OBG MANAGEMENT

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Judicious use of magnesium sulfate for eclampsia

The landmark Magpie study confirmed magnesium's effectiveness in treating and preventing pregnancy-related seizures. Some Ob/Gyns fear side effects and toxicity, however. This practical guide tells how to assess risk and select the appropriate regimen.

Although magnesium sulfate has been used to treat eclampsia since the 1920s, the most compelling evidence of its effectiveness has come in the past year. Yet some Ob/Gyns hesitate to use this agent because of potential side effects and the risk of toxicity.

Last year's headline-grabbing Magpie Trial[1] confirmed a previous, smaller randomized study[2] as well as a number of small controlled trials[3] indicating that magnesium sulfate is better than placebo[1,2] for seizure prophylaxis. Other large, randomized trials have demonstrated the drug's superiority to nimodipine[4] and phenytoin[5] in preventing convulsions and to diazepam and phenytoin[6] as therapy for eclampsia (**TABLE 1**).

As a result, magnesium sulfate remains a reliable tool for preventing eclampsia.[3] Because clinical symptoms and signs are notoriously unreliable in predicting which gravidas will develop seizures, it is reasonable to administer magnesium at the time of diagnosis to all preeclamptic patients who are to be delivered.

This article reviews the practical implications of recent findings on prophylactic and therapeutic use, patient selection and risk assessment, and administration and monitoring protocols.

KEY POINTS

- Give magnesium sulfate at the time of diagnosis to all preeclamptic patients who are to be delivered.
- Administration of magnesium sulfate for new-onset hypertension and preeclampsia remote from term is controversial.
- Even with therapeutic serum concentrations of magnesium, convulsions are possible.
- Magnesium sulfate should be administered for 24 hours after delivery or after the last postpartum seizure.
- Safe administration requires vigilant monitoring of reflexes, respiratory status, and urine output.

Magnesium increases vasodilatation

The prophylactic and therapeutic benefits of magnesium likely derive from its ability to counteract vasospasm; the mechanism by which magnesium protects against seizures has not been established.

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TABLE 1

Incidence of seizures according to therapy

PROPHYLAXIS

STUDY	THERAPY GROUPS	SEIZURES (%)	PREECLAMPSIA DEFINED AS . . .	STUDY CHARACTERISTICS
Magpie Trial[1]	Magnesium	0.8	BP ≥140/90 mm Hg, proteinuria, nulliparity	n = 10,110, *P*<.0001
	Placebo	1.9		
Coetzee et al[2]	Magnesium	0.3	Presence of 2 or more of the following: diastolic BP ≥110 mm Hg, proteinuria, prodromal symptoms	n = 699, *P*<.003
	Placebo	3.2		
Belfort et al[4]	Magnesium	0.8	BP ≥140/90 mm Hg and proteinuria with 1 or more of the following: headache, clonus, visual disturbances, epigastric/right upper quadrant pain, oliguria, pulmonary edema, elevated liver enzymes, elevated creatinine, hemolysis, thrombocytopenia, intrauterine growth retardation, oligohydramnios	n = 1,650, *P*≤.01
	Nimodipine	2.6		
Lucas et al[5]	Magnesium	0	BP ≥140/90 mm Hg	n = 2,138, *P*<.004
	Phenytoin	0.9		

TREATMENT

STUDY	THERAPY	RECURRENT SEIZURES (%)	STUDY CHARACTERISTICS
Eclampsia Trial Collaborative Group[6]	Magnesium	13.2	n = 905, *P*<.0005
	Diazepam	27.9	
Eclampsia Trial Collaborative Group[6]	Magnesium	5.7	n = 775, *P*<.0005
	Phenytoin	17.1	

BP = blood pressure

Transcranial Doppler ultrasound studies indicate that magnesium increases cerebral blood flow in preeclamptic[7] and eclamptic women.[8] Magnesium-induced vasodilatation involves a number of factors,[9] such as blockade of calcium entry into vascular smooth muscle, antagonism of intracellular calcium activity, and release of nitric oxide[10] and prostacyclin.[11]

In addition, magnesium inhibits platelet aggregation and protects endothelial cells from injury by free radicals. This action, along with stabilization of vascular tone, can potentially reduce the risk of cerebral thrombosis.[9,12] The anticonvulsant effects of magnesium in clinically relevant doses do not involve depression of the neuromuscular junction.[13]

Magnesium also can directly affect the central nervous system by antagonizing N-methyl-D-aspartate receptor activation, which inhibits calcium influx and subsequent neuronal injury.[9] This mechanism of action requires that plasma magnesium pass freely into the interstitial fluid of the brain. (Magnesium has already been shown to readily enter the cerebrospinal fluid after intravas-

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Mistaken identity: Tracing the etiology of eclampsia through time

Eclamptic women have undergone renal decapsulation, spinal fluid drainage, implantation of the ureters into the colon, mastectomy, and oophorectomy. Each of these treatments was once considered rational based on hypotheses about the cause of eclampsia.

Although descriptions of convulsions in pregnancy date to antiquity, it was not until the 18th century that eclampsia was distinguished from tonic-clonic seizures in the nonpregnant state.

Eventually eclampsia was thought to be one of the pregnancy toxemias caused by a circulating toxin that acted on "nerve centers."[1] Thus, in the 1920s, a popular treatment for eclampsia involved eliminative measures, such as stomach lavage and high colonic flushings, as well as phlebotomy. Later, sedation with morphine sulfate and chloral hydrate without bleeding, popularized by Stroganoff in the 1930s, became prominent.[2,3]

Magnesium enters the picture. In 1924, an intern at Los Angeles General Hospital suggested using intravenous magnesium sulfate to treat eclamptic seizures, knowing that it controlled tetanic convulsions and had mild sedative effects. As a result, intravenous magnesium sulfate was added to the elimination protocol for eclampsia. In the initial trial, which included 17 eclamptic women, all seizures were controlled by magnesium, and maternal mortality was only 6%, compared with the historical average of 30%.[4]

By the 1960s, magnesium therapy combined with antihypertensive medication and delivery had been adopted in the United States as frontline therapy for eclamptic seizures—an approach that reduced maternal mortality to 5% or less.[5-8] The associated perinatal mortality, which was due largely to abruptio placentae, prematurity, and complications of fetal growth restriction, also was substantially reduced—from 30% to about 10%.[5-8]

Criticism of this therapy has centered on 2 perceptions of the pharmacology of magnesium: It acted only at the neuromuscular junction, and it did not penetrate the blood-brain barrier.[9,10] These effects seemed less than optimal when compared to those of newly developed antiepileptic medications, which had well-described mechanisms of action involving rapid transfer from blood to brain and stabilization of neuronal membranes.

Newer findings. In the 1990s, however, small controlled studies suggested that magnesium is surprisingly effective in preventing seizures in both preeclampsia and eclampsia.[11] Recurrent seizures occurred in 9% of eclamptic women who received magnesium, which was about 40% less than in those given the anticonvulsants diazepam or phenytoin. In patients with severe preeclampsia, magnesium prophylaxis reduced the risk of seizures to 0.9% from 2.8% in women who received antihypertensive agents but no anticonvulsants. Large randomized trials confirmed these findings.[12-16]

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Quick facts on eclampsia

Incidence

• The maternal death rate for eclampsia varies geographically, according to the quality of the area's health-care system. In developed countries, the rate ranges from 1.8% to 7.2%, while in countries with less available medical care, it can exceed 25%.[1-3]

• Although the maternal mortality rate for preeclampsia is lower (approximately 0.34% in the United States) than for eclampsia, preeclampsia still accounts for more than half of the maternal deaths linked to pregnancy "toxemia."[3,4]

• Eclampsia-associated perinatal mortality remains high—about 10%—even in developed countries.

Risk of eclampsia

• Eclampsia usually involves reversible cerebral edema and endangers the mother principally through seizure-related aspiration (2%) or underlying disturbances such as acute renal failure (5%), pulmonary edema (4%), cardiorespiratory arrest (3%), and abruptio placentae.[5,6]

• Eclamptic seizures also carry the risk of permanent brain injury or death when they are associated with hemorrhagic or ischemic stroke or with tentorial herniation.

• Recurrent seizures—in which prolonged activation of N-methyl-D-aspartate receptors can produce toxic brain levels of calcium—also may lead to permanent injury and death.

• About 7% of eclamptic women develop significant neurologic sequelae, including aphasia, psychosis, cortical blindness, weakness, coma, or cerebrovascular accident.[7]

• More than half of eclamptic women who die within 48 hours after the onset of convulsions have cerebral petechiae, hemorrhage, or ischemic softening (nonhemorrhagic) of the brain,[8] which may result from thrombosis of cerebral vessels[9] or other complications of cerebral vasospasm.[8,10]

• Necrosis of the walls and endothelium of precapillary arterioles also can occur.

• Cerebral edema in gross specimens has not been a consistent finding at autopsy.[8,11] Although this seems to run counter to expectations, a detailed microscopic analysis of the brain would be necessary to identify focal edema affecting a small brain sector.

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cular injection.[14]) The extent to which blockade of N-methyl-D-aspartate receptors contributes to magnesium prophylaxis and therapy remains to be established.

Women with preeclampsia or eclampsia often have electroencephalogram abnormalities that typically involve diffuse slowing (delta waves). These nonspecific electroencephalogram changes develop independently of arterial pressure and are not suppressed by intravenous (IV) magnesium.[15,16]

Give magnesium to all preeclamptic patients to be delivered

Clinical symptoms and signs are unreliable predictors of which pregnant women will

A look at pathophysiology

Over the normal range of arterial pressure, cerebral blood flow and capillary hydrostatic pressures remain relatively constant thanks to accompanying adjustments in cerebral vascular resistance. But when arterial pressures are high, elevations in vascular resistance may not completely compensate for them. Thus, capillary blood flow and hydrostatic pressure are increased, disrupting endothelial tight junctions and promoting leakage of small ions and water into the brain parenchyma. The result is cerebral edema and convulsions.

Yet an increase in arterial pressure cannot be the sole mechanism at work, since eclampsia can occur in apparently normotensive patients. Nor is the risk of seizures in preeclamptic women directly proportional to the rise in arterial pressure. Cerebral vasogenic edema may also result from disruptions in cerebral vascular resistance and/or from increased capillary permeability due to endothelial dysfunction or injury, which are unrelated to changes in arterial pressure.[1,2] Cytotoxic edema as a result of vasoconstriction or infarction[3,4] is another possible mechanism, as are disturbances in brain metabolism.

Imaging studies. Until recently, imaging studies were unable to distinguish between vasogenic and cytotoxic edema; both present as hypodensities on computed tomography and magnetic resonance imaging.[5-7] But diffusion-weighted imaging techniques demonstrate that focal vasogenic edema, which disappears with resolution of clinical symptoms, is more consistently observed in eclamptic women.[8,9] Petechial brain hemorrhages also have been detected in patients with eclampsia or severe preeclampsia.[10]

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develop seizures. For example, eclampsia can occur in gravidas without hypertension or proteinuria. When these conditions are present, the risk of eclampsia is not proportional to their severity.[1,17-20] Thus, given the relative safety of magnesium therapy with appropriate monitoring, a reasonable approach is to initiate therapy at the time of diagnosis in all preeclamptic patients who are to be delivered.

If all clinicians followed this management approach, about 5% of gravidas would receive therapy to prevent a rare but potentially injurious event, although for most (more than 97%) the treatment would be unnecessary.

Pregnancy-induced hypertension. The administration of magnesium sulfate to women with new-onset hypertension (arterial blood pressure of 140/90 mm Hg or more) without proteinuria is controversial. Some physicians do not give magnesium to these patients because the risk of eclampsia is lower than in those with preeclampsia (as characterized by hypertension and proteinuria).

About 25% of women with pregnancy-induced hypertension will develop preeclampsia, but those who will go on to develop proteinuria or seizures cannot be identified prospectively. For this reason, other physicians favor prophylactic magnesium for this group.[5] They point out that, once a

TABLE 2

Magnesium sulfate administration*

INTRAVENOUS INFUSION	
Normal renal function	
Loading dose:	4-6 g over 10-15 min
Maintenance infusion:	2 g/h
Oliguria†	
Loading dose:	4 g over 15 min
Maintenance infusion:	1 g/h
INTRAMUSCULAR INJECTION	
Loading dose:	5 g in each buttock (10 g total)
Maintenance injection:	5 g in 1 buttock (5 g total) every 4 h

*All dosages refer to the hydrated form ($MgSO_4$ $7H_2O$)
†Must continuously monitor pulse oximetry and measure magnesium levels 2 hours after starting the infusion. Calcium chloride or calcium gluconate and emergency intubation should be immediately available, and fluids should be restricted provided renal failure is not due to hypovolemia.

seizure has occurred, recurrence may be more difficult to prevent. We do not routinely administer magnesium to women with pregnancy-induced hypertension unless they have or develop prodromal symptoms (e.g., headache, epigastric pain), high arterial pressures (more than 160/105 mm Hg), proteinuria, or hemolysis, elevated liver enzymes, and low platelets syndrome.

Clinical symptoms and signs are unreliable predictors of which pregnant women will develop seizures.

Mild preeclampsia. Similar arguments also have been given for and against magnesium prophylaxis in women with mild preeclampsia. In the Magpie trial, magnesium sulfate administration was associated with a reduction in the incidence of eclampsia of approximately 56% (placebo: 1.6%; magnesium: 0.7%) in 7,468 gravidas who did not have severe preeclampsia by the definition used in the study. In light of this evidence, we have maintained our practice of giving magnesium to those with mild preeclampsia.

Preeclampsia remote from term. The role of magnesium in the management of patients with preeclampsia remote from term (less than 34 weeks of gestation), when continuation of the pregnancy can provide fetal benefit, also is unclear. We administer magnesium sulfate for the first 24 to 48 hours of hospitalization in patients with severe preeclampsia.

The multiple mechanisms by which magnesium counters preeclampsia-induced vasoconstriction have the potential to improve blood flow in the pulmonary, renal, hepatic, gastrointestinal, and placental circulations, as well as the central nervous system, thus delaying the need for delivery. Whether prolonged infusion of magnesium can be an effective component of therapy to delay delivery and improve fetal outcome remains to be determined.

Abruptio placentae. Magnesium also may reduce the risk of abruptio placentae,[1] although 1 small study did not find IV magnesium infusion beneficial in this setting.[20]

Administration

Protocols based on observational data. Therapeutic magnesium concentrations in maternal plasma have been deduced from empiric studies.[21] In a protocol for eclampsia, both IV and intramuscular (IM) administration of magnesium sulfate were associated with initial maternal plasma magnesium levels of 7 to 9 mEq/L, with subsequent stabilization at 4 to 7 mEq/L. For patients with preeclampsia, IM administration of magnesium resulted in concentrations of 3.5 to 6 mEq/L. Because these protocols were generally effective, 4 to 7 mEq/L has been used as a therapeutic range, though no formal dose-response testing has been performed.

The lower limit of target plasma magnesium concentrations is about twice the mean physiologic concentration (approximately 1.7 mEq/L).

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Optimum IV infusion rate. Continuous IV infusion of magnesium sulfate—rather than IM injection—is now the norm in most US hospitals.[22] However, the infusion rate of 1 g/h, which is generally effective for prophylaxis and treatment of seizures,[22] often fails to meet target maternal serum magnesium concentrations.[19] Thus, an infusion rate of 2 g/h is recommended (**TABLE 2, page 50**).

We generally start with a loading dose of 4 to 6 g over 10 to 15 minutes in women with normal renal function, using the hydrated form of the drug. In patients with oliguria, we give a loading dose of 4 g over 15 minutes, followed by a maintenance infusion of 1 g/h. Even at the higher infusion rate (2 g/h), plasma levels are usually in the lower therapeutic range.[19]

IM injection remains an option. Intravenous infusion of magnesium sulfate may not always be practical—for example, when infusion pumps or close patient supervision are unavailable, or when a patient is transported to another facility. Intramuscular injections can be used in these situations.

We give an initial dose of 5 g (10 mL as a 50% solution) of magnesium sulfate with 1 mL of 2% xylocaine deep in the upper outer quadrant of each buttock (10 g total magnesium sulfate). The magnesium solution is injected in several different sites as the needle (3 inches long, 20 gauge) is advanced in muscle. Each injection should be preceded by aspiration to ensure that the needle tip is not in a blood vessel. Massaging the buttock after the injection will help disperse the magnesium in the tissue. Five grams of magnesium sulfate (10 mL as a 50% solution with 1 mL of 2% xylocaine) is subsequently administered as a single intramuscular injection every 4 hours to maintain circulating magnesium levels, provided there is no evidence of magnesium toxicity. Patients with severe preeclampsia, prodromal symptoms of eclampsia, or eclampsia should be given 4 g of magnesium sulfate intravenously (20 mL as a 20% solution) over 5 minutes to more rapidly establish therapeutic magnesium levels immediately prior to the initial intramuscular injection of 10 g of magnesium sulfate.

TABLE 3

Maternal serum magnesium concentrations associated with toxicity

	MMOL/L	MEQ/L	MG/DL
Loss of patellar reflexes	3.5–5	7–10	8.5–12
Respiratory depression	5–6.5	10–13	12–16
Altered cardiac conduction	>7.5	>15	>18
Cardiac arrest	>12.5	>25	>30

Source: Lu and Nightingale[14]

Convulsions may occur even at therapeutic levels. Even with therapeutic serum magnesium concentrations, seizures are possible.[18,23] Recurrent convulsions in patients already receiving magnesium should be treated with an additional 2 g IV magnesium sulfate administered over 5 minutes. Another 2-g dose (4 g total) can be given, but the patient must be carefully watched for signs of respiratory depression. If magnesium fails to control the seizures, additional measures are needed, such as IV anticonvulsants or muscular paralysis in conjunction with intubation and mechanical ventilation.[24]

Continue administration postpartum. Magnesium sulfate generally is administered for 24 hours after delivery or after the last postpartum seizure, although optimal length of treatment is not firmly established. The clinical state of the patient may be a useful index for individualizing duration of magnesium infusion,[25,26] but the risks and benefits of this approach have not been examined in a large patient population.

Know the contraindications. Contraindications to magnesium therapy include

TABLE 4

Monitoring guidelines for patients receiving magnesium

FUNCTION	WHEN TO MONITOR	SUSPECT MAGNESIUM TOXICITY AND COMPLICATIONS WHEN ...
Patellar reflexes	Every 1–4 h*	Reflexes are absent
Respiratory rate	Every 1–4 h*	Rate is <14 per min
Pulmonary auscultation	Every 12 h or with development of respiratory symptoms or signs	Rales are present
Pulse oximetry	Every 1–4 h*	<95% saturation
Urine output	Every 1–4 h*	<100 mL/4 h
Serum magnesium levels	In presence of oliguria, persistent seizures, or signs of toxicity	>8 mEq/L

*Depending on clinical state

myasthenia gravis and myocardial ischemia/failure. Magnesium, which is excreted almost exclusively by the kidneys, should be administered with extreme caution to patients in renal failure (because of the risk of cardiorespiratory depression) and with care to those receiving other calcium-channel antagonists, such as nifedipine (though the incidence of significant maternal hypotension under these circumstances is low).[13]

Magnesium can interact with other cardiovascular drugs to elicit arrhythmias or reduce myocardial contractility, and can potentiate the action of muscle relaxants and anesthetics. Thus, use the drug cautiously under these conditions.

The effects of magnesium toxicity can be rapidly reversed with 1 g intravenous calcium chloride or calcium gluconate.

Risks of magnesium

At therapeutic concentrations of magnesium, about one quarter of pregnant women experience nausea, emesis, flushing, or weakness.[1] Magnesium therapy also can be associated with lethargy, blurred vision, and urinary retention.[24] Toxic effects, which vary in a dose-dependent manner (**TABLE 3, page 53**), include loss of reflexes, respiratory depression, cardiac arrhythmias, and cardiac arrest.[14]

Theoretical concerns include prolonged labor or increased blood loss at delivery, but these have not posed a significant problem in actual practice.[1,27]

Magnesium-induced neonatal depression, as evidenced by hypotonia and low Apgar scores, also may occur, but have not been observed in all studies.[28,29] Obviously, pediatricians should attend these deliveries in case such complications are encountered.

Preventing magnesium toxicity

Closely monitor the patient. Safe administration requires vigilant monitoring of reflexes, respiratory status, and urine output. Prior to initiating therapy, document deep tendon reflexes, respirations of 16 or more per minute, and urinary excretion exceeding 25 mL/h.[14] During magnesium infusion, regularly assess respiratory rate, patellar reflexes, and urine output (**TABLE 4**).

Serum magnesium levels can guide therapy in patients with signs of toxicity, renal insufficiency, or recurrent seizures, but offer no advantage over close clinical scrutiny in typical patients. Steady-state plasma magnesium levels are about the same in the fetus as in the mother to whom

magnesium is administered.[21] High fetal levels can impair fetal breathing movements, which could lower biophysical profile scores in the absence of significant fetal hypoxia.

- **Pulmonary function**. Onset of a dry cough should raise suspicion of incipient pulmonary edema. Pulmonary auscultation detects rales that can accompany disease- or therapy-related pulmonary edema. Pulse oximetry, which provides continuous arterial oxygen saturation levels, can be very helpful in alerting the health-care team to both magnesium-induced respiratory depression and significant limitations in pulmonary gas exchange that accompany pulmonary edema.
- **Urine output**. In the presence of oliguria (less than 100 mL in 4 hours), the rate of magnesium administration should be reduced by 50%.

The effects of magnesium toxicity can be rapidly reversed with 1 g IV calcium chloride or calcium gluconate. Seriously affected patients, however, may require dialysis to lower maternal magnesium concentrations, due to the long half-life of magnesium in plasma (approximately 4 hours in normal gravidas).

Also give IV calcium chloride or calcium gluconate for respiratory depression or other signs of cardiorespiratory toxicity. Immediate intubation with assisted ventilation is necessary in cases of cardiorespiratory failure. Fortunately, this phenomenon occurs very rarely with proper patient selection and rigorous surveillance. ■

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