pregnancies are also more likely to develop cerebrovascular and cognitive disorders than those from non-PE pregnancies matched for gestation length, current age, or maternal hypertension during the index pregnancy [54]. They can have deficits in several cognitive functions as children, including the ability to verbal reasoning [55]. In addition, their total intelligence quotient (IQ) [17] and mental development indices (MDI) are lower [18,19].

Deficits in verbal and arithmetic reasoning persist as these children progress through adolescence and adulthood [54].

CONCLUSIONS

Preeclampsia is a hypertensive, multisystem condition that impairs multiple organs during pregnancy, including the maternal brain [4]. Once thought to be a pregnancy-limited disease [46], recent studies have shown that PE has several long-term gestational complications in addition to the immediate ones, affecting both the mother and the baby [46]. The most common cause of maternal morbidity and mortality in PE is acute neurological complications, including cerebral edema, seizures, and stroke, all of which can result from preeclampsia’s vascular dysfunction [4]. Long-term mothers with a history of PE and eclampsia have been reported to have cognitive changes, lower perceived quality of life, increased lifetime cerebrovascular risk, and even persistent white matter lesions within the maternal brain [22,23]. Additionally, pregnancies with fetal exposure to PE appear to have an increased risk of cerebrovascular and neuroanatomical changes during the development of the brain. These changes could cause increased lifetime risks for several health issues, such as neurological, cardiovascular, and endocrine diseases [46].

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