Eclampsia in the 21st century
Michal Fishel Bartal, MD; Baha M. Sibai, MD

Definition and Incidence
Eclampsia is one of the most serious acute complications of pregnancy, and it carries high morbidity and mortality for both the mother and baby.⁹ Eclampsia is defined as the occurrence of 1 or more generalized, tonic-clonic convulsions unrelated to other medical conditions in women with hypertensive disorder of pregnancy. Although 10% of pregnancies are complicated by hypertensive disorders, eclampsia continues to occur in 0.8% of women with hypertensive disorders.² During the past 50 years, there has been a reduction in the rate of eclampsia in developed countries with a reported incidence ranging from 1.6 per 10,000 deliveries to 10 per 10,000 deliveries.⁵⁻¹⁴ In some low-resource or developing countries, the reported rate of eclampsia ranges from 50 to 151 per 10,000 deliveries (Figure 1).¹⁴⁻¹⁸ Although the rate of eclampsia and the number of maternal deaths from hypertension in pregnancy have fallen steadily over recent years in developing countries, hypertensive disorders still feature among the top 6 causes of maternal mortality in the United States and are responsible for up to 14% of all maternal deaths worldwide.¹,¹⁹⁻²¹ Our impression is that differences in the incidence and complication rates between developed and developing countries result from gaps in access to care, appropriate and early prenatal care, surveillance and management protocols for timely hospitalization and delivery, antihypertensive therapy for prevention of stroke, pulmonary edema, congestive heart failure and magnesium sulfate prophylaxis during the peripartum period in women with severe preeclampsia.²²,²³

The reported incidence of eclampsia is 1.6 to 10 per 10,000 deliveries in developed countries, whereas it is 50 to 151 per 10,000 deliveries in developing countries. In addition, low-resource countries have substantially higher rates of maternal and perinatal mortalities and morbidities. This disparity in incidence and pregnancy outcomes may be related to universal access to prenatal care, early detection of preeclampsia, timely delivery, and availability of healthcare resources in developed countries compared to developing countries. Because of its infrequency in developed countries, many obstetrical providers and maternity units have minimal to no experience in the acute management of eclampsia and its complications. Therefore, clear protocols for prevention of eclampsia in those with severe preeclampsia and acute treatment of eclamptic seizures at all levels of healthcare are required for better maternal and neonatal outcomes. Eclamptic seizure will occur in 2% of women with preeclampsia with severe features who are not receiving magnesium sulfate and in <0.6% in those receiving magnesium sulfate. The pathogenesis of an eclamptic seizure is not well understood; however, the blood-brain barrier disruption with the passage of fluid, ions, and plasma protein into the brain parenchyma remains the leading theory. New data suggest that blood-brain barrier permeability may increase by circulating factors found in preeclamptic women plasma, such as vascular endothelial growth factor and placental growth factor. The management of an eclamptic seizure will include supportive care to prevent serious maternal injury, magnesium sulfate for prevention of recurrent seizures, and promoting delivery. Although routine imaging following an eclamptic seizure is not recommended, the classic finding is referred to as the posterior reversible encephalopathy syndrome. Most patients with posterior reversible encephalopathy syndrome will show complete resolution of the imaging finding within 1 to 2 weeks, but routine imaging follow-up is unnecessary unless there are findings of intracranial hemorrhage, infarction, or ongoing neurologic deficit. Eclampsia is associated with increased risk of maternal mortality and morbidity, such as placental abruption, disseminated intravascular coagulation, pulmonary edema, aspiration pneumonia, cardiopulmonary arrest, and acute renal failure. Furthermore, a history of eclamptic seizures may be related to long-term cardiovascular risk and cognitive difficulties related to memory and concentration years after the index pregnancy. Finally, limited data suggest that placental growth factor levels in women with preeclampsia are superior to clinical markers in prediction of adverse pregnancy outcomes. This data may be extrapolated to the prediction of eclampsia in future studies. This summary of available evidence provides data and expert opinion on possible pathogenesis of eclampsia, imaging findings, differential diagnosis, and stepwise approach regarding the management of eclampsia before delivery and after delivery as well as current recommendations for the prevention of eclamptic seizures in women with preeclampsia.

Key words: abruption, angiogenic, cardiovascular, cerebral edema, convulsions, fetal death, fetal growth restriction, hypertensive disorder of pregnancy, magnesium sulfate, maternal mortality, placental growth factor, posterior reversible encephalopathy syndrome, seizures, severe maternal morbidity, soluble endoglin, soluble fms-like tyrosine kinase-1, vascular endothelial growth factor
Pathophysiology

The pathogenesis of eclamptic seizures is not well understood. Several hypotheses and pathologic mechanisms have been implicated, but none has been proven. One proposed model for eclampsia is the alteration of autoregulation in the cerebral circulation similar to hypertensive encephalopathy with blood-brain barrier (BBB) disruption and passage of fluid, ions, and plasma proteins into the brain parenchyma. The BBB created by the endothelial cells lining the walls of the capillaries regulates the paracellular (transfer of substances across an epithelium by passing through the intercellular space between the cells) and transcellular (transfer of substances travel through the cell, through both the apical membranes) passages of molecules and solutes between the cerebral vessels and the brain. The capillary endothelium is characterized by the presence of tight junctions with lack of fenestrations. The tight junctions between the endothelial cells form a barrier, which selectively excludes most substances from entering the brain, protecting it from systemic influences.24 The BBB provides not only a stable environment for neural function but also a combination of specific ion channels and transporters to keep the ionic composition optimal for synaptic signaling function.25,26 The autoregulation of the cerebral circulation is a mechanism to maintain constant cerebral blood flow during changes in blood pressure. With normal response, vasodilatation of the cerebral vessels will occur in response to elevated blood pressure, whereas vasodilatation occurs when blood pressure is lowered. Cerebral blood flow autoregulation is mediated and modulated through myogenic, neurogenic, metabolic, or endothelial control.27–29 Myogenic control induces vascular smooth muscle constriction or dilation in response to transmural pressure. Neurogenic control occurs through perivascular sympathetic and cholinergic responses. Metabolic control occurs in response to changes in carbon dioxide, oxygen, and protons and is tightly linked to neuronal activity. Endothelial control occurs in response to factors released from endothelial cells, such as nitric oxide, which acts as a vasodilator or endothelin-1, a vasoconstrictor. With the increase in plasma volume and cardiac output during pregnancy, the adaption of the cerebral circulation to pregnancy is unique from other organs because of the need to maintain constant flow, whereas other organ systems undergo substantial increases in blood flow.30 One mechanism suggested for eclampsia is similar to the pathophysiological changes described in hypertensive encephalopathy, autoregulation failure in acute hypertension, which leads to increased hydrostatic pressure and decreased cerebral vascular resistance, potentially damaging the microvessels and resulting in increased BBB permeability, microbleeds, focal cerebral edema, neuroinflammation, and neuronal damage.29,31–33 This theory cannot explain all the cases of eclampsia as some women with eclampsia do not have severe hypertension (systolic blood pressure [SBP] of ≥160 mm Hg or diastolic blood pressure [DBP] of ≥110 mm Hg) before an eclamptic seizure. One possible explanation previously suggested is a shift in the autoregulation curve to a lower blood pressure during pregnancy. This mechanism can potentially improve cerebral blood flow during hemorrhagic hypotension but could be related to autoregulation failure even without severe range blood pressure during pregnancy.34–36 However, recent data did not find any difference in cerebral blood flow or autoregulation breakthrough between nonpregnant and pregnant animal models.31,37

Furthermore, new data suggest that BBB permeability may increase by circulating factors found in the plasma of women with preeclampsia, such as vascular endothelial growth factor (VEGF) and placental growth factor (PIGF).38,39 One mechanism suggested to affect the BBB includes increased levels of oxidized low-density lipoprotein (oxLDL) in women with preeclampsia.40 Increased oxidative stress in the placental circulation during preeclampsia causes oxidative conversion of LDL to oxLDL. oxLDL initiates multiple pathways in both endothelial and vascular smooth muscle cells, mostly through binding to its receptor lectin-like oxLDL receptor (LOX-1).42 oxLDL binding to LOX-1 generates complex signaling cascades leading to the induction of the inflammatory pathway and increase production of superoxide in endothelial cells that can further promote vascular dysfunction.43,44 Superoxide decreases the concentration of nitric oxide by binding nitric oxide to form peroxynitrite, a stable reactive oxygen and nitrogen species that has deleterious effects on endothelial function.45–47 Increased BBB permeability caused by oxLDL may promote vasogenic edema formation and the neurologic sequelae.44 BBB dysfunction has also been suggested as an important etiologic player in seizure disorders and has recently been described as another suggested mechanism for seizure activity in women preeclampsia.48 In this mechanism, increased BBB permeability will allow the passage of serum constituents into the brain, subsequently causing microglial activation. Microglial activation has been shown to decrease seizure threshold through the secretion of proinflammatory cytokines in different animal models.49

As discussed, the mechanisms by which eclampsia occurs is not clearly understood, but it may involve a pathologic process involving BBB dysfunction with increased BBB permeability. With imaging studies being done after eclamptic seizures, it is impossible to state whether vasogenic edema was present before the seizure and is therefore a cause or whether it is an effect of eclamptic seizures because seizures themselves cause disruption of the BBB and often include hypertensive crises. Another possible mechanism for eclampsia previously suggested was cerebral overregulation and vasospasm. Cerebral overregulation will occur when the normally protective cerebral vasocostrictive response to acute severe hypertension progresses to vasospasm. Vasospasm is thought to cause local ischemia, necrosis, and disruption of the
BBB, which leads to cerebral edema. If this theory was true, then a specific cerebral vasodilator would be more effective at relieving vasospasm (and thus a better drug to prevent eclampsia) than magnesium sulfate. The nimodipine study (in which women with severe pre-eclampsia were randomly assigned to receive a selective cerebral vasodilator: nimodipine vs magnesium sulfate) indicated that deliberate cerebral vasodilation, which interfered with the protective physiological vasoconstriction, actually increased the eclampsia rate (2.6% with nimodipine vs 0.8% with magnesium sulfate). Those findings suggest that seizures in patients with eclampsia are more likely related to overperfusion than vasospasm or ischemia.

Cerebral Pathology

Cerebral pathology autopsy findings typical in eclampsia include massive cerebral edema, white matter hemorrhage, and necrosis. Brain lesions assessed in 317 cases of maternal death from eclampsia were characterized by perivascular edema (68.4%), hemorrhage (36.8%), hemosiderin (31.6%), small vessel thrombosis (10.5%), and parenchymal necrosis (15.8%). The lesions in the brain are not specific; there are similar changes in other forms of systemic endothelial injury, such as thrombotic microangiopathy, atypical hemolytic-uremic syndrome, malignant hypertension, and antiphospholipid antibody syndrome.

Neurodiagnostic Tests

Several neurodiagnostic tests, such as electroencephalography (EEG), computed tomography (CT), magnetic resonance imaging (MRI), and cerebral angiography, have been studied in women with eclampsia. In reviewing an EEG, abnormalities in waveform, frequency, amplitude, symmetry, and reactivity patterns (ie, slow waves or spikes or spike-wave complexes) are documented, including localization (focal vs diffuse or generalized). A review evaluating the available medical literature concerning EEG findings in patients with eclampsia included 153 patients from 8 available studies. On average, 81% of the EEGs of women with eclampsia showed EEG abnormalities following the seizure with resolution of those abnormalities in 90% of cases soon after delivery. The nonpathognomonic EEG findings in patients with eclampsia were slow waves most frequently localized in the occipital lobe and spike discharges. In addition, the abnormal EEG findings in women with eclampsia were seen even with appropriate administration of magnesium sulfate. This finding may suggest that the central anticonvulsant activity in eclamptic seizures does not completely explain the magnesium sulfate mechanism of action (discussed below).

Abnormal neuroimaging findings in eclampsia are similar to those found in hypertensive encephalopathy, including cerebral edema, infarction, and hemorrhage. The classic finding following an eclamptic seizure is referred to as posterior reversible encephalopathy syndrome (PRES) (Figure 2). PRES is a reversible neurologic disorder characterized by a range of neurologic signs and symptoms, including headache, impaired visual acuity or visual field deficits, disorders of consciousness, confusion, seizures, and focal neurologic deficits. The distinctive neuroimaging findings in PRES are focal or confluent vasogenic edema with classic posterior

FIGURE 1
Rate of eclampsia and hypertensive related maternal mortality

Rate of eclampsia per 10,000 deliveries and rate of eclampsia or HDP mortality per 10,000 deliveries in developed and developing countries based on the current published data.

HPD, hypertensive disorder of pregnancy.

Parietal and occipital lobe involvement. Subcortical white matter is usually involved, but even cortical gray matter can be involved, depending on the severity of the disease. Some reports of MRI angiography in women with eclampsia or preeclampsia with neurologic symptoms with PRES have shown blood vessel irregularities consistent with reversible vasoconstriction (Figure 3). The leading theories regarding the pathophysiology of PRES are elevation of blood pressure levels above the upper autoregulatory limit that leads to cerebral hyperperfusion, with vascular leakage and vasogenic edema, and endothelial injury by circulating endogenous or exogenous toxins, which leads to the breakdown of the BBB and subsequent brain edema. PRES can be seen in up to 90% of women with eclampsia but has also been described in up to 20% of women with preeclampsia and neurologic symptoms limited to headache and visual disturbances.

The clinical picture of women with eclampsia, either with or without associated PRES, is similar. However, some studies suggest that PRES might be indicative of a more severe disease process. The prognosis of PRES following eclampsia is favorable, and most patients will recover within 1 week, although some patients can occasionally take several weeks to achieve full recovery. In rare cases, severe neurologic injury and fatality can occur because of intracranial hemorrhage, posterior fossa edema with brainstem compression, or cerebral infarction.

We do not recommend neuroimaging routinely for patients with eclampsia. Neuroimaging studies could generally be limited to those women who have focal neurologic signs, recurrent convulsions, and prolonged coma. Imaging can also be considered in atypical cases, such as seizures that develop at or before 20 weeks of gestation and >48 hours after delivery and for women that have some of the signs and symptoms of preeclampsia without the usual hypertension. In these patients, intracranial hemorrhage and other serious abnormalities that require specific pharmacologic therapy or surgical intervention must be excluded.

Most patients with PRES will show complete resolution of the imaging finding in 1 to 2 weeks, and others will show widespread regression in up to 1 month. Based on our clinical experience, we recommend follow-up imaging in 3 to 4 weeks only if there is evidence for cerebral hemorrhage or infarction or if there is ongoing neurologic deficit.

Imaging studies several years following an eclamptic seizure found that white matter lesions are more
common in women with previous pregnancies complicated by preeclampsia or eclampsia than in parous women in a control group. MRI scans 7 years after the index pregnancy of 39 women who formerly had eclampsia were compared with 29 control women. Women with eclampsia demonstrated subcortical white matter lesions more than twice as often than controls (41% vs 17%); odds ratio [OR], 3.3; 95% confidence interval [CI], 1.05–10.61; P = .04). In addition, there was a positive correlation between the number of seizures and the presence of white matter lesions. Women who had experienced 3 or more seizures (n = 10) demonstrated white matter lesions more than 3 times as often as controls.78

**Risk Factors**

Risk factors for eclampsia are similar to those that have been associated with preeclampsia or gestational hypertension. Several factors have been associated with increased risk of eclampsia, including black and Hispanic race, advanced maternal age, nulliparity, maternal age of \(<\)20 years, multifetal gestation, preterm delivery at \(<\)32 weeks of gestation, and lack of prenatal care.6,79,80 With the implementation of protocols for magnesium sulfate prophylaxis for women presenting with severe hypertension, eclampsia may be considered a preventable disease in many of the cases. The rate of seizures in women with severe preeclampsia not receiving magnesium sulfate is 2.0%, whereas it is 0.6% in those receiving magnesium sulfate. Thus, 71 women with severe preeclampsia need to be treated to prevent 1 case of eclampsia. The rate of seizures in women with preeclampsia without severe features not receiving magnesium sulfate is very low. Based on data from observational studies and the 2 randomized placebo trials, this rate is estimated to be about 1 in 200 women.81 Therefore, it is anticipated that the rate of eclampsia in gestational hypertension will be lower than 1:200. A recent national population-based retrospective cohort study of deliveries in Norway, including 1387 women with eclampsia or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), emphasizes the importance of available obstetrics hospitals. Nulliparous women living >1 hour from any obstetrical institution had a 50% increased risk of eclampsia or HELLP syndrome and parous women living >1 hour from emergency institutions had a doubled risk of eclampsia (0.6% vs 0.3%, adjusted relative risk [RR], 2.0; 95% CI, 1.2–3.3) compared with women living \(\leq\)1 hour from an obstetrical institution.82

**Presentation and Diagnosis**

Several signs and symptoms may precede eclampsia, such as visual disturbances, epigastric pain, and severe persistent occipital or frontal headaches, but none can accurately predict or exclude eclampsia.6,83–85 Visual changes may include blurring vision, diplopia (double vision), scotoma (partial loss of vision or blind spot), photopsia (flashes of light in the field of vision), and transient cortical blindness.86,87 In a systematic review of 2163 women with eclampsia and reported symptoms, the most common symptoms were headache (66%), visual disturbance (27%), and right upper quadrant or epigastric pain (25%).88

When a woman presents with hypertension, proteinuria, and convulsions, most clinicians would agree that the diagnosis of eclampsia is clear. However, although hypertension is the hallmark for the diagnosis of eclampsia, it may be absent in up to 25% of cases. Furthermore, severe hypertension is more common in women who developed antepartum eclampsia than in women with postpartum preeclampsia.89 The American College of Obstetricians and Gynecologists Task Force report on hypertension in pregnancy, and the International Society for the Study of Hypertension in Pregnancy removed the requirement of proteinuria for the diagnosis of preeclampsia if there are other findings suggestive of end-organ involvement (thrombocytopenia, elevated liver transaminases, renal insufficiency, pulmonary edema, or new-onset neurologic symptoms).80,91 Women with eclampsia can present with proteinuria, but previous studies have found that substantial proteinuria (\(\geq\)3 on a dipstick) was present only in 48% of cases and proteinuria was absent in 14% of cases.87

The most common finding during the neurologic examination following a seizure is altered mental status and deficits of memory or visual perception.87

**Time of Onset**

The onset of eclamptic convulsions can be in the antepartum, intrapartum, or postpartum period with 50% to 70% of eclamptic seizures in developing countries occurring in the community and not in the hospital.17 Up to 59% to 70% of seizures will occur during the antepartum period, whereas around 20% to 30% will occur during labor and 20% to 30% in the postpartum period.16,88,89 Almost all cases of antepartum eclampsia will occur after 28 weeks of gestation. Eclampsia that occurs before 20 weeks of gestation is usually associated with a molar pregnancy, with or without a coexistent fetus.73,92 Furthermore, the presence of hypertension, proteinuria, and abnormal laboratory tests at 20 weeks of gestation may be owing to lupus nephritis, hemolytic-uremic syndrome, antiphospholipid antibody syndrome, or thrombotic thrombocytopenic purpura. Women presenting with eclampsia before 20 weeks of gestation should be evaluated for these different disorders. Although exceedingly rare, women in whom convulsions develop in association with hypertension and proteinuria during the first half of pregnancy should be considered to have eclampsia until proven otherwise. These women should have an ultrasound examination to rule out molar pregnancy and an extensive neurologic and medical evaluation to rule out another pathologic process. Historically, preeclampsia and eclampsia were believed to occur only within 48 hours following delivery. However, retrospective data evaluating timing of postpartum eclampsia in 29 women found that 79% had late-onset seizures (\(>\)48 hours from delivery).93 Late postpartum eclampsia can occur
Based on our experience and review of literature, we recommend that after delivery, any woman with convulsions >48 hours after delivery who is hypertensive or has either proteinuria or symptoms of preeclampsia should be considered eclamptic, while other causes are being ruled out.75

Differential Diagnosis

The clinical presentation and symptoms of eclampsia may overlap with other medical and surgical conditions. When a woman is presenting with convulsions that develop in association with hypertension or proteinuria during pregnancy or immediately postpartum, the most common etiology is eclampsia.75 Alternative diagnoses should especially be considered in the following scenarios: normal blood pressures with absence of proteinuria, focal neurologic deficits, onset before 20 weeks of gestation or >48 hours after delivery, or prolonged loss of consciousness.96 The differential diagnosis of seizures that should be taken into consideration is listed in Table 1.97,98 When an alternative diagnosis is considered, the path toward the diagnosis of a seizure in pregnant women will begin with a thorough history and physical examination. Underlying causes, including medications, substance abuse, and medical comorbidities, should be evaluated. Although not routinely recommended, complete blood count, blood glucose, electrolyte panels, urinary analysis for protein, lumbar puncture, and toxicology studies may be helpful based on clinical circumstances. Brain imaging with CT scan or MRI for further assessment should be done.99 The distinction of etiology is critical, because therapy must be directed at the underlying disorder.

Maternal and Neonatal Complications

Eclampsia is associated with a slightly increased risk of maternal death in developed countries, but the maternal mortality rate may be as high as 7% in developed countries.17,100 In a recent cross-sectional study from 29 countries including Africa, Asia, Latin America, and the Middle East, the risk of death in women with eclampsia increased exponentially (adjusted OR [aOR], 42.38; 95% CI, 25.14–71.44) compared with the risk of death in women without preeclampsia. Furthermore, in eclampsia, the risk of life-threatening conditions involving the central

| TABLE 1 Differential diagnosis of seizure during pregnancy or after delivery |
|-----------------------------|---------------------------------|
| **Potential causes of seizures in pregnancy and after delivery** | |
| **Seizure disorder** | |
| Pregnancy related | O Eclampsia |
| O Thrombotic thrombocytopenic purpura |
| O Amniotic fluid emboli |
| Neurovascular | O Intracranial hemorrhage |
| O Subarachnoid hemorrhage (ruptured aneurysm or malformation) |
| O Arterial embolism or thrombosis |
| O Cerebral venous thrombosis |
| O Angiomas |
| O Space occupying lesion (benign, neoplastic, primary, metastatic) |
| O Posterior reversible encephalopathy syndrome |
| O Congenital brain defects |
| Metabolic | O Liver or renal failure |
| O Hypoglycemia |
| O Hyponatremia |
| O Hyperosmolar states (hyperosmolar nonketotic hyperglycemia) |
| O Hypocalcemia |
| Autoimmune | O Systemic lupus erythematosus |
| O Antiphospholipid syndrome |
| Infectious encephalitis or meningitis: bacterial, viral, parasitic, tuberculosis |
| Drug or substance overdose or withdrawal (ie, antipsychotics, tricyclic antidepressants, salicylate overdose, withdrawal from alcohol, barbiturates, benzodiazepines, illicit drug use such as cocaine, methylenedioxymethamphetamine) |
| Trauma |
| Psychogenic nonepileptic seizures (pseudoseizures) |

nervous system, such as coma or loss of consciousness lasting 12 hours, stroke, status epilepticus, or total paralysis, were up to 60 times more frequent than those in women without preeclampsia. Maternal adverse outcomes and death from a complication related to preeclampsia are most common among women who are older than 35 years, foreign-born Hispanic and African American women, at 20 to 28 weeks of gestation, have multiple gestations, and among women with the first live birth. In a retrospective review of all preeclampsia-related deaths identified by the California Pregnancy-Related Mortality Review from 2002 to 2007, there were 333 pregnancy-related maternal deaths in California. Of these, 54 (16%) were associated with pre-eclampsia, whereas eclampsia occurred in 36% of cases.

Beyond the increased risk of mortality, eclampsia is associated with substantial acute maternal complications (Table 2). Women with eclampsia have increased risk of severe maternal complications, such as placental abruption, HELLP, disseminated intravascular coagulation, pulmonary edema, aspiration pneumonia, cardiopulmonary arrest, and acute renal failure (Figure 4). Women in whom eclampsia developed at $\leq 32$ weeks of gestation have a reported higher incidence of placental abruption, HELLP syndrome, and acute renal failure than those in whom eclampsia developed later.

Perinatal mortality and morbidity remain high in eclamptic pregnancies. The reported perinatal death rate ranges from 5.6% to 11.8%. Most perinatal death cases are related to placental abruption, fetal growth restriction, or extreme prematurity. Neonates of women with eclampsia are at increased risk of being small for gestational age (SGA) and having complications related to prematurity, such as respiratory distress syndrome and neonatal death.

**Long-term Maternal Prognosis**

Women with a history of eclampsia are at increased risk of preeclampsia in a subsequent pregnancy. The rate of preeclampsia in subsequent pregnancies is about 25%, with higher risk if the onset of eclampsia was in the second trimester of pregnancy. The rate of recurrent eclampsia is about 2%. Beyond the acute morbidities in those with eclampsia, there is the potential for long-term sequela. A recent retrospective cohort study of 569,900 women, of whom 39,624 had hypertensive disorder of pregnancy and 319 (0.06%) had eclampsia, evaluated cardiovascular morbidity during delivery hospitalization. Eclampsia was associated with a 12-fold increased risk of cardiovascular morbidity, such as myocardial infarction, cerebrovascular disease, acute heart failure, cardiomyopathy, or cardiac arrest. The risk of a future seizure disorder following an eclamptic seizure was evaluated in a large retrospective database of 1,565,733 births, of whom 1615 women

**TABLE 2**

<table>
<thead>
<tr>
<th>Complication</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.0–1.0</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2.0–4.0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.0–9.5</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1.0</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0.5</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>2.0–4.0</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>3.0–12.0</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>7.0–12.0</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3.0–8.8</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>6.0–7.0</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>4.7</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>24.0</td>
</tr>
</tbody>
</table>

**FIGURE 4**

Chest X-ray reveals pulmonary edema in a woman presenting with eclampsia.
were previously affected by eclampsia. A future seizure disorder (defined as more than 30 days after the index birth discharge date and not more than 20 weeks of gestation in a subsequent pregnancy) was more likely after a pregnancy with eclampsia (4.58 per 10,000 person-years) than a pregnancy without a hypertensive disorder of pregnancy (0.72 per 10,000 person-years; crude RR, 6.09; 95% CI, 2.73–13.60). Although the RR of a seizure disorder is higher than unaffected women, the absolute risk is extremely low (approximately 1 seizure per 2200 person-years).\textsuperscript{108}

Moreover, women who suffered eclampsia may report more long-term cognitive difficulties related to memory and concentration years after the index pregnancy.\textsuperscript{109–112} A study evaluating 123 women 6 to 24 months after an eclampsia noted that 51% of women had at least 1 persistent symptom, 10% of women reported persistent amnesia, 22% reported loss of memory, 11% reported visual disturbances, 10% had vertigo or balance problems, and 18% reported ongoing headaches.\textsuperscript{112} Another study evaluating subjective cognitive functioning several years after a pregnancy complicated with eclampsia (n=30), women with a history of eclampsia, reported impaired cognitive functioning compared with healthy parous women. In addition, women who experienced multiple eclamptic seizures reported greater cognitive impairment than those who experienced 1 seizure.\textsuperscript{109}

One study has evaluated visual fields and the presence of brain white matter lesions on MRI in 47 women who had experienced eclampsia-related PRES. Women with a history of eclampsia reported worse vision-related quality of life compared with women who had normotensive pregnancies. Furthermore, 36% of women had white lesions on MRI, but none of them had visual field defects on MRI. The lower vision-related quality of life was associated with the presence of cerebral white matter lesions; however, these lesions did not seem to induce visual field loss.\textsuperscript{113}

Although women with history of eclampsia may report subjective cognitive dysfunction, data do not demonstrate impaired cognitive functioning using objective neurocognitive assessments.\textsuperscript{105,114,115} A recent study evaluated the cognitive functioning with an average follow-up of 7 years in women who had preeclampsia and eclampsia using neurocognitive tests and self-reported cognitive dysfunction and measures of anxiety and depression. Aside from minor slowing in motor speed, no differences were seen in objective measures of visual perception, working memory, long-term memory, attention, and executive functioning in women with eclampsia (n=46) or pre-eclampsia (n=51) compared with controls. Women with eclampsia and women with preeclampsia reported more cognitive failures in daily life and scored higher for anxiety and depression. Women with eclampsia did not demonstrate worse cognitive or motor performance than women with preeclampsia.\textsuperscript{114}

**Prevention of Eclampsia**

Primary prevention aims to prevent disease or injury before it ever occurs. For primary prevention of eclampsia, low-dose aspirin (dosage ranging 60–150 mg daily) has been proven to reduce the risk of preeclampsia by 10% to 15%.\textsuperscript{116–119} Low-dose aspirin is recommended to women with a history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal disease, and autoimmune disease (ie, systemic lupus erythematosus, antiphospholipid syndrome). Low-dose aspirin should also be considered if the patient has more than 1 of the following risk factors: nulliparity, obesity, family history of preeclampsia, sociodemographic characteristics (African American race, low socioeconomic status), age of ≥35 years, and personal history factors (low birthweight or SGA, previous adverse pregnancy outcome, more than 10-year pregnancy interval).\textsuperscript{120} Secondary prevention will include intervention for early detection of the disease and reducing the impact of a disease. Secondary prevention of eclampsia will include weekly monitoring for women with gestational hypertension or preeclampsia, use of antihypertensive medications for blood pressure regulation, timely delivery, and prophylactic use of magnesium sulfate during labor and immediately after delivery in women with preeclampsia with severe features.\textsuperscript{120} We recommend that women with gestational hypertension or preeclampsia will have weekly follow-up with close monitoring of blood pressure, weekly laboratory test (complete blood count, serum creatinine, aspartate aminotransferase [AST], alanine transaminase [ALT]), serial ultrasound to determine fetal growth every 3 to 4 weeks, and weekly antepartum testing. If there is no progression to preeclampsia with severe features, induction of labor at 37 weeks of gestation is recommended. If there are signs or symptoms for preeclampsia with severe features (ie, SBP of ≥160 mm Hg or DBP of ≥110 mm Hg, thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, new-onset headache, or visual disturbances), the patient should be admitted to the hospital and managed according to the guidelines for pre-eclampsia with severe features (discussed below). It is important to emphasize that about 20% to 40% of women with eclampsia do not have any preceding symptoms before the onset of the convulsions. In fact, in up to 60% of cases, seizure is the first sign of preeclampsia.\textsuperscript{121,122}

There is substantial evidence regarding the use of magnesium sulfate to prevent convulsions in women with preeclampsia with severe features.\textsuperscript{2,55} Magnesium sulfate was found to be superior to phenytoin, diazepam, or nimodipine for the prevention of eclampsia in women with preeclampsia and is the drug of choice for the prevention of a seizure.\textsuperscript{5,123–126} The largest randomized controlled trials of magnesium sulfate for the prevention of eclampsia are listed in Table 3. In a meta-analysis, magnesium sulfate more than halves the risk of eclampsia in women with preeclampsia (RR, 0.41; 95% CI, 0.29–0.58), with a nonsignificant reduction in maternal death (RR, 0.54; 95% CI, 0.26–1.10), with no clear difference in serious maternal morbidity (RR, 1.08; 95% CI, 0.89–1.32), and with...
Magnesium sulfate should be continued. It is currently not clear for how long.

A number needed to treat of 102 (95% CI, 72–173) compared with placebo.\textsuperscript{125}

Although this randomized control study was well conducted with a sample size calculation for a noninferiority study, the major limitation of this study is the sample size. The sample size was based on a much higher eclampsia rate than observed in the study in the control group (2% vs 0.38%), this sample size calculation was based on the reported rate of eclampsia without magnesium sulfate. The rate of eclampsia in this trial was only 0.35% in women who discontinued magnesium sulfate after labor, but this rate was still 50% higher than women who continued magnesium sulfate for 24 hours after delivery.\textsuperscript{128}

Therefore, until further evidence develops; we recommend continuing magnesium sulfate for 24 hours after labor for women with preeclampsia with severe features.

A few studies have described the use of magnesium sulfate for women with preeclampsia without severe features.\textsuperscript{133–135}

Because of the limited number of patients in all published studies, the current evidence does not support the use of magnesium sulfate prophylaxis for women with preeclampsia without severe features.

Tertiary prevention aims to soften the impact of an ongoing illness or injury that has lasting effects. For women with eclampsia, tertiary prevention will include magnesium sulfate for the prevention of recurrent seizures. For women with eclampsia, magnesium sulfate reduced the risk of maternal death (RR, 0.59; 95% CI, 0.37–0.94) and recurrence of seizures (RR, 0.44; 95% CI, 0.24–0.80) compared with diazepam.\textsuperscript{124,136} Magnesium sulfate also reduces the risk of further seizures compared to phenytoin (RR, 0.31; 95% CI, 0.20–0.47), or to a lytic cocktail (usually chlorpromazine, promethazine, and pethidine) (RR, 0.09; 95% CI, 0.03–0.24).\textsuperscript{137}

Although the effectiveness of magnesium sulfate in treating and preventing eclampsia has been established, its mechanism of action remains unclear. Several possible mechanisms of action have been proposed, including acting as a vasodilator (either peripherally or in the cerebral circulation to relieve vasospasm), protecting the BBB to decrease cerebral edema formation, and acting as a central anticonvulsant.\textsuperscript{138,139}

Magnesium sulfate is a calcium antagonist that acts both intracellularly and extracellularly on calcium channels in vascular smooth muscle, resulting in a decrease in intracellular calcium with a vasodilator effect.\textsuperscript{140–142} However, a vasodilator, such as magnesium sulfate, would seem to be a paradoxical treatment choice for hypertensive encephalopathy in which acute elevations in blood pressure cause increased BBB permeability and cerebral edema. Further studies have suggested that
magnesium sulfate causes concentration-dependent vasodilation in both cerebral and mesenteric resistance arteries, with mesenteric arteries more sensitive to magnesium sulfate.\textsuperscript{143} Other studies have found that magnesium sulfate did not change cerebral blood flow, large cerebral artery diameter, or middle cerebral artery velocity.\textsuperscript{144,145} It seems that the magnesium sulfate vasodilator effect may prevent eclampsia by reducing peripheral vascular resistance and lower systemic blood pressure and not by a vasodilator effect on the cerebral blood flow.\textsuperscript{138} Another suggested mechanism of magnesium sulfate is decreasing cerebral edema formation. This could be explained by magnesium sulfate’s action as a calcium antagonist at the level of the endothelial cell actin cytoskeleton (composed of actin filaments, intermediate filaments, and microtubules) while decreasing calcium cell contraction, tight junction permeability, and the paracellular movement of solutes, thereby limiting edema formation and improving clinical outcomes in eclampsia.\textsuperscript{138,146} The third possible mechanism of magnesium sulfate is as a central anticonvulsant. Seizures are thought to be mediated at least in part by stimulation of glutamate receptors, such as the N-methyl-D-aspartate (NMDA) receptor. Magnesium sulfate has been found to have a central action on NMDA-induced seizures in different animal models.\textsuperscript{147–149} The possible anticonvulsant activity of magnesium sulfate may be related to its role in increasing the seizure threshold by inhibiting NMDA receptors. Finally, one of the suggested mechanisms of eclampsia described before involves increased BBB permeability, subsequently causing microglial activation and secretion of proinflammatory cytokines causing decrease seizure threshold. The newer anti-inflammatory theory for magnesium sulfate mechanism of action suggests that the effect of magnesium sulfate may be related to a direct effect on microglial activation, as opposed to limiting BBB permeability. Magnesium sulfate may limit lipopolysaccharide-induced microglial secretion of proinflammatory cytokines, such as TNF-\(\alpha\) and interleukin (IL)-6 in a cell culture.

Management of Severe Hypertension

In a retrospective analysis of 465 women with severe hypertension, timely management (within 60 minutes) of confirmed diagnosis of severe maternal hypotension was associated with a 72% reduction (1.9% vs 6.4%; \(P=0.02\)) in RR of severe maternal morbidity (defined as prolonged hospital stay, readmission, admission to the intensive care unit [ICU], or transfusion of \(\geq 4\) units of packed red blood cells).\textsuperscript{151} A standardized approach for treatment with intravenous blood pressure medication and magnesium sulfate for sustained severe maternal blood pressures (SBP of \(\geq 160\) mm Hg or DBP of \(\geq 110\) mm Hg) resulted in a marked reduction in severe maternal morbidity.\textsuperscript{8} Antihypertensive drugs for treatment of severe hypertension include intravenous hydralazine or labetalol or oral nifedipine in doses described in Figure 5.\textsuperscript{152}

Management of Eclampsia

The management of eclampsia requires the availability of a medical ICU, and women with eclampsia at term should be cared for only in a level II or III hospital with adequate medical ICU. For women with eclampsia remote from term, referral should be made to a tertiary care center. Before transferring a patient with critical illness, it is important to stabilize blood pressure and control convulsions. The patient should be given a loading dose of magnesium sulfate and fetal monitoring should be undertaken (Figure 6). Patients should be sent in an ambulance with medical personnel in attendance for proper management in the event of subsequent convulsions.

Acute care during a seizure

During or immediately after the acute convulsive episode, supportive care should be given to prevent serious maternal injury, assessing and

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**FIGURE 5**

Protocols for the treatment of severe hypertension

<table>
<thead>
<tr>
<th>Time</th>
<th>LABETALOL</th>
<th>HYDRAZINE</th>
<th>NIFEDIPINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>IV (mg)</td>
<td>IV (mg)</td>
<td>Oral (mg)</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>10-15</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>SBP (\geq 160) or DBP (\geq 110)</td>
<td>Check Blood pressure</td>
<td>Check Blood pressure</td>
</tr>
<tr>
<td>30</td>
<td>SBP (\geq 160) or DBP (\geq 110)</td>
<td>Check Blood pressure</td>
<td>Check Blood pressure</td>
</tr>
<tr>
<td>40</td>
<td>Check Blood pressure</td>
<td>SBP (\geq 160) or DBP (\geq 110)</td>
<td>Check Blood pressure</td>
</tr>
<tr>
<td>50</td>
<td>SBP (\geq 160) or DBP (\geq 110) Consult</td>
<td>SBP (\geq 160) or DBP (\geq 110) Consult</td>
<td>SBP (\geq 160) or DBP (\geq 110) Consult</td>
</tr>
</tbody>
</table>

SBP of \(\geq 160\) mm Hg or a DBP of \(\geq 110\) mm Hg and persistent for 15 minutes.

DBP, diastolic blood pressure; IV, intravenous; SBP, systolic blood pressure.

establishing airway patency, ensuring oxygenation, and avoiding aspiration. During this time, the bedside rails should be elevated and padded. We do not recommend holding the patient down or trying to stop their movement. To minimize the risk of aspiration, the patient should lie in the lateral decubitus position, and oral secretions should be suctioned as needed. Adequate oxygenation should be maintained during the convulsive episode. Although the initial seizure usually lasts only a few minutes, it is important to maintain oxygenation by supplemental oxygen administration through a facemask at 8 to 10 L/min. Pulse oximetry can be used for monitoring. Arterial blood gas analysis will be required only if the pulse oximetry results are abnormal (oxygen saturation ≤92%). After the convulsion has ceased, the patient typically begins to breathe again, and oxygenation is rarely an issue. However, maternal hypoxia may develop in women who have repetitive convulsions, aspiration pneumonia, or pulmonary edema.

Maternal hypoxia and hypercarbia can cause fetal heart rate and uterine activity changes during and immediately after a convulsion. Fetal heart rate changes may reveal bradycardia, late decelerations, decreased variability, or compensatory tachycardia. Uterine contractions can increase in frequency and tone. These changes usually resolve within 3 to 10 minutes after the termination of convulsions and correction of maternal hypoxia (Figure 7). As discussed before, the patient should lie in the lateral decubitus position; if possible, supplemental oxygen should be administered, but we do not recommend giving fluid for fetal heart rate resuscitation. The patient should not be rushed to an emergency cesarean delivery based on these findings, especially if the maternal condition is stable.

### Treatment of convulsions

The next step in the management would be to prevent recurrent seizures as discussed before. Magnesium sulfate is the drug of choice to prevent subsequent convulsions in women with eclampsia. A loading dose of 6 grams over 15 to 20 minutes is recommended, followed by a maintenance dose of 2 grams per hour as a continuous IV solution. Maintenance infusion of 2 g/h following either a 4- or a 6-g loading dose has a higher likelihood of producing the mean therapeutic concentration of magnesium sulfate with fewer fluctuations during the period of administration compared with 1 g/h. In women without an available intravenous access, magnesium sulfate can be administered by intramuscular (IM) injection, 10 grams initially as a loading dose (5 g IM in each buttock), followed by 5 g every 4 hours. Overall, the serum concentration fluctuates much more with this regimen than with continuous IV regimens described above, and serum level is less consistent. About 10% of women with eclampsia may have a second convulsion after receiving magnesium sulfate. In this case, a second bolus of 2 g of magnesium sulfate can be given intravenously (IV) over 3 to 5 minutes. In the occasional scenario of recurrent convulsions while receiving adequate and therapeutic doses of magnesium sulfate, recommended treatment is lorazepam 4 mg IV over 3 to 5 minutes. Because magnesium sulfate is excreted almost exclusively in the urine, if renal function is impaired, serum magnesium levels will increase quickly, placing the patient at risk of adverse effects. Therefore, in patients with a serum creatinine level of >1.2 mg/dL or oliguria (<30 mL urine output per hour for more than 4 hours), the loading dose of 4 to 6 g should be followed by a maintenance dose of only 1 g/h.

The adverse effects of magnesium sulfate (ie, respiratory depression and cardiac arrest) come largely from its action as a smooth muscle relaxant. Deep tendon reflexes are lost at a serum magnesium level of 9 mg/dL (7 mEq/L), respiratory depression occurs at 12 mg/dL (10 mEq/L), and cardiac arrest occurs at 30 mg/dL (25 mEq/L). Patients at risk of impending respiratory depression may require intubation and emergency correction with calcium gluconate 10% solution, 10 mL IV over 3 minutes. As such, provided deep tendon reflexes are present, the likelihood for more serious toxicity is extremely low. We recommend monitoring magnesium levels every 4 to 6 hours only in women with renal dysfunction (creatinine >1.2 mg/dL or urine output was <30 mL/h for more than 4 hours) or in women with signs concerning magnesium toxicity. If the serum level exceeds 9.6 mg/dL (8

![FIGURE 6](Image)

**Figure 6** Emergency treatment algorithm for eclamptic seizure

<table>
<thead>
<tr>
<th>Time</th>
<th>Emergency treatment algorithm for Eclamptic seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 min</td>
<td>1. Airway: lateral decubitus position, oxygen, suction</td>
</tr>
<tr>
<td></td>
<td>2. IV access</td>
</tr>
<tr>
<td></td>
<td>3. Avoid maternal injury: elevate and pad bed rails</td>
</tr>
<tr>
<td>10-15 min</td>
<td>Prevent recurrent convulsions:</td>
</tr>
<tr>
<td></td>
<td>1. Magnesium sulfate 6g over 15-20 minutes</td>
</tr>
<tr>
<td></td>
<td>2. Continue with maintenance dose of 2g per hour as continuous solution</td>
</tr>
<tr>
<td>15-20 min</td>
<td>Control of severe hypertension (see figure 5)</td>
</tr>
<tr>
<td></td>
<td>- Obtain lab work:</td>
</tr>
<tr>
<td></td>
<td>- CBC with platelet count, basic metabolic panel, liver enzyme, creatinine, blood type &amp; cross</td>
</tr>
<tr>
<td></td>
<td>- Fetal monitoring</td>
</tr>
<tr>
<td></td>
<td>Another bolus of Mg sulfate over 3-5 minutes</td>
</tr>
<tr>
<td></td>
<td>Refractory seizure:</td>
</tr>
<tr>
<td></td>
<td>Lorazepam 4mg</td>
</tr>
<tr>
<td></td>
<td>Consider need for intubation</td>
</tr>
</tbody>
</table>

ICU: intensive care unit; IV, intravenous.
mEq/L), the infusion should be stopped, and serum magnesium levels should be determined at 2-hour intervals. The infusion can be restarted at a lower rate when the serum level decreases to < 8.4 mg/dL (7 mEq/L).120,156

Management of the eclamptic patient after a seizure
The presence of eclampsia would be an indication for delivery but is not an indication for cesarean delivery.158,159 The decision to perform a cesarean delivery should be based on gestational age, fetal condition, presence of labor, and cervical bishop score. Once the maternal and fetal status are stable, and the patient is alert and oriented to person, place, and time, induction should be started. We believe that induction is reasonable as long as the patient is in the active phase within 24 hours.

Based on the available data and our experience, patients with eclampsia before 30 weeks of gestation who are not in labor with an unfavorable cervix (Bishop score of <5) have very low (<10%) success rate in induction of labor, and cesarean delivery is recommended.

On admission, we recommend obtaining the following laboratory test: complete blood count with platelets, serum creatinine, AST, and ALT. If the patient presented with abruption, severe bleeding, or severe liver dysfunction, we recommend obtaining a fibrinogen level. If the first laboratory results are normal, we do not recommend repeating them. We recommend repeating the laboratory assessment in 6 hours if there is evidence of thrombocytopenia (<100,000/μL) or elevated creatinine (>1.0 mg/dL). In a stable woman who is not bleeding, we recommend platelet transfusion if the platelet count is <50,000/μL before a cesarean delivery or <20,000/μL for a vaginal delivery.160

Maternal pain relief during labor and delivery can be provided by epidural anesthesia. Regional anesthesia is contraindicated in the presence of coagulopathy or severe thrombocytopenia. A recent retrospective review, including 573 patients with a platelet count <100,000/μL who received a neuraxial technique, noted that the risk of epidural hematoma from neuraxial anesthesia is <0.2% with platelet count of more than 70,000/μL.161 In women with eclampsia, general anesthesia increases the risk of aspiration and failed intubation because of airway edema. Women with airway or laryngeal edema may require awake intubation under fiberscope observation with availability of immediate tracheostomy.162

Following delivery, women with eclampsia should receive close monitoring of vital signs, input, output, and symptoms for at least 72 hours. Women with eclampsia, especially those with abnormal renal function, are at increased risk of pulmonary edema, and careful attention to fluid status is essential.163 Magnesium sulfate should be continued for 24 hours after delivery and at least 24 hours after the last convolution.

Angiogenic Factors and Eclampsia
An important area of research is whether we can predict severe maternal outcomes, such as eclampsia in women with preeclampsia. Angiogenic factors, including PIGF and soluble fms-like tyrosine kinase-1 (sFlt-1), have been the dominant focus of placental biomarker studies in preeclampsia over the past 15 years.164–166 PIGF, a proangiogenic member of the VEGF family, normally increases during pregnancy as a function of gestational age. A reduction in PIGF is observed in women with preeclampsia, which precedes the onset of disease and reflects the underlying placental dysfunction. Therefore, several studies have examined the utility of PIGF-based tests for predicting preeclampsia.167–168 A large United Kingdom pragmatic multicenter randomized controlled trial that aimed to determine whether knowledge of the PIGF levels would reduce time to diagnosis and maternal and perinatal adverse outcomes in women with suspected preeclampsia was recently published. This study included 1035 women with
suspected preeclampsia; 576 (56%) women were assigned to the intervention (revealed PlGF testing) group, and 447 (44%) women were assigned to receive usual care with additional concealed testing (concealed PlGF testing group). Suspected preeclampsia in this study was defined as new-onset or worsening of existing hypertension, dipstick proteinuria, epigastric or right upper quadrant pain, headache with visual disturbances, fetal growth restriction, or abnormal maternal blood tests that were suggestive of the disease (such as thrombocytopenia or hepatic or renal dysfunction). The documented diagnosis of preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy 2014 statement.\(^\text{166}\) The main finding from this study was that the availability of PlGF results substantially reduced the time to clinical confirmation of preeclampsia (1.9 vs 4.1 days; time ratio, 0.36; 95% CI, 0.15–0.87; \(P=0.027\)) and reduced severe maternal adverse outcomes (4% vs 5%; aOR, 0.32; 95% CI, 0.11–0.96; \(P=0.043\)) compared with the concealed testing group. There were 5 serious events (2 eclamptic seizures, 2 strokes, and 1 cardiac arrest in 4 women, all of whom had low PlGF concentrations) in the concealed testing group, whereas there were no similarly serious events in the revealed testing group. Furthermore, a higher proportion of women in the concealed testing group received blood products transfusion (3% vs 2%) compared with the revealed testing group.\(^\text{170}\) A secondary analysis of the prospective multicenter Preeclampsia Triage by Rapid Assay Trial that enrolled women with suspected preeclampsia\(^\text{171}\) evaluated whether abnormal PlGF level is associated with adverse neonatal and maternal outcomes. The parent trial included women with hypertension, proteinuria, laboratory abnormalities, excessive maternal weight gain, fetal growth restriction, or clinical symptoms (such as headache, epigastric pain, and nausea and vomiting). For the secondary analysis, 1112 participants with a singleton pregnancy between 20 and 41 weeks of gestation were included, whereas plasma PlGF was low in 742 (67%) of them. Low PlGF levels (≤100 pg/mL) at the time of clinical presentation were associated with a higher risk (6.2% vs 1.9%; aRR, 3.6; 95% CI, 1.7–8.0) of maternal complications attributable to preeclampsia (death, eclampsia, HELLP syndrome, pulmonary edema, placental abruption, receipt of a third antihypertensive agent, or occurrence of other rare maternal complications, such as acute renal failure, myocardial infarction, hypertensive encephalopathy, cortical blindness, retinal detachment, stroke, disseminated intravascular coagulation, microangiopathy acute fatty liver of pregnancy, or liver hematomata or rupture). In this analysis, there were 3 cases of eclampsia in the PlGF of ≤100 pg/mL group compared with no cases in the PlGF of >100 pg/mL group. The difference in eclampsia rate did not reach statistical significance.\(^\text{172}\)

Furthermore, excessive production of sFlt-1 leads to a binding of circulating VEGF and inhibition of its function. Although there is a lack of data signifying the clinical utility of sFlt-1 in the clinical setting, there is some evidence that the mean serum level of sFlt-1 in eclampsia is higher than in uncomplicated preeclampsia cases (298.3±75.2 vs 128.1±36.5; \(P<0.001\)).\(^\text{173}\) Eclampsia was also found to be associated with higher maternal circulating concentrations of soluble VEGF receptor 1 and soluble endoglin and lower concentrations of PlGF than normal pregnancy but with similar concentrations to severe preeclampsia. These findings strengthen the assumption that eclampsia shares a common pathogenic pathway with severe preeclampsia.\(^\text{174}\)

Although recent data suggest that PlGF levels are superior to clinical markers in the prediction of adverse pregnancy outcomes, including eclampsia in preeclamptic women, randomized trials are still required to determine their value as clinical markers and utility in clinical decision making, such as the need for admission, follow-up, and medical therapy for the prevention of eclampsia in women presenting with hypertension during pregnancy.

### Summary and Future Directions

Because eclampsia is a rare but life-threatening condition, protocols should be in place for education and implementation of antenatal and postpartum care for women presenting with seizure. As discussed above, the pathophysiology of eclampsia is poorly understood, and 25% of women will not have hypertension before an eclamptic seizure. Although new data are emerging regarding the biomarker to identify women at risk, blood pressure monitoring and assessment of clinical symptoms remain the most effective methods to diagnose preeclampsia and eclampsia, thereby providing the opportunity for expeditious intervention and preventative strategies. There are needs to (1) determine the optimal duration for magnesium sulfate prophylaxis after delivery for women with preeclampsia with severe features; (2) assess whether women presenting with late postpartum preeclampsia with severe features (>48 hours after delivery) will benefit from magnesium sulfate prophylaxis; (3) better understand long-term neurologic complications for women with a history of eclampsia; (4) prospectively study obstetrical complications in subsequent pregnancies following eclampsia; and (5) evaluate cost-effectiveness and clinical utility of postpartum follow-up for women with preeclampsia, including the frequency of blood pressure monitoring, symptoms evaluation, and prevention of significant maternal complications, such as eclampsia.

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FEBRUARY 2022 American Journal of Obstetrics & Gynecology S1249


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