SEIZURES IN WOMEN WITH PREECLAMPSIA: MECHANISMS AND MANAGEMENT

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INTRODUCTION

Eclampsia is defined in the obstetrical literature as the occurrence of unexplained seizure during pregnancy in a woman with preeclampsia.1,2 In the Western world, the incidence of eclampsia is ~1 per 2000 to 1 per 3000 pregnancies3–5, but the incidence is 10-fold higher in tertiary referral centers and undeveloped countries where there is poor prenatal care, and in multi-fetal gestations.6,7 Nearly 1 in 50 women with eclampsia die as do 1 in 14 of their offspring, and mortality rates are considerably higher in undeveloped countries.3,8,9 Eclampsia is also associated with significant life-threatening complications, including neurological events. Seizure acutely can cause stroke, haemorrhage, oedema and brain herniation10–13 and thus lead to epilepsy and cognitive impairment later in life.13,14

Preeclampsia is by definition a prodrome for eclampsia, making hypertension and proteinuria prerequisite for seizure during pregnancy. However, women who develop eclampsia exhibit a wide spectrum of signs and symptoms ranging from severe hypertension and proteinuria to mild or absent hypertension with no proteinuria.6,9,15 In a study of 53 pregnancies complicated by eclampsia, only 7 women (13%) could be considered to have severe preeclamptic disease prior to seizure.15 A similar result was found in a United Kingdom study in which high blood pressure (≥120 mmHg diastolic) was recorded in only 20% of patients with eclampsia.3 The finding that a fair number of women with eclampsia do not fulfill the clinical definition of hypertension or proteinuria suggests eclampsia is not always a progression from severe preeclamptic disease to seizure. While this alternative view of the eclamptic seizure was presented over 10 years ago, there has been little progress in understanding the underlying cause of eclampsia.3

While eclampsia remains a life-threatening complication of pregnancy, there are no reliable tests or symptoms for predicting the development of seizure. Magnesium sulfate (MgSO₄) is the primary treatment in preeclamptic women for prevention
of eclampsia, but its use is controversial because of potential serious side effects including areflexia and respiratory distress. This review highlights our current understanding of how pregnancy and preeclampsia affect the brain and cerebral circulation to promote neuronal excitability (seizure) and ways in which to manage seizure in preeclamptic women.

MECHANISMS OF SEIZURE DURING PREECLAMPSIA

Role of cerebral circulation and autoregulation of cerebral blood flow in eclampsia

The mechanism by which women experience a seizure during preeclampsia is not known. Adding to the difficulty is the observation that women with eclampsia show varying degrees of haemorrhage, cerebral oedema and vasculopathy. Two hypothesis regarding the cause of eclampsia have received the most attention, both of which focus on the cerebral vasculature and autoregulation of cerebral blood flow (CBF) during hypertensive episodes. The first concept is that the cerebral circulation is in a state of “overautoregulation” during preeclampsia in response to elevated cerebral perfusion pressure causing ischaemia. This hypothesis is based on brain imaging in eclamptic women that revealed areas of vasospasm. Since cytotoxic and vasogenic oedema have been demonstrated in eclampsia, ischaemic brain injury may be a cause of seizures. However, the reversibility of both neurologic symptoms and neuroradiologic lesions within days or weeks postpartum in most cases argues against true cerebral ischaemic necrosis. In fact, clinical and neuroimaging findings are more consistent with vasogenic oedema. For example, the neuroradiologic hallmarks of eclampsia are reversible abnormalities that appear hypodense on computed tomography (CT) and hyperintense on T2-weighted magnetic resonance (MR) images, both suggestive of oedema. Further studies using diffusion-weighted MR images reveal these hyperintense areas on MR have a high diffusion coefficient value, indicative of vasogenic rather than cytotoxic oedema.

The second hypothesis on the underlying mechanism for the neurological symptoms and oedema formation during eclampsia is that it is a form of hypertensive encephalopathy during which a rapid rise in blood pressure overcomes the myogenic vasoconstriction of cerebral arteries and arterioles causing the loss of autoregulatory capacity and blood-brain barrier (BBB) disruption with subsequent vasogenic oedema. This process has more recently been termed the posterior reversible encephalopathy syndrome (PRES) in order to highlight the propensity for oedema formation to occur in the posterior cerebral cortex. The propensity for hyperperfusion and oedema to form posteriorly is unexplained, but many suggest decreased sympathetic innervation of the posterior cerebral arteries for lack of a better explanation. However, there are a number of reasons other than sympathetic innervation as to why oedema formation would be increased posteriorly. For example, capillary density is increased in the posterior brain...
region, an effect that would increase transcapillary filtration and promote greater oedema in that region of the brain during acute hypertension. In any case, the diagnosis of eclampsia as a form of hypertensive encephalopathy or PRES has arisen from numerous similarities in clinical presentation including comparable imaging findings on CT and MR, the same neurological features, including severe and persistent headache, uncontrolled vomiting, cortical blindness and seizures, and the prompt reversibility of symptoms after blood pressure has been restored.

Clinical studies consistently find little correlation between blood pressure and seizure during pregnancy. In fact, ~40% of women with eclampsia have seizure in the setting of a normal blood pressure and without proteinuria. These findings suggest that preeclampsia is not necessarily a prodrome for eclampsia and implies that factors or processes associated with normal pregnancy may promote the eclamptic seizure. As a result, our own studies have focused on the adaptation of the brain and cerebral circulation to pregnancy and how those adaptations might contribute to the neurological complications of preeclampsia and eclampsia.

**Effect of pregnancy on cerebral haemodynamics**

In normotensive adults, CBF is maintained at approximately 50 mL per 100 g of brain tissue per minute provided cerebral perfusion pressure is in the range of ~60 to 150 mmHg. Above and below this limit, autoregulation is lost and there is a linear relationship between CBF and mean arterial pressure. The importance of understanding how pregnancy and preeclampsia affect autoregulation of CBF is that significant brain tissue damage occurs including BBB disruption and oedema formation when autoregulatory mechanisms are lost. At pressures above the autoregulatory limit, the myogenic vasoconstriction of vascular muscle is overcome by the excessive intravascular pressure, and forced dilatation of cerebral vessels occurs. The loss of myogenic tone during forced dilatation decreases cerebrovascular resistance and increases CBF, resulting in hyperperfusion, BBB disruption and vasogenic oedema formation. This sequence of events is considered the underlying cause of neurological complications of hypertensive encephalopathy, PRES and in eclampsia associated with an elevated arterial pressure.

Because numerous studies have shown eclampsia can occur at normal blood pressure, it has been suggested that autoregulation of CBF is shifted during pregnancy to the lower range of pressures. Thus, forced dilatation of cerebral arteries and arterioles would occur at lower pressures, causing vasogenic oedema at pressures that, outside of pregnancy, would be considered within the autoregulatory range. However, studies of normal human and animal pregnancy reveal that autoregulation is intact and unchanged from the nonpregnant state. In our laboratory, we used a rat model of pregnancy to measure autoregulation of CBF and found there was no difference between nonpregnant and late-pregnant animals in autoregulatory capacity or the pressure at which breakthrough occurred (Figure 1A). Importantly, only pregnant animals developed significant oedema based
on measurements of brain water content (Figure 1B). Thus, it appears that at least in animals, pregnancy predisposes the brain to oedema when blood pressure is acutely elevated to the point of breakthrough of autoregulation. However, the autoregulatory curve is not shifted to lower pressures during pregnancy.

In a recent study, we explored the mechanisms by which pregnancy caused an increase in oedema formation in response to acute hypertension. 34 We used microspheres to measure absolute changes in CBF under basal conditions and in response to acute hypertension. While pregnancy was not associated with differences in CBF, it was associated with a ∼40% increase in CBF in response to autoregulatory breakthrough (Figure 2). The increase in CBF in the pregnant animals was accompanied by selective outward remodeling of penetrating brain arterioles due to pregnancy-induced activation of peroxisome proliferator-activated receptor gamma (PPARγ; Figure 3). Thus, it appears that pregnancy promotes a decrease in small vessel resistance in the brain when blood pressure is acutely elevated, an effect that would be expected to increase BBB permeability and oedema formation. These findings are in agreement with transcranial Doppler and MR imaging studies of humans during normal pregnancy.48,49 Thus, pregnancy appears to alter the structure of cerebral parenchymal vessels to increase vascular space. However, because of the prominent role of large arteries to vascular resistance in the brain, the increase in vascular space is inconsequential until pressures rise to the point of forced dilatation. Once large artery resistance is decreased and hydrostatic pressure is transmitted to the capillary bed, there is greater BBB disruption and oedema formation (Figure 4).
Effect of preeclampsia on cerebral haemodynamics

Impaired CBF autoregulation is thought to be a major influence in the development of eclampsia due to decreased vascular resistance and increased pressure on the microcirculation promoting vasogenic oedema.\textsuperscript{27,50,32–35} Numerous investigators have attempted to measure cerebral perfusion pressure and autoregulation of CBF in women with preeclampsia and eclampsia.\textsuperscript{26,47,51–54} Most report that preeclampsia is associated with elevated cerebral perfusion pressure, a result that is not surprising given the appearance of hypertension.\textsuperscript{47,53} Whether autoregulation is intact under these conditions is unclear as some studies conclude the increased perfusion pressure was associated with increased cerebrovascular resistance, suggesting autoregulation is intact.\textsuperscript{47} In other studies, preeclampsia and eclampsia were associated with decreased vascular resistance and hyperperfusion.\textsuperscript{26,51} Dynamic CBF autoregulation, a noninvasive technique that uses physiological changes in blood pressure to assess autoregulation, was measured on patients with eclampsia and revealed a substantial disturbance in CBF autoregulation.\textsuperscript{53,54}

Whether or not autoregulation is intact in women with preeclampsia and eclampsia may be related to the occurrence of seizure. Seizure causes excessive neuronal excitation and significant increases in sympathetic outflow that releases large amounts of epinephrine and norepinephrine into the circulation.\textsuperscript{55,56} The resulting increased peripheral vascular resistance during seizure causes acute hypertension and PRES-like symptoms including autoregulatory breakthrough and oedema formation.\textsuperscript{57} It is therefore possible that seizure actually precedes and is the cause of hypertension and loss of autoregulation in the brain in women with eclampsia.
Figure 3 Effect of pregnancy and PPARγ activation on remodeling of brain penetrating arterioles. Penetrating brain arterioles isolated from nonpregnant control (NP), late-pregnant control (LP), NP treated with the PPARγ agonist rosiglitazone for 3 weeks to mimic pregnancy (NP+Rosi) or LP and treated with the PPARγ inhibitor GW9662 (LP+GW9662) for the last half of pregnancy were used to measure lumen diameter and wall thickness under pressurized conditions. (A) Passive pressure vs. diameter curves of cerebral (pial) arteries from NP and LP rats. Pregnancy did not affect the luminal size of cerebral arteries. (B) Penetrating brain arterioles from LP and NP rosiglitazone-treated animals had significantly larger lumen diameters compared to NP control and LP GW9662-treated animal; **p < 0.01 vs. NP; †† p < 0.01 vs. LP-GW. (C) Wall thickness was significantly decreased in penetrating arterioles during pregnancy and PPARγ activation; ***p < 0.01 vs. NP; † †† p < 0.01 vs. LP-GW. Thus, pregnancy and PPARγ activation cause outward hypotrophic remodeling of brain penetrating arterioles. (D) Active pressure vs. diameter curves of penetrating arterioles shows that all vessels had myogenic reactivity within the autoregulatory pressure range from 25 to 100 mmHg then underwent forced dilatation. Arterioles from LP and rosiglitazone-treated NP animals had larger lumens than NP and GW9662-treated LP animals; ***p < 0.01 vs. NP; † †† p < 0.01 vs. LP-GW. Published as Cipolla MJ, et al. J Appl Physiol 2010, Am Physiol Soc., used with permission.

The role of the BBB in eclampsia

If the primary explanation for the eclamptic seizure is that it represents a form of hypertensive encephalopathy or PRES in which severely elevated blood pressure secondary to the preeclamptic state causes autoregulatory breakthrough, BBB disruption and vasogenic brain oedema, how these events develop and proceed to
Figure 4 Summary diagram of cerebral vascular adaptation to pregnancy and the effect of acute hypertension. (A) Cerebral arteries and arterioles that lie on top of the brain give rise to smaller arterioles that penetrate into the brain tissue, passing first through the Virchow-Robin Space. After passing through this space, arterioles are closely associated with multiple cell types, including pericytes, astrocytes and neurons. Penetrating arterioles are long and largely unbranched segments of the vasculature that connect upstream vessels to the capillary microcirculation and as such contribute significantly to cerebrovascular resistance in the brain. (B) During pregnancy, penetrating arterioles undergo outward hypotrophic remodeling under the influence of PPARγ activation that is increased during pregnancy. In addition to outward remodeling of arterioles in the brain, capillary density increases. These alterations in structure appear to occur only in the vasculature associated with brain parenchyma, a segment of the vasculature in which expression of PPARγ is relatively low. Thus, we speculate that PPARγ-dependent mechanisms in brain parenchyma have a paracrine influence on the associated vasculature. We further speculate that upstream cerebral arteries, that appear unaffected by pregnancy and PPARγ activation, maintain vascular resistance that is protective in downstream microvessels in relation to hydrostatic pressure. (C) During acute hypertension, similar to what occurs during severe preeclampsia and eclampsia, forced dilatation of large cerebral arteries occurs, decreasing vascular resistance and allowing greater transmission of hydrostatic pressure to downstream arterioles and capillaries. Because the arterioles have undergone outward hypotrophic remodeling, wall stress is significantly elevated, an effect that could promote increases in permeability as well as rupture and haemorrhage (denoted in the figure by the black arrows). Increases in hydrostatic pressure also affect the capillary bed to increase transcapillary filtration and promote oedema formation that is greater during pregnancy due to decreased vascular resistance and increased vascular volume and capillary density. Published as Cipolla MJ, et al. J Appl Physiol 2010, Am Physiol Soc, used with permission.
into the brain tissue are the presence of high electrical resistance tight junctions that limit paracellular transport and the low rate of pinocytotic vesicle formation that reduces transcellular transport. In addition, cerebral endothelial cells have a very low rate of hydraulic conductivity, making the passage of water into the brain in response to hydrostatic pressure limited. These unique features of the BBB make the cerebral endothelium more similar to epithelium than to endothelium, a protective feature that limits brain oedema formation.

When there is an increase in permeability of the BBB, either via transcellular or paracellular routes, vasogenic oedema can occur. The expansion of the extracellular space during vasogenic oedema occurs within the closed space of the skull, causing progressive brain compression and the classic neurological symptoms of headache, nausea, vomiting, cortical blindness, and convulsions. BBB disruption can also allow the passage of damaging proteins and serum constituents into the brain that can cause seizure. Studies have found that increased BBB permeability alone is sufficient to provoke seizure activity. Passage of other damaging proteins, most notably albumin, into the brain parenchyma is also seizure provoking. Thus, the BBB has a central role in the development of neurological complications, including seizure.

**BBB permeability during preeclampsia and eclampsia**

Increased BBB permeability in women with severe preeclampsia and eclampsia can be caused by several factors. First, severely elevated microvascular pressure secondary to preeclampsia increases transcapillary filtration in the brain and vasogenic oedema formation. Studies have shown that forced dilatation of cerebral artery and arteriole myogenic tone causes a substantial increase in pinocytotic vesicle formation in cerebral endothelium. Thus, factors or events that cause increased hydrostatic pressure on the cerebral microcirculation, such as autoregulatory breakthrough that has been shown to occur in PRES and eclampsia, have the potential to increase vasogenic oedema formation and passage of damaging proteins into the brain parenchyma.

Second, there could be pregnancy- or preeclampsia-induced increases in BBB permeability without an increase in hydrostatic pressure, such as an effect on tight junctional protein expression. Tight junctions are not passive structures, but can be rapidly modulated by signaling pathways that affect the structure of the tight junction and the organization of the endothelial cell actin cytoskeleton. Similarly, transcellular transport is regulated by mediators such as vascular endothelial growth factor (VEGF) and other inflammatory mediators. Recently, we found that plasma from severely preeclamptic women significantly increased BBB permeability compared to normal pregnant women, an effect that was completely prevented by a non-selective VEGF receptor tyrosine kinase inhibitor (Figure 5). This suggests there are circulating factors during preeclampsia that increase BBB permeability.
independent of inherent changes in barrier properties because permeability in response to plasma was assessed in cerebral veins from normal pregnant animals.

**Role of elevated TNF-α during preeclampsia on the BBB and seizure**

Another important feature of the BBB important for seizure induction is that it regulates passage of cytokines from the blood into the brain. Most cytokines do not readily cross into the brain, but rather are regulated by transporters on the BBB.\(^7^5\) This may be of particular importance during preeclampsia because it has been shown this condition is associated with a large increase in proinflammatory cytokines in the blood, most notably tumor necrosis factor alpha (TNF-α).\(^7^6\)–\(^7^8\) Elevated TNF-α could have significant effects on the brain during preeclampsia. Unlike most cytokines, circulating TNF-α can cross the BBB through receptor-mediated endocytosis.\(^7^9\) The binding of TNF-α to its receptors on the BBB increases paracellular permeability that can then promote vasogenic oedema.\(^8^0\) In addition, TNF-α is a recognized innate cytokine that initiates peripheral and vascular inflammatory responses.\(^8^1\) Peripheral
inflammation has been shown to cause TNF-α dependent microglial activation that increases neuronal excitability in the brain.\(^{82,83}\) TNF-α up regulates endothelial cell adhesion molecules such as E-selectin, ICAM-1 and VCAM-1 that facilitate passage of leukocytes into the brain.\(^{80}\) Leukocyte infiltration of the BBB can provoke seizure by activating microglia that then produce TNF-α.\(^{84}\) TNF-α production in the brain can both lower the seizure threshold and cause seizure itself\(^{82,83}\) via effects on AMPA and GABAA receptors.\(^{85}\) The importance of TNF-α in seizure induction is underscored by the findings that TNF-α infused into rats increases seizure susceptibility and decreases seizure threshold.\(^{82,83}\) How TNF-α is regulated during pregnancy, both peripherally through induction of soluble receptors and at the BBB where there could be an effect of receptor expression is not known. However, the observation that TNF-α crosses the BBB by receptor-mediated endocytosis suggests regulation is possible. In fact, one study found that while TNF-α was significantly elevated in preeclamptic women, the fractional excretion was less despite proteinuria.\(^{77}\) The decreased clearance and renal excretion of TNF-α during preeclampsia could represent regulation by soluble receptors. How pregnancy or preeclampsia affect TNF-α receptors on the BBB is unknown but seems an important area for investigation given the central role this cytokine has in seizure induction.

**Role of aquaporins (AQPs) in seizure and eclampsia**

The AQPs are a family of channel forming transmembrane proteins that facilitate the movement of water, glycerol, and other solutes across the plasma membrane of cells.\(^{86–89}\) Aquaporin 4 (AQP4), the predominant aquaporin in the brain, has been localized to the astrocytic endfeet surrounding blood vessels, and is not in endothelium.\(^{91–93}\) One role of astrocytic AQP4 may be to regulate water transport once it has crossed the BBB, mainly because of the highly polarized localization of AQP4 in the perivascular endfeet of astrocytes.\(^{89,94}\) AQP4 in astrocytes is thought to contribute to BBB properties by taking up excess water brought into the brain by disruption of the BBB.\(^{94}\) Numerous studies that have shown increased AQP4 expression during conditions that cause vasogenic brain oedema, including brain tumors, focal ischaemia, and brain injury.\(^{94–98}\) Interestingly, AQP4 is increased in the brain during pregnancy.\(^{99,100}\) The effect of increased expression of AQP4 in the brain during pregnancy is unclear, but may affect seizure threshold as AQP4 knockout mice are less susceptible to seizure.\(^{101}\)

**Animal models of preeclampsia and eclampsia**

Because of the difficulty in predicting and studying neurological complications associated with severe preeclampsia and eclampsia, there is a need for animal models to help us understand these conditions. Animal models of preeclampsia have been described and many have been useful for understanding particular aspects
of this condition. For example, reduced uteroplacental perfusion (RUPP) and high soluble fms-related tyrosine kinase 1 (sflt-1) have been used extensively as models of preeclampsia, however, it is not known whether they mimic other pathological events, such as changes at the BBB or neuronal excitability that occur during preeclampsia. Endothelial dysfunction and oxidative stress have been measured in vascular beds outside the brain in women with preeclampsia. It is reasonable to assume that similar changes occur in the cerebral circulation. If so, these events could have a significant influence on brain excitability as upregulation of adhesion molecules could cause the passage of leukocytes into the brain parenchyma and promote seizure. However, it cannot be assumed that events that happen peripherally are mimicked by the BBB because of the unique nature of the cerebral endothelium. In addition, neurological complications have yet to our knowledge been assessed in any model of preeclampsia. Thus, animal models of preeclampsia may be useful for understanding the development of hypertension, proteinuria and placental ischaemia during pregnancy, but they have yet to be applied to understanding how neurological complications arise.

MANAGEMENT OF ECLAMPSIA

Consequences of seizure

Although the complications of seizure during pregnancy are rare, prolonged generalized tonic-clonic seizure activity during pregnancy causes maternal acidosis, hypoxia and brain trauma, including haemorrhage. Abruptio placenta is common after prolonged seizure, occurring in 20–50% of women. Convulsive seizures are also dangerous for the fetus. The fetal heart rate slows during and for up to 20 minutes after a maternal convulsion, suggesting fetal hypoxia. In addition to acute events, recent studies conclude that women with prior eclampsia have increased white matter lesions and lasting psychological and cognitive effects. Thus, maternal convulsions cause trauma to mother and fetus acutely and have long-lasting negative consequences.

Clinical presentation, diagnostic evaluation and differential diagnosis

Headache and visual disturbances with occipital lobe oedema are common symptoms of eclamptic encephalopathy. Hyperperfusion and oedema occur most often and more pronounced posteriorly in the subcortical white matter of the occipital lobes, although grey matter and anterior circulation is involved in the most severe cases. Seizures may be focal or secondary generalized. Some women have neurological complications without seizures, including confusion, aphasia, cognitive deficits and depressed level of consciousness. Although hypertension and preeclampsia occur most often in
eclamptic women, it is not uncommon for women to present with seizures in late-pregnancy and early postpartum with mild or absent hypertension, as discussed above.

The diagnosis of eclampsia is based on the findings of encephalopathy or seizures in late-pregnancy or postpartum with imaging. Computed tomography or MR imaging should be used to provide evidence of oedema and to rule out alternative brain lesions or haemorrhage. MR imaging with diffusion-weighted imaging is useful to distinguish reversible oedema from ischaemic stroke. Patients may have intracerebral or cerebellar haemorrhage due to vascular anomalies or the trauma associated with seizure. Other common causes of seizure during pregnancy other than eclampsia include idiopathic epilepsy, trauma, congenital defects, neoplasms, meningitis, intracerebral haemorrhage, and drug and alcohol toxicity.

Management of the eclamptic patient

The mainstays of management of the neurological symptoms of severe preeclamptic and eclamptic patients are the rapid lowering of blood pressure, administration of MgSO4 and delivery of the fetus. Mean arterial blood pressure should be lowered in patients with severe hypertension by 15–20%. Intravenous labetalol, hydralazine, or nicardipine work rapidly and safely. Nitroprusside and nitroglycerine contain cyanide and have the potential to cause fetal toxicity. Angiotensin-converting enzyme (ACE) inhibitors are recognized teratogens and contraindicated throughout pregnancy. Fluid therapy can be beneficial to eclamptic patients and those with severe preeclampsia because of the associated volume contraction (or lack of expansion of plasma volume associated with normal pregnancy), however, this should be monitored closely in women with severe and persistent hypertension, oliguria and pulmonary oedema.

Prevention of the eclamptic seizure in a woman with preeclampsia is obvious and justified. Traditionally, obstetricians have favored the use of MgSO4 for the prevention of the eclamptic convulsion whereas neurologists have favored anti-epileptic agents such as phenytoin. A single first-onset seizure that occurs during pregnancy and resolves within minutes can usually be managed without anti-convulsant agents. MgSO4 has been shown to be more effective than anti-convulsant agents including phenytoin and is the treatment of choice for preventing eclampsia in preeclamptic women.109–111 Therapy is initiated with a loading dose of 4g MgSO4 followed by 1g/hr infusion. Serum levels do not need to be monitored as long as urine output exceeds 50mL per hour. A supplemental dose of 2g can be given if seizure recurs.

There is concern over the use of high doses of MgSO4. Dose-related depression of neuromuscular transmission occurs in preeclamptic women receiving traditional MgSO4 therapy.112 Studies also show there is little or no change in electroencephalograms (EEGs) of eclamptic women during MgSO4 treatment.112,113 At levels of 8 to 10 mEq/L, tendon reflexes are depressed. At levels of 10 to 12 mEq/L, there is a high risk of respiratory depression. Renal insufficiency can also occur with high MgSO4. Thus, respiratory function and urine output should be followed closely. It is more important to follow women for signs of neurological depression rather than
serum levels and adjust therapy accordingly. When petellar reflexes are lost, MgSO₄ should be discontinued. If respirations are depressed in association with elevated magnesium levels, calcium gluconate should be given. Although MgSO₄ is more effective at preventing eclamptic convulsions than phenytoin or diazepam, refractory seizures should be aggressively treated with traditional anti-convulsant agents when adequate magnesium has failed. The cause of the seizure should be determined and a decision made on whether further seizures are likely, and thus the need for anti-epileptic medication. If needed, monotherapy with pentobarbital or phenytoin are effective.

**Mechanisms of MgSO₄ for seizure prevention**

MgSO₄ is the therapy of choice for preventing eclamptic convulsions. The mechanisms by which MgSO₄ is effective at preventing eclamptic convulsions are likely multifactorial and have been recently reviewed and will only be summarized here. MgSO₄ is a calcium antagonist and as such could inhibit vascular smooth muscle contraction. MgSO₄ is a potent vasodilator, however, its effects in the cerebral circulation are considerably less effective than systemic vasculature. In addition, the sensitivity to MgSO₄ is decreased in cerebral arteries from late-pregnant and postpartum animals, suggesting MgSO₄ is not acting as a vasodilator in the cerebral circulation. MgSO₄ has been shown to protect the BBB, likely through its calcium antagonist effects in the cerebral endothelium. When pregnant rats were treated with clinically relevant doses of MgSO₄, they had significantly less BBB permeability during acute hypertension. Thus, MgSO₄ could prevent recurrent seizure by protecting the BBB. Lastly, MgSO₄ is an NMDA receptor antagonist and thus would act as an anti-convulsant if it were present at a high enough concentration in the brain.

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