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Magnesium Sulfate Prophylaxis in Preeclampsia: Evidence From Randomized Trials

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Introduction

In the United States, parenteral magnesium sulfate has been used for the prevention of recurrent seizures in patients with eclampsia for over 80 years. As a natural extension to its use for the treatment of eclamptic convulsions in the United States, magnesium sulfate was then adopted for seizure prophylaxis in women with varying degrees of hypertensive disorders of pregnancy.[1] In 1990, I suggested that magnesium sulfate is the "ideal anticonvulsant in preeclampsia–eclampsia."[1] That recommendation was based on personal experience and the results of few observational studies available at that time. Until recently, this recommendation was criticized as being empiric and dogmatic because it had never been tested in large randomized trials.

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During recent years, several randomized trials were reported that compared the efficacy of magnesium sulfate with other anticonvulsants in eclamptic women. In these trials, magnesium sulfate was compared with diazepam, phenytoin, or a lytic cocktail.[2–6] Only 1 of these trials was multicenter and had an adequate sample size.[2] The results of these trials were summarized by Witlin and Sibai (Table 1).[7] The overall results of these studies demonstrate that magnesium sulfate was associated with a significantly lower rate of recurrent seizures (relative risk [RR] = 0.41; 95% confidence interval [CI], 0.32–0.51) and lower rate of maternal death (RR = 0.62; 95% CI, 0.39–0.99) than that observed with other anticonvulsants (Table 2). Furthermore, there was a decreased rate of pneumonia, less need for mechanical ventilation, and fewer admissions to the intensive care unit in women receiving magnesium sulfate therapy.[7] Therefore, there is level 1

TABLE 1. Randomized Trials Comparing Magnesium Sulfate ($MgSO_4$) Therapy With Other Anticonvulsant Agents for Eclampsia

Author	Antihypertensive Therapy	Recurrent Seizures		
		$MgSO_4$	Other	
		No. (%)	No. (%)	RR (95% CI)
Dommisse[3]	Dihydralazine	0/11 (0)	4/11 (36.7)	
Crowther[4]	Dihydralazine	5/24 (20.8)	7/27 (26)†	0.8 (0.29–2.2)
Bhalla et al[5]	Nifedipine	1/45 (2.2)	11/45 (24.4)‡	0.09 (0.01–0.68)
Friedman et al[6]	Nifedipine, labetalol	0/11 (0)	2/13 (15.4)*	
Collaborative Trial[2]	NR	60/453 (13.2)	126/452 (27.9)	0.48 (0.36–0.63)
	NR	22/388 (5.7)	66/387 (17.1)	0.33 (0.21–0.53)
All studies		88/922 (9.4)	216/935 (23.1)	0.41 (0.32–0.51)

* Phenytoin.

† Diazepam.

‡ Lytic cocktail.

CI, confidence interval; NR, not reported; RR, relative risk.

evidence indicating that magnesium sulfate is the best available anticonvulsant in patients with eclampsia.[7]

Magnesium Sulfate in Preeclampsia

The primary objective of magnesium sulfate prophylaxis in women with preeclampsia is to prevent or reduce the rate of eclampsia and complications associated with eclampsia. Secondary benefits also include reduced maternal and perinatal mortalities and morbidities even in women who do not develop convulsions. In addition, in women with mild preeclampsia, a secondary benefit could be a reduction in the rate of progression to severe preeclampsia.

Magnesium Sulfate in Severe Preeclampsia

There are 2 large prospective observational studies describing the rate of eclampsia in women with severe preeclampsia not receiving prophylactic magnesium sulfate.[8,9] Both of these studies were performed at the same medical center in South Africa. The clinical criteria for severe preeclampsia in those studies were similar to those in the United States.

TABLE 2. Maternal Deaths in Trials Comparing Magnesium Sulfate ($MgSO_4$) Therapy With Other Anticonvulsant Agents for Eclampsia

Author	Comparison Group	Maternal Deaths		
		$MgSO_4$	Other	
		No. (%)	No. (%)	RR (95% CI)
Dommisse[3]	Phenytoin	0/11	0/11	
Crowther[4]	Diazepam	1/24 (4.2)	0/27	
Bhalla et al[5]	Lytic cocktail	0/45	2/45 (4/4)	
Friedman et al[6]	Phenytoin	0/11	0/13	
Collaborative	Phenytoin	10/388 (2.6)	20/387 (5.2)	0.50 (0.24–1.00)
Trial[2]	Diazepam	17/453 (3.8)	23/452 (5.1)	0.74 (0.40–1.36)
All studies		28/932 (3.0)	45/935 (4.8)	0.62 (0.39–0.99)

CI, confidence interval; RR, relative risk.

Odendaal and Hall[8] studied 1001 women with severe preeclampsia; 510 received magnesium sulfate prophylaxis based on the clinical impression of impending eclampsia and 491 women did not receive magnesium sulfate. Five patients (0.5%) developed eclampsia, 2 (0.4%) in the magnesium group (both occurred before delivery) and 3 (0.6%) in the no magnesium group (all 3 developed postpartum). Interestingly, 2 of the 3 with postpartum seizures occurred beyond 48 hours and thus would not have been eligible for their standard magnesium sulfate regimen. In a subsequent report, Hall and associates[9] reported on 318 women with preeclampsia (mostly severe and remote from term and not in labor) who were managed expectantly with antihypertensive drugs and without magnesium sulfate. Twenty-six of the women subsequently received magnesium sulfate during labor or because of antepartum seizures (n = 4). Five (1.5%) developed eclampsia; 2 (0.7%) developed within 24 hours of hospitalization, 2 (0.7%) at 8 and 14 days after hospitalization, and 1 developed 4 days postpartum. Therefore, only 2 would have been prevented by their standard magnesium sulfate prophylaxis regimen. In addition, none of the 5 women had serious morbidity because of seizures. The authors of these studies therefore questioned the need for magnesium sulfate prophylaxis in patients with severe preeclampsia.[8,9] However, it is important to note that selection bias was obvious regarding decision to use magnesium sulfate in these studies.

There are 4 large randomized, controlled trials comparing the use of magnesium sulfate to prevent convulsions in patients with severe preeclampsia (Table 3).[10–13] Two of the trials were single center,[10,11] and the other 2 were multicenter with large sample sizes.[12,13] Two of the trials were placebo-controlled,[11,12] one trial used a no treatment group,[10] and the remaining trial compared magnesium sulfate to a cerebral vasodilator (nimodipine).[13] All 4 trials allowed the use of various antihypertensive agents to control hypertension. The Magpie trial[12] included 10,110 women with preeclampsia and was conducted in 175 hospitals in 33 countries with considerable heterogeneity of clinical characteristics, obstetric care, and availability of maternal and neonatal intensive care units. In addition, many aspects of clinical characteristics or management were poorly defined or controlled at time of randomization. Some of these women received study medications antepartum during expectant management for 24 hours only (no subsequent magnesium sulfate in labor or postpartum), some were discharged home, others received drug during labor and delivery, and some were randomized only during the postpartum period.[12] Fifty percent of patients received antihypertensives before randomization and 75% received antihypertensives after randomization. Moreover, 9% received

TABLE 3. Randomized Controlled Trials of Magnesium Sulfate in Severe Preeclampsia

	Rates of Seizures		
Authors	**Magnesium Sulfate No. (%)**	**Control No. (%)**	**RR (95% CI)**
Moodley and Moodley[10]	1/112 (0.9)	0/116 (0)	NA
Coetzee et al[11]	1/345 (0.3)	11/340 (3.2)*	0.09 (0.01–0.69)
Magpie Trial Group[12]	40/5055 (0.8)	96/5055 (1.9)*	0.42 (0.26–0.60)
Belfort et al[13]	7/831 (0.8)	21/819 (2.6)†	0.33 (0.14–0.77)
Total	49/6343 (0.6)	128/6330 (2.0)	0.39 (0.28–0.55)

* Placebo.

† Nimodipine.

RR, relative risk; CI, confidence interval.

NA, not applicable.

anticonvulsants before randomization and 6% received magnesium sulfate or other anticonvulsants after randomization; 17 women had eclampsia before randomization.[8] This trial revealed a significant reduction in the rate of eclampsia in women assigned to magnesium sulfate (Table 3). This benefit was primarily found in women enrolled in developing countries, and no significant reduction in eclampsia was found in women enrolled in the Western world (RR = 0.67; 95% CI, 0.19–2.37).[12] However, the number of women enrolled in the Western world was too few. Based on the rate of eclampsia found in this group, with an α of 0.05 and a β of 0.2, 11,263 women from the Western world need to be enrolled in each group to find a significant reduction in rate of eclampsia in women treated with magnesium sulfate.

The trial by Belfort et al[13] compared the use of magnesium sulfate with nimodipine, a calcium channel blocker with cerebral vasodilatory effects. In this trial, the authors enrolled women at 14 sites in 8 countries who were given study drugs during labor and for 24 hours postpartum. All study women had well-defined clinical characteristics before randomization.[13] The authors found a significant reduction in the rate of eclampsia in the magnesium sulfate group (Table 3); most of the difference was the result of a lower eclampsia rate in the postpartum period among group assigned to magnesium sulfate (0 of 831 vs. 9 of 819 in nimodipine; P = 0.01).[13] The trial by Coetzee et al[11] included 822 randomized women; however, 137 (17%) were excluded after randomization. There were no cases of eclampsia among these women. This study did not include intention-to-treat analysis. The overall results of the 4 trials listed in Table 3 demonstrate that magnesium sulfate prophylaxis in severe preeclampsia is associated with a significantly lower rate of eclampsia (RR = 0.39, 95% CI, 0.28–0.55).

Effects of Magnesium Sulfate on Maternal Mortality and Morbidities

The trials mentioned here provided information regarding maternal mortality, and some of the studies provided information about maternal morbidities such as abruptio placentae,[10,12,13] respiratory depression,[10–13] and cerebrovascular accidents.[10–13] There were no maternal deaths reported in 2 of the trials[10,13] and 1 trial reported 1 death among 340 women assigned to placebo.[11] This woman presented 10 days after discharge from the hospital with signs of pelvic sepsis.[11] In the Magpie trial, there were 11 maternal deaths in the magnesium group and 20 deaths in the placebo group (RR = 0.55; 95% CI, 0.26–1.14).[12] However, 3 of the deaths in the placebo group were the result of renal failure, 3 were attributed to pulmonary embolism, and 2 because of infection. These 8 deaths can hardly be ascribed to magnesium whose actions are to prevent status epilepticus and aspiration. In addition, the deaths resulting from pulmonary embolism and infection could not be attributed to cesarean section because the rate of cesarean was similar between the 2 groups (50% in magnesium and 48% in placebo).[12] Moreover, it is not clear

TABLE 4. Effects of Magnesium Sulfate on the Rate of Abruptio Placentae in Women With Severe Preeclampsia

Authors	Magnesium Sulfate No. (%)	Control No. (%)	RR (95% CI)
Moodley and Moodley[10]	0/112	0/116	NA
Magpie Trial Group[12*]	62/4387 (1.4)*	113/4331 (2.6)*	0.54 (0.40–0.74)
Belfort et al[13]	8/831 (1.0)	6/819 (0.7)	1.30 (0.46–3.77)
Total	70/5330 (1.3)	119/5266 (2.3)	0.67 (0.38–1.19)

* Excluded 28 women in each group who probably had abruptio before randomization.

NA, not applicable; RR, relative risk; CI, confidence interval.

from this trial how many women had renal failure before randomization. Overall, the results of these trials demonstrate no benefit of magnesium sulfate on maternal mortality. Nevertheless, the numbers are too small to draw any certain conclusions.

Table 4 summarizes the data from randomized trials regarding the effects of magnesium sulfate on the rate of abruptio placentae.[10,12,13] Magnesium sulfate is not associated with a significant reduction in the rate of abruptio placentae (RR = 0.67; 95% CI, 0.38–1.19).

Randomized, controlled trials evaluating the effects of magnesium sulfate on the frequency of respiratory depression are summarized in Table 5. The use of magnesium sulfate in severe preeclampsia is associated with a significant increase in the rate of respiratory depression (RR = 2.06; 95% CI, 1.33–3.18). There were 3 cases of cerebrovascular accidents among 6343 women (0.05%) assigned to magnesium sulfate and 6 cases among 6330 women (0.09%) assigned to placebo.[10–13] The power regarding this outcome is too low for valid conclusions.

Effects of Magnesium Sulfate on Perinatal Deaths and Neonatal Morbidities

Three of the 4 trials mentioned here provided adequate information regarding perinatal deaths (Table 6).[10–12] The use of magnesium sulfate in severe preeclampsia does not affect the rate of perinatal deaths (RR = 1.03; 95% CI, 0.87–1.22). Only 2 of the randomized trials provided information regarding neonatal morbidities.[12,13] The use of magnesium sulfate in severe preeclampsia does not affect the rates of Apgar <7 at 5 minutes, respiratory distress, need for intubation, hypotonia, or days in a special care baby unit.[12,13]

Magnesium Sulfate in Mild Preeclampsia

There are only 2 double-blind, placebo-controlled trials evaluating the use of magnesium sulfate in patients with mild preeclampsia (Table 7).[14,15] In both trials, patients with well-defined mild preeclampsia were randomized during labor or postpartum, and there was no difference in the percentage of women who progressed to severe preeclampsia (12.5% vs. 13.8%; RR = 0.90; 95% CI, 0.52–1.54). There were no instances of eclampsia among 181 patients assigned to placebo. In one of these trials,[14] there was higher rates of postpartum hemorrhage and 2 instances of magnesium toxicity among those assigned to magnesium sulfate.

Because the number of patients studied in the 2 placebo trials is limited,[10,11] a larger number of patients needs to be studied before the effectiveness or safety of magnesium sulfate can be stated with certainty. Thus, there is a definite need for a multicenter trial to address the value of magnesium sulfate prophylaxis in mild preeclampsia. Based on a rate of eclampsia of 0.5% and assuming 50% reduction by magnesium sulfate (0.25% rate), with an α of 0.05 and a β of 0.2, 9383 women would need to be

TABLE 5. Effects of Magnesium Sulfate on the Proportion With Respiratory Depression in Women With Severe Preeclampsia

Authors	Magnesium Sulfate No. (%)	Control No. (%)	RR (95% CI)
Moodley and Moodley[10]	0/112	0/116	NA
Coetzee et al[11]	1/345 (0.3)	0/340	NA
Magpie Trial Group[12]	51/4999 (1.0)	26/4993 (0.5)	1.96 (1.22–3.14)
Belfort et al[13]	11/831 (1.3)	3/819 (0.4)	3.61 (1.01–12.90)
Total	63/6287 (1.0)	29/6268 (0.46)	2.06 (1.33–3.18)

NA, not applicable; RR, relative risk; CI, confidence interval.

TABLE 6. Effects of Magnesium Sulfate on the Rate of Perinatal Deaths in Severe Preeclampia

Authors	Magnesium Sulfate No. (%)	Control No. (%)	RR (95% CI)
Moodley and Moodley[10]	20/117 (17)	25/118 (21)	0.81 (0.47–1.37)
Coetzee et al[11]	38/348 (11)	38/354 (8.0)	1.38 (0.87–2.20)
Magpie Trial Group[12]	576/4538 (13)	558/4486 (12)	1.02 (0.92–1.14)
Total	634/5003 (13)	601/4958 (13)	1.03 (0.87–1.22)

RR, relative risk; CI; confidence interval.

enrolled in each group to find a significant reduction in eclampsia in women with mild preeclampsia treated with magnesium sulfate.

There are 4 randomized trials comparing magnesium sulfate with phenytoin in women with various hypertensive disorders of pregnancy (Table 8).[16–19] Only one of these trials had an adequate sample size to evaluate development of convulsions.[19] The results of these studies reveal that magnesium sulfate is superior to phenytoin to prevent eclamptic seizures in these women (Table 8).[16–19]

The largest randomized trial was reported by Lucas et al.[19] The trial compared the use of intramuscular magnesium sulfate to phenytoin in women with various hypertensive disorders (hypertension only, mild preeclampsia, and a small percentage with severe preeclampsia). The phenytoin group included 178 women who were given either no phenytoin (n = 139) or only a partial loading dose (n = 39). There were no cases of seizures among 1049 women assigned to magnesium sulfate as compared with 10 (0.9%) among 1089 women assigned to phenytoin ($P = 0.004$). Four of the 10 women with seizures had clinical findings consistent with severe preeclampsia. This study suggests that the rate of seizures in women with mild hypertension or mild preeclampsia receiving phenytoin is 0.6% (6 of 1000 women).

Side Effects and Toxicity of Magnesium Sulfate

The use of magnesium sulfate is associated with a high rate of minor side effects such as feeling warm, flushed, nausea or vomiting, muscle weakness, dizziness, and irritation at the site of injections. The reported rates of these effects in randomized trials ranged from 15% to 67%.[12–14] These side effects were the most common reason for the woman's request to stop treatment early in the Magpie trial.[12] In addition, the use of magnesium sulfate is associated with major side effects such as respiratory depression[12–14] and postpartum hemorrhage.[13,14] However, postpartum hemorrhage was not increased with magnesium sulfate use in the Magpie trial.[12]

Life-threatening magnesium toxicity is extremely rare with correct dosing and proper monitoring of the patient during magnesium sulfate therapy. Nevertheless, maternal

TABLE 7. Placebo-Controlled Trials of Magnesium Sulfate in Mild Preeclampsia

	Rate of Seizures		Progression to Severe		
Authors	Magnesium Sulfate	Placebo	Magnesium Sulfate	Placebo	RR (95% CI)
Witlin et al[10]	0/67*	0/68	8/67 (12%)	6/68 (9.1%)	1.35 (0.5–3.7)
Livingston et al[11]	0/109	0/113	14/109 (12.8%)	19/113 (16.8%)	0.76 (0.4–2.4)
Total	0/176	0/181	22/176 (12.5%)	25/181 (13.8%)	0.90 (0.52–1.54)

*Two cases of magnesium toxicity.

RR, relative risk; CI, confidence interval.

TABLE 8. Randomized Trials of Magnesium Sulfate ($MgSO_4$) Versus Phenytoin in Hypertensive Disorders of Pregnancy

	Convulsions	
	$MgsO_4$	**Phenytoin**
Appleton et al[16]	0/24	0/23
Friedman et al[17]	0/60	0/43
Atkinson et al[18]	0/28	0/26
Luca et al[19]	0/1049	0/1089
Total	0/1161	10/1181 (0.8%)*

* $P < 0.001$.

deaths from magnesium overdose have been reported from the United States[20] and from South Africa.[21] In addition, magnesium toxicity from overdose nearly led to maternal deaths in 2 other reports.[22,23]

Time, Duration, Dose, and Route of Administration

There is no agreement in the published randomized trials regarding the optimal time to initiate magnesium sulfate, the dose to use (both loading and maintenance), the route of administration (intramuscular or intravenous), as well as the duration of therapy. In all trials except in some of the women enrolled in the Magpie trial,[12] magnesium sulfate was started once the decision for delivery was made. In some trials, magnesium sulfate was given during labor, delivery, and for up to 24 hours postpartum.[11,13–15] In contrast, in 2 of the trials, magnesium sulfate was given for a maximum of 24 hours.[10,12] In addition, in the Magpie trial, some of the patients did not receive the drug during labor, delivery, or postpartum.[12] Among the trials using the intravenous regimen, the loading dose ranged from 4 to 6 g, and the maintenance dose ranged from 1 to 2 g per hour. The route of administration was by continuous intravenous infusion in most of the trials,[11,13–15] by a combination of intravenous loading dose and intramuscular maintenance in the trial by Moodley and Moodley,[10] and by a combination of these in the Magpie trial.[12] In the Magpie trial, there were significantly higher rates of side effects with the intramuscular regimen (28% vs. 5%), and as a result, more women in this group stopped the medication early. The Magpie trial found no differences regarding the efficacy of these 2 regimens in preventing seizures. This variation in the route of administration and the total amount of magnesium sulfate used in the various trials help explain the differences in the rates of seizures and side effects among those assigned to magnesium sulfate.

Recently, investigators from the University of Mississippi Medical Center suggested using an individually determined postpartum magnesium sulfate protocol based on patient clinical parameters in patients with preeclampsia.[24,25] The first study[24] included 194 women with mild (n = 103), severe (n = 55), or superimposed preeclampsia (n = 10). Women with mild disease received a minimum of 6 hours of intravenous magnesium sulfate, whereas those with severe received a minimum of 12 hours infusion in the postpartum period. This protocol was based on the level of blood pressures, need for antihypertensive therapy, presence of diuresis, and presence of maternal symptoms. Women with mild preeclampsia required an average magnesium sulfate therapy for 9.5 ± 4.2 hours, whereas those with severe disease required an average infusion of 16 ± 5.9 hours. Those with HELLP syndrome required an average duration of magnesium sulfate therapy for 20 ± 6.7 hours. There was no case of eclampsia during the study. The authors concluded that this protocol was cost-effective. However, the sample size is inadequate to evaluate efficacy for convulsions considering an expected rate of less than 1% in this group without using magnesium sulfate.

In a subsequent report, Isher et al[25] evaluated an individualized protocol for

postpartum magnesium sulfate therapy in 495 women with mild preeclampsia (n = 284), severe preeclampsia (n = 105), HELLP syndrome (n = 45), or superimposed preeclampsia (n = 61). This protocol also was based on level of blood pressures, use of antihypertensive drugs, diuresis, and maternal symptoms. It also required these women to be evaluated every 4 hours with vital signs and presence of symptoms. Magnesium sulfate was used for a minimum of 2 hours, but up to 72 hours in some of those with mild disease and up to 77 hours postpartum in those with severe disease. Magnesium sulfate therapy had to be reinstituted again based on clinical parameters in 6.3% of women with mild or severe disease and in 18% in those with superimposed preeclampsia. There were no cases of eclampsia among these women. Again, the number of women included in this study (mostly mild disease) is inadequate to draw any conclusions regarding efficacy to prevent eclampsia. In addition, this protocol requires intensive patient monitoring on the postpartum ward, which is not practical in most hospitals in the United States.

Dayicioglu et al[26] evaluated serum magnesium levels and efficacy of a standard dose of magnesium sulfate (4.5 g loading dose over 15 min followed by 1.8 g/hr) in 183 women with preeclampsia. Serum magnesium levels were obtained within the first 2 hours and every 6 hours in the subsequent 42 hours. In addition, serum creatinine levels and creatinine clearances were also studied to correlate with magnesium levels. The authors found that most serum levels of magnesium were below 4.8 mg/dL (therapeutic level?) in women with a body mass index of $\geq$36 kg/m^2. Nine women developed convulsions while receiving magnesium sulfate in the postpartum period; eclamptic seizures developed in 4 women with low body mass indices. The authors also found that there was no association between treatment failures and body mass index or with magnesium levels. In addition, they found no association among serum magnesium levels, serum creatinine, or creatinine clearance. The authors concluded that eclamptic convulsions did not correlate with either body mass index or circulating plasma magnesium levels. Therefore, questions remain regarding the optimal time to initiate magnesium sulfate as well as to the dose and the duration of administration in the postpartum period.

Recommendation

Most women with preeclampsia, particularly those with mild disease, will have a favorable maternal outcome and go on to deliver a healthy term infant. In contrast, in approximately 5% to 10% of patients with severe preeclampsia, the mother will have serious complications such as pulmonary edema, respiratory failure, abruptio placentae with or without disseminated intravascular coagulopathy, renal or liver failure, rupture liver hematomas, stroke, and seizures (eclampsia).[10–13] The risks of seizures are severe hypoxia from recurrent seizures or status epilepticus, maternal trauma, and aspiration pneumonia. These risks are particularly encountered in women who develop seizures before admission to a hospital and without being attended by a medical provider.[2–5]

Prophylactic magnesium sulfate is recommended only for women who are hospitalized because of diagnosed preeclampsia. In the United States, magnesium sulfate is recommended only during labor and for 12 to 24 hours postpartum. Therefore, it can be expected to have a potential effect on reduction of eclampsia that occurs only during this time period, which represents only 30% to 40% of 452 eclampsia cases reported in 2 recent series.[27,28] Thus, it will reduce the rate of eclampsia and its morbidity only in those women. Most of the morbidity and mortality associated with eclampsia is the result of out-of-hospital seizures in unattended women, and such events are more frequent among patients in developing countries without prenatal care and poor medical facilities.[29–32] Even in those who are

hospitalized with severe preeclampsia, maternal outcome will depend on the patient's condition and how advanced the disease process is at the time of hospitalization.[12,13] In these women, the risks to the mother and fetus will be more related to the irreversible maternal or fetal conditions before the onset of seizures rather than to the eclampsia itself. Thus, there is more to preeclampsia–eclampsia than prevention of seizures.[27,29]

The rate of seizures in women with mild preeclampsia not receiving magnesium sulfate is very low. Based on data from observational studies and the 2 randomized, placebo trials (Table 7), this rate is estimated to be approximately 1 in 200 women. Most of the women will have preeclampsia at term or immediately postpartum. If seizures develop during labor, they are usually self-limited, benign, and witnessed without adverse maternal effects.[8,9,11,13,19] If magnesium sulfate prophylaxis reduces the risk of seizure by 50%, then 400 women need to be treated to prevent a single seizure without possibly additional benefit to either mother or fetus. In this group, magnesium sulfate may potentially be associated with higher number of adverse maternal effects than the seizure itself. Therefore, the benefit-to-risk ratio does not support routine use of magnesium sulfate prophylaxis in mild preeclampsia.

The rate of seizures in women with severe preeclampsia not receiving magnesium sulfate is 2.0%, whereas it is 0.6% in those receiving such therapy (Table 3). Thus, 71 women with severe preeclampsia need to be treated to prevent 1 case of eclampsia that might not be associated with untoward adverse effects on the mother, fetus, or neonate. Women with severe preeclampsia are a heterogeneous group with substantially different risks for seizure. The Magpie trial provided data about the rate of eclampsia according to the rate of perinatal mortality in countries participating in the trial as well as according to presence or absence of imminent eclampsia (severe headaches, blurred vision, or epigastric pain).[12] In those who had imminent eclampsia, the number needed to be treated to prevent 1 case of eclampsia was 36. Thus, one can conclude that women with imminent eclampsia are the best candidates to receive magnesium sulfate prophylaxis. Even then, magnesium sulfate might prevent complications related to seizures (status epileptics, maternal trauma, or aspiration), but it may not affect serious maternal complications of severe preeclampsia such as pulmonary edema, stroke, liver, hematoma, or renal failure. In contrast, in women without symptoms the number of women needed to treat to prevent 1 case of eclampsia was 129. In addition, among those enrolled in the Western world, the number needed to be treated to prevent 1 case of eclampsia was 385. In these women, the benefit-to-risk ratio from routine prophylaxis is less compelling. However, in rare occasions, a patient may have aspiration or may develop a complication because of hypoxia related to the seizure. Because of this rare event, magnesium sulfate prophylaxis may be justified in all women with severe preeclampsia.

Finally, magnesium sulfate will not prevent most maternal and perinatal mortality and morbidity related to preeclampsia. Therefore, irrespective of magnesium sulfate therapy, progression from mild to severe disease and development of serious maternal complications during delivery and postpartum cannot be predicted without close maternal surveillance. Thus, the use of magnesium sulfate should not be misconstrued as license for reduced surveillance of these women. Continued close antepartum, intrapartum, and postpartum surveillance is crucial for optimal maternal and perinatal outcomes.

References

1. Sibai BM. Magnesium sulfate is the ideal anticonvulsant in preeclampsia–eclampsia. *Am J Obstet Gynecol*. 1990;162:1141–1145.
2. The Eclampsia Collaborative Group. Which anticonvulsant for women with eclampsia?

Evidence from the Collaborative Eclampsia Trial. *Lancet*. 1995;345:1455–1463.
3. Dommisse J. Phenytoin sodium and magnesium sulfate in the management of eclampsia. *Br J Obstet Gynaecol*. 1990;97:104–109.
4. Crowther C. Magnesium sulfate versus diazepam in the management of eclampsia: a randomized controlled trial. *Br J Obstet Gynaecol*. 1990;97:110–117.
5. Bhalla AK, Dhall GI, Dhall K. A safer and more effective treatment regimen for eclampsia. *Aust N Z J Obstet Gynecol*. 1994;34: 144–148.
6. Friedman SA, Schiff E, Kao L, et al. Phenytoin versus magnesium sulfate in patients with eclampsia: Preliminary results from a randomized trial [Abstract 452]. *Am J Obstet Gynecol*. 1995;175:384S.
7. Witlin AG, Sibai BM. Randomized trials for prevention and treatment of eclamptic convulsions. In: Sibai BM, ed. *Hypertensive Disorders in Women*. Philadelphia: WB Saunders; 2001:221–227.
8. Odendaal HJ, Hall DR. Is magnesium sulfate prophylaxis really necessary in patients with severe preeclampsia? *J Matern Fetal Investig*. 1996;6:14–18.
9. Hall DR, Odendaal HJ, Smith M. Is prophylactic administration of magnesium sulfate in women with pre-eclampsia indicated prior to labour? *Br J Obstet Gynaecol*. 2000;107: 903–908.
10. Moodley J, Moodley VV. Prophylactic anticonvulsant therapy in hypertensive crises of pregnancy—the need for a large, randomized trial. *Hypertens Pregnancy.* 1994;13:245–252.
11. Coetzee E, Dommisse J, Anthony J. A randomised controlled trial of intravenous magnesium sulfate versus placebo in the management of women with severe preeclampsia. *Br J Obstet Gynaecol*. 1998; 105:300–303.
12. The Magpie Trial Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulfate? The Magpie trial: a randomised, placebo-controlled trial. *Lancet*. 2002;359:1877–1890.
13. Belfort MA, Anthony J, Saade GR, et al, for the Nimodipine Study Group. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. *N Engl J Med*. 2003;348:304–311.
14. Witlin AG, Friedman SA, Sibai BM. The effect of magnesium sulfate therapy on the duration of labor in women with mild preeclampsia at term: a randomized, double-blind, placebo-controlled trial. *Am J Obstet Gynecol*. 1997;176:623–627.
15. Livingston JC, Livingston LW, Ramsey R, et al. Magnesium sulfate in women with mild preeclampsia: a randomized controlled trial. *Obstet Gynecol*. 2003;101:217–220.
16. Appleton MP, Kuehl TJ, Raebel MA, et al. Magnesium sulfate versus phenytoin for seizure prophylaxis in pregnancy-induced hypertension. *Am J Obstet Gynecol*. 1991; 165:907–913.
17. Friedman SA, Lim KH, Baker CA, et al. Phenytoin versus magnesium sulfate in preeclampsia: a pilot study. *Am J Perinatol*. 1993;10:233–238.
18. Atkinson MW, Guinn D, Owen J, et al. Does magnesium sulfate affect the length of labor induction in women with pregnancy-associated hypertension? *Am J Obstet Gynecol*. 1995;173:1219–1222.
19. Lucas MJ, LeVeno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med*. 1995;333:201–205.
20. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. *Am J Obstet Gynecol*. 1984;148: 951–963.
21. Richards A, Stather-Dunn L, Moodley J. Cardio-pulmonary arrest after the administration of magnesium sulfate. *S Afr Med J*. 1985;67:145.
22. McCubbin JH, Sibai BM, Abdella TN, et al. Cardiopulmonary arrest due to acute maternal hypermagnesemia. *Lancet*. 1981;ii:1058.
23. Bohman VR, Cotton DB. Supralethal magnesemia with patient survival. *Obstet Gynecol*. 1990;76:984–986.
24. Ascarelli MH, Johnson V, May WL, et al. Individually determined postpartum magnesium sulfate therapy with clinical parameters to safely and cost-effectively shorten treatment for preeclampsia. *Am J Obstet Gynecol*. 1998;179:952–956.
25. Isler CM, Scott Barrilleaux P, Rinehart BK, et al. Postpartum seizure prophylaxis: using maternal clinical parameters to guide therapy. *Obstet Gynecol*. 2003;101:66–69.

26. Dayicioglu V, Sahinoglu Z, Kol E, et al. The use of standard dose of magnesium sulfate in prophylaxis of eclamptic seizures: does body mass index alterations have any effect on success? *Hypertens Pregnancy.* 2003;22:257–265.
27. Mattar F, Sibai FM. Eclampsia VIII. Risk factors for maternal morbidity. *Am J Obstet Gynecol*. 2000;182:307–312.
28. Katz VL, Farmer R, Kuller JA. Preeclampsia into eclampsia: toward a new paradigm. *Am J Obstet Gynecol*. 2000;182:1389–1396.
29. Lopez-Llera MM. Complicated eclampsia. Fifteen years experience in a referral medical center. *Am J Obstet Gynecol*. 1982;142: 28–35.
30. Adetoro OO. A sixteen year survey of maternal mortality associated with eclampsia in Ilorin, Nigeria. *Int J Gynaecol Obstet*. 1989; 30:117–121.
31. Obed SA, Wilson JB, Elkins TE. Eclampsia: 134 consecutive cases. *Int J Gynaecol Obstet*. 1994;45:97–103.
32. Taner CE, Hakverdi AU, Aban M, et al. Prevalence, management and outcome in eclampsia. *Int J Gynaecol Obstet*. 1996;53: 11–15.