Preeclampsia

Association With Posterior Reversible Encephalopathy Syndrome and Stroke

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Pregnancy and the postpartum period are associated with an increased risk of ischemic and hemorrhagic stroke.[1–3] Based on the estimate from 11 studies published between 1990 and January 2017, stroke is most common in the peripartum and postpartum periods.[4] Stroke is estimated to affect 30 per 100 000 pregnancies. Some of the mechanisms underlying this increased risk include venous or arterial thrombosis because of estrogen-related hypercoagulability; cerebral hypoperfusion related to acute blood loss; cardioembolism because of peripartum cardiomyopathy; and endotheliopathy, vasospasm, and hypertensive intracerebral hemorrhage (ICH) related to hypertensive disorders of pregnancy.[2,5–7]

Hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension, and preeclampsia/eclampsia. Gestational hypertension is defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg in a previously normotensive woman at ≥20 weeks of gestation.[8] Preeclampsia is distinct from gestational hypertension in that it additionally involves at least one of the following criteria: proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms (Table). Preeclampsia can progress to eclampsia, which is characterized by seizure activity in a preeclamptic woman. Preeclampsia most commonly occurs during pregnancy and the peripartum period although postpartum preeclampsia can occur.[9,10]

Preeclampsia is a systemic, multiorgan endotheliopathy, affecting the kidneys, heart, liver, and brain. Preeclampsia can be associated with premature birth, placental abruption, and stillbirth.[11,12] Potential cerebral complications of preeclampsia include ischemic stroke, hemorrhagic stroke, cerebral edema, and seizure.[13] Preeclampsia has been associated with posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS). The differential diagnosis of preeclampsia with cerebral complications may commonly include metabolic derangement, toxic ingestion, central nervous system infection, and cerebral venous sinus thrombosis.

The pathophysiology underlying preeclampsia remains incompletely characterized. Preeclampsia has been associated with aberrant trophoblast (blastocyst cell) invasion into the uterus and uterine spiral arteries[14]; reduced placental perfusion[15]; imbalance of pro- and antiangiogenic factors[16]; and an excessive intravascular inflammatory response to placental tissue.[17]

Preeclampsia is generally reported to complicate <5% of all pregnancies[18,19] although the incidence may be increasing.[20] A retrospective study of 120 000 births included in Centers for Disease Control and Prevention data sets in the United States from 1980 to 2010 found a prevalence of preeclampsia of 3.4%.[18] A systematic review and meta-analysis of studies reporting incidence of hypertensive disorders of pregnancy between 2002 and 2010 found a global prevalence estimate of preeclampsia of 4.6%.[19] Risk factors for preeclampsia include nulliparity, obesity, pregestational diabetes mellitus, thrombophilia, and preexisting hypertension or renal disease.[21]

Preeclampsia and eclampsia are associated with an increased risk of maternal death in the United States and abroad. An analysis of the 2006 to 2010 Pregnancy Mortality Surveillance System found that preeclampsia and eclampsia were responsible for 4.8% and 4.1% of pregnancy-related deaths in the United States, respectively.[22] In addition, preeclampsia and eclampsia may have directly contributed to the maternal deaths in this study that were attributed to cerebrovascular accident (6.2%) and cardiovascular conditions (14.6%). Hypertensive disorders of pregnancy are the primary cause of maternal death in Latin America and the Caribbean.[23]

In this review, we will discuss the epidemiology of preeclampsia and stroke; the relationship between preeclampsia and PRES; the potential pathophysiologic mechanisms leading to cerebral dysfunction and injury in preeclampsia/eclampsia; imaging in preeclampsia/eclampsia; the prevention and treatment of preeclampsia/eclampsia; and, finally, the risk of future ischemic stroke in women with preeclampsia.

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Table. Diagnostic Criteria for Preeclampsia (Derived From the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy)[8]

Criterion	Definition	Note
Hypertension after 20 wk of gestation in a previously normotensive woman	SBP ≥140 mm Hg, or	Blood pressure must be elevated on 2 measurements taken at least 4 h apart
	DBP ≥90 mm Hg	
or		
Hypertension after 20 wk of gestation in a previously normotensive woman	SBP ≥160 mm Hg, or	Blood pressure must be elevated on 2 measurements which can be taken minutes apart
	DBP ≥110 mm Hg	
and 1 of the following:		
Proteinuria	≥300 mg/protein per 24-h urine collection, or	Dipstick method permissible if quantitative methods are not available
	Protein/creatinine ratio ≥0.3, or	
	Urine dipstick reading of 1+	
Thrombocytopenia	Platelets <100 000/mL	
Renal insufficiency	Creatinine >1.1 mg/dL or doubling of serum creatinine	Not permissible if presence of other renal disease
Impaired liver function	Doubling of serum transaminases	
Pulmonary edema		
Cerebral or visual symptoms		

DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

Epidemiology of Preeclampsia and Stroke

Hypertensive disorders of pregnancy serve as risk factors for both ischemic and hemorrhagic strokes in pregnancy. A cross-sectional study of ≈82 000 000 pregnancy hospitalizations from the 1994 to 2011 Nationwide Inpatient Sample found that women with hypertensive disorders of pregnancy were 5.2× more likely than their healthy peers to have an ischemic or hemorrhagic stroke.[24]

A single-center study of 240 women with cerebral venous thrombosis, ischemic stroke, and ICH during pregnancy from 1988 to 2005 found that preeclampsia/eclampsia was seen in 57.5% of the patients with hemorrhagic stroke and 36% of the patients with ischemic stroke.[25] A Taiwanese population-based cohort study of 1.1 million patients from 1999 to 2003 found that the relative risk of preeclampsia/eclampsia for ischemic stroke was 40.9 (95% confidence interval: 12.1, 137.5) and for hemorrhagic stroke was 10.7 (95% 95% confidence interval: 3.4, 33.6) within 3-month antepartum.[26] These findings are in keeping with the results of a cross-sectional analysis of 423 women with a discharge diagnosis consistent with pregnancy-related ICH and 7 million women delivering without ICH from the 1993 to 2002 Nationwide Inpatient Sample that found a 10.4 (95% confidence interval: 8.3, 13.0) increased odds of ICH in women with preeclampsia/eclampsia.[27]

A study of New York State Department of Health claims data from 2003 to 2012 found that women with preeclampsia and stroke were more likely than preeclamptic women without stroke to have infections present on admission, prothrombotic states and coagulopathies, and chronic hypertension.[28] Stroke associated with preeclampsia seems to most commonly occur in the postpartum period.[27,28]

Preeclampsia, PRES, and RCVS

PRES is characterized by vasogenic cerebral edema that causes focal neurological symptoms. PRES was first described in 1996 and has become increasingly diagnosed in the age of magnetic resonance imaging (MRI).[29] Because the edema of PRES tends to preferentially involve the parietal and occipital lobes, visual symptoms are common. In addition, headache and altered mental status are frequent features of PRES. Although parieto-occipital involvement is most common, PRES can affect the frontal lobes, temporal lobes, cerebellum, and brain stem.[30] Cerebral ischemia and hemorrhage can be seen in PRES.[31] In severe cases, PRES can lead to seizure, status epilepticus, and coma. The cerebral edema and symptoms are often reversible although permanent parenchymal injury and clinical disability can occur in severe cases.

The first description of PRES in 1996 included 15 patients, 3 of whom had eclampsia.[29] Additional studies have shown that PRES is highly prevalent in patients with severe preeclampsia and eclampsia. A retrospective cohort study of 47 patients diagnosed with eclampsia at a single center found radiographic evidence of PRES in 46 (97.9%).[32] In a single-center case series of 39 patients with eclampsia or preeclampsia complicated by neurological symptoms, 12 of 13 patients with eclampsia (92.3%) and 5 of 26 with preeclampsia patients (19.2%) showed evidence of PRES on MRI.[33] Interpretation of these studies is complicated by the risk of selection bias given the small sample sizes and that imaging was presumably performed for patients with the most severe symptoms.

The notable overlap between the diagnoses of eclampsia and PRES has caused some to suggest that eclampsia represents obstetric PRES.[34] Indeed, a small study of 21 patients with PRES, 8 of whom were pregnant and 13 of whom were not, found no significant difference in the prevalence of seizures, disturbed vision, headache, altered mental function, nausea/vomiting, or brain stem symptoms between the pregnant and nonpregnant patients.[35] In addition, there was no significant difference in mean systolic blood pressure between the pregnant and nonpregnant patients.

Although the term obstetric PRES is a useful heuristic, it is important to note that there may be clinical differences between PRES associated with preeclampsia/eclampsia and PRES from another cause (eg, nongestational hypertension or calcineurin inhibitors). A retrospective study of 24 patients with preeclampsia/eclampsia and PRES and 72 patients with PRES from another cause found that patients with

preeclampsia/eclampsia had a significantly higher prevalence of headaches (58%) compared with the nonpregnant patients (18%). Patients with preeclampsia/eclampsia and PRES had a significantly lower prevalence of altered mental status (12.5%) than the nonpregnant patients (45%).[36] There was no significant difference in the prevalence of seizures or disturbed vision between the 2 groups. The systolic blood pressure and mean arterial pressure at the time of onset of symptoms did not differ between the 2 groups.

Although few studies have directly addressed the question, the outcomes of patients with preeclampsia/eclampsia and PRES may be less severe than those with PRES from another cause,[34] possibly because of baseline differences in health status. Most notably, women with preeclampsia/eclampsia and PRES tend to be younger and have a lower prevalence of alcohol abuse, diabetes mellitus, coronary artery disease, and liver failure than patients with PRES from another cause.[35]

RCVS is a disorder that shares clinical and radiographic features with PRES.[37] RCVS is a generally monophasic disorder that is usually, though not always, characterized by thunderclap headache.[38] RCVS can be complicated by seizure, ischemic and hemorrhagic strokes, brain edema, and subarachnoid hemorrhage.[39] Angiography typically reveals bilateral, diffuse, and ultimately reversible cerebral vasoconstriction of the intracerebral arteries. In one prospective study of 77 consecutive male and female patients with RCVS, 7 (9.1%) developed PRES.[40] Like PRES, RCVS can occur in the postpartum period.[39] In one Japanese retrospective analysis of stroke associated with pregnancy and the puerperium, RCVS was the suspected cause in one quarter of the ischemic stroke cases.[41] Cases of women who develop both RCVS and PRES in the antepartum[42] and postpartum[43] period have been reported, suggesting that the 2 entities are interrelated and may share underlying pathophysiologic mechanisms.[44]

Pathophysiology of Cerebral Dysfunction and Injury in Preeclampsia/Eclampsia

The mechanism for cerebral dysfunction and injury in preeclampsia remains unknown. Impaired cerebral blood flow autoregulation has been proposed although the evidence is mixed. Several studies using transcranial Doppler sonography have suggested vasodilation and decreased cerebral vascular resistance in women with preeclampsia[45–47] while other transcranial Doppler studies have found normal cerebral vascular resistance[48] and normal cerebral blood flow.[49] Others have argued that pathologically increased cerebral perfusion pressure, rather than impaired cerebral blood flow, is the underlying pathogenic mechanism in preeclampsia/eclampsia.[49]

Although the upstream mechanism remains uncertain, it is generally accepted that endothelial dysfunction and blood–brain barrier disruption ultimately play a central role in the cerebral dysfunction seen in preeclampsia/eclampsia. Most studies of blood–brain barrier dysfunction in preeclampsia involve experimental rat models.[13] However, in a study of 28 patients with preeclampsia/eclampsia and neurological symptoms (and without hemolysis, elevated liver enzymes, and low platelet count syndrome) who underwent MRI, 20 patients (71%) had abnormal MRI findings.[50] In these patients, imaging abnormalities were similar and involved subcortical edema almost always including the occipital lobes. Those patients who had abnormal MRI findings had significantly higher lactate dehydrogenase levels and a greater incidence of abnormal red blood cell morphology than the patients with normal MRI scans. The study's authors proposed that these findings were suggestive of microangiopathic hemolysis and endothelial dysfunction.

Imaging in Preeclampsia/Eclampsia

Posterior Reversible Encephalopathy Syndrome

PRES is characterized by subcortical white matter and cortical edema predominantly involving the bilateral parietal and occipital lobes.[51] Computerized tomographic scans may show evidence of vasogenic edema (hypodense regions) in some patients. Brain MRI is a more sensitive modality. In addition to edema, restricted diffusion suggesting ischemia and evidence of intracranial hemorrhage can be seen on MRI in patients with PRES.

Whether radiological differences exist for pregnant patients with PRES compared with nonpregnant patients with PRES remains unclear. A single-center study of 30 consecutive patients with MRI findings of PRES, 14 of whom had preeclampsia/eclampsia, found no significant difference in the radiographic distribution or extent of lesions in patients with preeclampsia/eclampsia compared with those without.[52] Similarly, a study of 8 pregnant patients and 13 nonpregnant patients with PRES found no difference in the location or severity of imaging abnormalities between the pregnant and nonpregnant patients.[35]

In contrast, a retrospective study of 24 patients with preeclampsia/eclampsia and PRES and 72 patients with PRES from another cause found that, compared with the MRI scans of patients with PRES from other causes, MRI scans of patients with preeclampsia/eclampsia showed relative sparing of the thalamus, midbrain, and pons.[36] No patients with preeclampsia/eclampsia and PRES had severe edema compared with 22.2% of patients without preeclampsia/eclampsia. Hemorrhage was seen in 12.5% of patients with preeclampsia/eclampsia and 36.2% of patients without. Apparent diffusion coefficient restriction was significantly less frequent in the preeclampsia/eclampsia group (5.3%) than in the group with PRES from another cause (34%). Similarly, contrast enhancement was seen on MRI in 8.3% of the preeclampsia/eclampsia group compared with 39.3% of those with PRES from another cause. On follow-up imaging, complete edema resolution and absence of structural residua were more common in the preeclampsia/eclampsia group.

White Matter Lesions

Cerebral white matter lesions can be seen on MRI in women with preeclampsia and eclampsia, even years after the acute illness. Formerly, preeclamptic women have a higher prevalence of cerebral white matter lesions than women without a history of preeclampsia. A retrospective cohort study of 73 formerly preeclamptic women with age-matched controls found that formerly preeclamptic women had white matter lesions significantly more often than controls (21% compared

with 37%) after a mean of ≈5 years since index pregnancy.[53] Current hypertension and preeclampsia with onset <37 weeks gestation were independently associated with the presence of white matter lesions.

A study of 94 women with severe preeclampsia identified and recruited during admission found white matter lesions in 61.7% of the women at delivery, 56.4% at 6 months, and 47.9% at 1 year.[54] In this study, the presence of white matter lesions at 1 year was positively associated with the number of drugs needed to control blood pressure during pregnancy.

Prevention and Treatment of Preeclampsia/Eclampsia

Prevention of Preeclampsia

Blood Pressure Screening

Timely diagnosis and appropriate management of severe hypertension in pregnancy are essential for prevention of serious maternal and fetal complications. The United States Preventive Services Task Force recommends blood pressure measurement for all women at each prenatal care visit throughout pregnancy.[55] The American College of Obstetricians and Gynecologists recommends twice-weekly blood pressure measurement for women with gestational hypertension.[8]

Aspirin

Several meta-analyses have investigated the efficacy of aspirin in the prevention of preeclampsia. Askie et al,[56] in an analysis incorporating patient-level data from 30 822 women across 24 randomized trials, found a 10% lower risk of developing preeclampsia in subjects who received aspirin compared with control. Bujold et al[57] found that, across 27 randomized controlled trials, aspirin started at 16 weeks or earlier was associated with a relative risk of preeclampsia of 0.47, whereas aspirin started after 16 weeks was not associated with a lower relative risk. Finally, Roberge et al,[58] in a meta-analysis across 5 randomized controlled trials enrolling 556 women, found that aspirin started before 16 week was associated with an 89% reduction in the risk of preterm preeclampsia but no significant reduction in risk of term preeclampsia.

A recently published randomized controlled trial of 1776 women at high risk for preterm preeclampsia found that women treated with aspirin from 11 to 14 to 36 weeks gestation had an ≈60% lower risk of developing preterm preeclampsia than those treated with placebo.[59] There was no difference between groups in the occurrence of adverse events, including miscarriage or stillbirth, small-for-gestational-age status, or placental abruption.

Current American Heart Association/American Stroke Association guidelines for the prevention of stroke in women recommend that women with chronic hypertension or previous pregnancy-related hypertension take low-dose aspirin starting at the 12th week gestation until delivery (Class I; Level of Evidence A).[60]

Calcium

Early epidemiological observations showed an inverse relationship between calcium intake and incidence of eclampsia.[61] Several subsequent randomized controlled trials assessed this relationship. A 2014 Cochrane review of 13 studies enrolling 15 730 women found that women treated with calcium supplementation had a 45% lower risk of preeclampsia compared with patients who received placebo or no calcium.[62] The effect appeared greatest for women with low calcium diets. American Heart Association/American Stroke Association guidelines recommend that women with low calcium intake receive oral calcium supplementation (≥1 g daily) to prevent preeclampsia (Class I; Level of Evidence A).[60]

Treatment of Preeclampsia and Eclampsia

Antihypertensives

American College of Obstetricians and Gynecologist guidelines recommend that women with preeclampsia and severe hypertension during pregnancy (sustained systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥110 mm Hg) be treated with antihypertensive therapy.[8] Oral nifedipine, labetalol, and methyldopa are appropriate agents to treat severe hypertension in pregnancy.[60,63] Intravenous hydralazine, intravenous labetalol, or immediate-release oral nifedipine may also be used for severe, acute-onset hypertension.[64] Second-line agents include nicardipine or esmolol infusion. Sodium nitroprusside should be avoided given concerns for cyanide toxicity in the mother; cyanide toxicity in the fetus or newborn; and the possibility of increased intracranial pressure in the mother, potentially causing or worsening cerebral edema. Routine invasive hemodynamic monitoring is not recommended.[8]

Magnesium

Magnesium was first used in eclampsia in 1906.[65] A 2010 Cochran review of 6 randomized trials enrolling 11 444 women found that magnesium conferred a 59% lower risk of eclampsia compared with placebo or no anticonvulsant.[66] Magnesium was also more effective in preventing eclampsia than phenytoin and nimodipine. American College of Obstetricians and Gynecologist guidelines recommend administration of parenteral magnesium sulfate for women with eclampsia and intrapartum-postpartum for women with severe preeclampsia.[8] Magnesium is generally given as a loading dose followed by a continuous intravenous infusion.

Delivery

American College of Obstetricians and Gynecologist guidelines recommend maternal stabilization and delivery for women with severe preeclampsia at ≥34 weeks gestation and for women with unstable maternal or fetal conditions regardless of gestational age.[8] In addition, for women with mild gestational hypertension or preeclampsia without severe features (only hypertension and proteinuria) at ≥37 weeks, delivery is recommended. The mode of delivery should be determined by gestational age, fetal presentation, cervical status, and other maternal and fetal conditions.

Risk of Future Ischemic Stroke in Women With Preeclampsia

The first study to associate preeclampsia and risk of ischemic stroke remote from pregnancy was published in 2006.[67] This case–control study of 261 women with ischemic stroke and 421 controls found that a history of preeclampsia was associated with a 63% increased odds of ischemic stroke.

Since that publication, 4 meta-analyses have addressed the risk of future stroke in women with preeclampsia, with relative risks/odds ratios for stroke ranging from 1.77 to 2.02.[68–71] Most recently, Wu et al[71] found a relative risk of 1.81 (95% confidence interval: 1.29–2.55) across 7 studies. Taken together, these studies suggest an ≈80% increased risk of stroke in women with preeclampsia compared with women without preeclampsia.

The reason(s) for the increased risk of ischemic stroke in women with preeclampsia remains uncertain. One possibility is that preeclampsia simply serves as a marker, rather than a cause, of increased stroke risk. One population-based study found that women who develop preeclampsia/eclampsia had higher baseline body mass index and systolic and diastolic blood pressures than women who did not have preeclampsia/eclampsia.[72] Another possibility is that preeclampsia independently increases the risk of future stroke. One literature review-based study using risk prediction models found a 55% increased risk of stroke in women with a history of preeclampsia after correction for known cardiovascular risk factors.[73] Large prospective studies are required to confidently establish whether preeclampsia is a cause of stroke or a mediator on the causal pathway of stroke.

Current American Heart Association/American Stroke Association guidelines recommend consideration of evaluating women at 6 to 12 months postpartum for a history of preeclampsia/eclampsia and documenting this history as a risk factor for future stroke (Class IIa; Level of Evidence C).[60]

Conclusions

Preeclampsia is a treatable and possibly preventable condition that complicates up to 5% of pregnancies. Preeclampsia/eclampsia is associated with stroke and PRES. The risk of stroke in women with preeclampsia/eclampsia seems highest in the postpartum period. Women whose pregnancy is complicated by preeclampsia or eclampsia should be counseled on the signs and symptoms of stroke and monitored closely in the postpartum period. It is likely that endothelial dysfunction and blood–brain barrier disruption play a central role in the cerebral dysfunction seen in preeclampsia/eclampsia. The treatment for preeclampsia/eclampsia includes antihypertensives and magnesium.

Preeclampsia is a sex-specific risk factor for future stroke that is likely under-recognized. The risk of future ischemic stroke is ≈80% greater in women with a history of preeclampsia than in those without it, suggesting a need to increase awareness among women with this condition and their providers, so they can make risk factor modifications and lifestyle changes needed to reduce their risk of stroke.

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