American Journal of Obstetrics and Gynecology (2004) **190**, 1520–6

ELSEVIER

AMERICAN JOURNAL of OBSTETRICS and GYNECOLOGY

www.elsevier.com/locate/ajog

Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials

Baha M. Sibai, MD*

Department of Obstetrics and Gynecology, University of Cincinnati, Cincinnati, Ohio

Received for publication October 29, 2003; revised December 15, 2003; accepted December 22, 2003

KEY WORDS
Preeclampsia
Magnesium sulfate
Prophylaxis

In the US, the routine use of magnesium sulfate for seizure prophylaxis in women with preeclampsia is an ingrained obstetric practice. During the past decade, several observational studies and randomized trials have described the use of various regimens of magnesium sulfate to prevent or reduce the rate of seizures and complications in women with preeclampsia. There are only 2 double-blind, placebo-controlled trials evaluating the use of magnesium sulfate in mild preeclampsia. There were no instances of eclampsia among 181 women assigned to placebo, and there were no differences in the percentage of women who progressed to severe preeclampsia (12.5% in magnesium group vs 13.8% in the placebo group, relative risk [RR] 0.90; 95% CI 0.52-1.54). However, the number of women enrolled in these trials is too limited to draw any valid conclusions. There are 4 randomized controlled trials that compare the use of no magnesium sulfate, or a placebo vs magnesium sulfate, to prevent convulsions in patients with severe preeclampsia. The rate of eclampsia was 0.6% among 6343 patients assigned to magnesium sulfate vs 2.0 % among 6330 patients assigned to a placebo or control (RR 0.39; 95% CI 0.28-0.55). However, the reduction in the rate of eclampsia was not associated with a significant benefit in either maternal or perinatal outcome. In addition, there was a higher rate of maternal respiratory depression among those assigned magnesium sulfate (RR 2.06; 95% CI 1.33-3.18). The evidence to date confirms the efficacy of magnesium sulfate in reduction of seizures in women with eclampsia and severe preeclampsia; however, this benefit does not affect overall maternal and perinatal mortality and morbidities. The evidence regarding the benefit-to-risk ratio of magnesium sulfate prophylaxis in mild preeclampsia remains uncertain, and does not justify its routine use for that purpose.

In the US, 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 US, magnesium sulfate was adopted for seizure prophylaxis in women with varying degrees of hypertensive disorders of pregnancy.[1] In 1990, it was suggested that magnesium sulfate was 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. Subsequent studies have shown to be at least partially wrong.

* Reprint requests: Baha M. Sibai, University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267.
E-mail: baha.sibai@uc.edu

0002-9378/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.ajog.2003.12.057

Table I Randomized controlled trials of magnesium sulfate in severe preeclampsia

	Rate of seizures		
Authors	Magnesium sulfate No. (%)	Control No. (%)	RR (95% CI)
Moodley and Moodley[6]	1/112 (0.9)	0/116 (0)	N/A
Coetzee et al[7]	1/345 (0.3)	11/340 (3.2)*	0.09 (0.01—0.69)
Magpie Trial Group[8]	40/5055 (0.8)	96/5055 (1.9)*	0.42 (0.26—0.60)
Belfort et al[9]	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)

RR, Relative risk.
* Placebo.
† Nimodipine.

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. Only one of these trials was multicenter and had an adequate sample size.[2] The results of these trials have been summarized by Witlin and Sibai.[3] The overall results of these studies demonstrate that magnesium sulfate is associated with a significantly lower rate of recurrent seizures (RR 0.41; 95% 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.[3] Therefore, there is level one evidence indicating that magnesium sulfate is the best available anticonvulsant for patients with eclampsia.[3] In contrast, the risk of eclampsia and the benefit-to-risk ratio of using magnesium sulfate as prophylaxis in patients with preeclampsia is less clear, and is therefore reviewed in this manuscript.[4-12]

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.[4,5] Secondary benefits also include reduced maternal and perinatal mortalities and morbidities, even in women who do not develop convulsions.[6-9] In addition, in women with mild preeclampsia, a secondary benefit could be a reduction in the rate of progression to severe preeclampsia.[10,11]

There are 4 large randomized controlled trials comparing the use of magnesium sulfate to prevent convulsions in patients with severe preeclampsia (Table I).[6-9] Two of the trials were single-center,[6,7] and the other 2 were multicenter with a large sample size.[8,9] Two of the trials were placebo-controlled,[7,8] 1 trial used a no treatment group,[6] and the remaining trial compared magnesium sulfate with a cerebral vasodilator (nimodipine).[9] All 4 trials allowed the use of various antihypertensive agents to control hypertension. The Magpie trial[8] 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 postpartum period.[8] Fifty percent of patients received antihypertensives before randomization, and 75% received antihypertensives after randomization. Moreover, 9% received 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 I). 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).[8] 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 .05 and a β of .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 [9] compared the use of magnesium sulfate with nimodipine, a calcium channel blocker with cerebral vasodilatory effects. In this trial the authors enrolled women who were given study drugs during labor and for 24 hours postpartum at 14 sites in 8 countries. All study women had well defined clinical characteristics before randomization.[9] The authors found a significant reduction in the rate of eclampsia in the magnesium sulfate group (Table I); most of the difference was caused by lower eclampsia rate in the postpartum period among group assigned to magnesium sulfate (0 of 831 vs 9 of 819 in nimodipine; $P = .01$).[9] The overall results of the 4 trials listed in Table I 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).

Table II 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[6]	0/112	0/116	N/A
Magpie Trial Group[8]	62/4387 (1.4)	113/4331 (2.6)	0.54 (0.40—0.74)
Belfort et al[9]	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)

N/A, Not applicable; RR, relative risk.

Table III 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[6]	0/112	0/116	N/A
Coetzee et al[7]	1/345 (0.3)	0/340	N/A
Magpie Trial Group[8]	51/4999 (1.0)*	26/4993 (0.5)*	1.96 (1.22—3.14)
Belfort et al[9]	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)

N/A, Not applicable; RR, relative risk.
* Thirty percent (0.6%) in magnesium group and 18 (0.4%) in placebo group required ventilatory support.

Effects of magnesium sulfate on maternal mortality and morbidities

The above trials provided information regarding maternal mortality, and some of the studies provided information about maternal morbidities such as abruptio placentae,[6,8,9] respiratory depression,[6-9] and cerebrovascular accidents.[6-9] There were no maternal deaths reported in 2 of the trials,[6,9] and 1 trial reported 1 death among 340 women assigned to placebo. This woman presented 10 days after discharge from hospital with signs of pelvic sepsis. 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). However, 3 of the deaths in the placebo group were attributed to 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. Unfortunately, autopsy results were not available. In addition, the deaths considered caused by pulmonary embolism and infection could not be attributed to cesarean section because the rate of cesarean delivery was similar between the 2 groups (50% in magnesium and 48% in placebo). Moreover, it is not clear 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 II summarizes the data from randomized trials regarding the effects of magnesium sulfate on the rate of abruptio placentae.[6,8,9] 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 III. 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. The power regarding this outcome was too low for valid conclusions.

Effects of magnesium sulfate on perinatal deaths and neonatal morbidities

Three of the 4 trials provided adequate information regarding perinatal deaths (Table IV).[6,7,9] 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.[8,9] 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 special care baby unit.[8,9]

There are several randomized studies describing the perinatal-neonatal effects of maternal magnesium sulfate when used as a tocolytic agent. In a systemic review of these studies, Crowther et al[12] reported that magnesium sulfate use was associated with increased rates of fetal, neonatal, and infant mortalities. This increased risk was limited to women receiving relatively high maintenance doses of magnesium sulfate (≥ 2 g/hour).

Table IV Effects of magnesium sulfate on the rate of perinatal deaths in severe preeclampsia

Authors	Magnesium sulfate No. (%)	Control No. (%)	RR (95% CI)
Moodley and Moodley[6]	20/117 (17)	25/118 (21)	0.81 (0.47—1.37)
Coetzee et al[7]	38/348 (11)	38/354 (8.0)	1.38 (0.87—2.20)
Magpie Trial Group[8]	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.

Table V 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)

RR, Relative risk.
* Two cases of magnesium toxicity.

However, the results of a recent large randomized trial comparing the perinatal effects in women assigned either to magnesium sulfate (n = 535) or a placebo (n = 527) revealed no adverse effects on either the fetus or the infant.[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 V).[10,11] 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,[10] there were higher rates of postpartum hemorrhage, and 2 instances of magnesium toxicity among those assigned to magnesium sulfate.

There is one large randomized trial comparing the use of intramuscular (i.m.) magnesium sulfate to phenytoin in women with various hypertensive disorders (hypertension only, mild preeclampsia, and a small percentage with severe preeclampsia).[14] The phenytoin group included 178 women who were given either no phenytoin (n = 139), or only 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 ($P = .004$). 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% (6/1000 women).

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 .2, approximately 10,000 women would need to be enrolled in each group to find a significant reduction in eclampsia in women with mild preeclampsia treated with magnesium sulfate. The number of women necessary to be studied to address serious maternal morbidity other than eclampsia is even higher than that.

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%.[8-10] These side effects were the most common reason for the woman's request to stop treatment early in the Magpie Trial.[8] In addition, the use of magnesium sulfate is associated with major side effects such as respiratory depression[8-10] and postpartum hemorrhage (2.4% vs 1.0%, $P = .03$).[9]

Life-threatening magnesium toxicity is extremely rare with correct dosing and proper monitoring of the patient during magnesium sulfate therapy. Nevertheless, maternal deaths from magnesium overdose have been reported from the US[15] and from South Africa.[16] In addition, magnesium toxicity from overdose nearly led to maternal deaths in 2 other reports.[17,18]

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 (i.m. or intravenous [i.v.]), as well as the duration of therapy. In all trials, except in some of the women enrolled in the Magpie Trial,[8] 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.[7, 9-11] In contrast, in 2 of the trials, magnesium sulfate was given for a maximum of 24 hours.[6,8] In addition, in the Magpie Trial, some of the patients did not receive the drug during labor, delivery, or postpartum.[8] Among the trials using the i.v. regimen, the loading dose ranged from 4 to 6 g, and the maintenance dose ranged from 1 to 2/hour. The route of administration was by continuous i.v. infusion in most of the trials,[7,9-11] by a combination of i.v. loading dose and i.m. maintenance in the trial by Moodley and Moodley,[6] and by a combination of the above in the Magpie Trial.[8] In the Magpie Trial, there were significantly higher rates of side effects with the i.m. regimen (28% vs 5%), and as a result, more women in this group stopped the medication early. 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.

Comment

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 about 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, ruptured liver hematomas, stroke, and seizures (eclampsia). 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.

Prophylactic magnesium sulfate is recommended only for women who are hospitalized because of diagnosed preeclampsia. In the US, 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.[19,20] 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 caused by 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.[21-24] Even in those patients who are hospitalized with severe preeclampsia, maternal outcome will depend on the patient's condition and how advanced the disease process is at time of hospitalization. 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.[19-21]

There are approximately 4 million births per year in the US, with an estimated rate of preeclampsia of 5% (200,000 pregnancies/year). Assuming that 50% of those women are given prophylactic magnesium sulfate during delivery and/or postpartum, 100,000 women will be exposed to magnesium sulfate annually. The majority of these women (75%) will have mild preeclampsia, and the remaining 25% will have severe disease. The universal administration of parenteral magnesium sulfate to all women with preeclampsia may lead to mortality and morbidity from overdosage and administration errors. As a result, a number of women may die or experience major morbidity from magnesium toxicity. These errors are more likely to occur in the presence of inadequate resources and if there is lack of trained personnel.

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 V), this rate is estimated to be about 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.[4,5,7,9,14] If magnesium sulfate prophylaxis reduces the risk of seizure by 50% then 400 women need to be treated to prevent a single seizure without possible additional benefit to either mother or fetus. In this group, magnesium sulfate may potentially be associated with a 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%, while it is 0.6% in those receiving such therapy (Table I). Thus, 71 women with severe preeclampsia need to be treated to prevent 1 case of eclampsia that is not 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).[8] 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 one case of eclampsia was 129. In addition, among those enrolled in the Western world, the number necessary 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 women with severe preeclampsia. In contrast, the evidence to date does not justify routine use of magnesium sulfate prophylaxis in women with mild preeclampsia.

Based on results of observational studies, randomized trials, and my own experience, it is recommended that magnesium to be used intravenously as a 6 g loading dose over 20 to 30 minutes, and followed by a maintenance dose of 2 g/hour. The infusion should be started at the beginning of labor and continued for at least 24 hours' postpartum. For women requiring cesarean delivery, the infusion should begin at least 1 hour before surgery and continued during the surgery.

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;162:1141-5.
2. The Eclampsia Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet 1995;345:1455-63.
3. Witlin AG, Sibai BM. Randomized trials for prevention and treatment of eclamptic convulsions. In: Sibai BM, editor. Hypertensive disorders in women. Philadelphia; Saunders, 2001. p. 221-7.
4. Odendaal HJ, Hall DR. Is magnesium sulfate prophylaxis really necessary in patients with severe preeclampsia? J Matern Fetal Invest 1996;6:14-8.
5. 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;107:903-8.
6. Moodley J, Moodley VV. Prophylactic anticonvulsant therapy in hypertensive crises of pregnancy—The need for a large, randomized trial. Hypertens Preg 1994;13:245-52.
7. 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;105:300-3.
8. 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;359:1877-90.
9. Belfort MA, Anthony J, Saade GR, Allen JC, for the Nimodipine Study Group. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med 2003;348:304-11.
10. 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;176:623-7.
11. Livingston JC, Livingston LW, Ramsey R, Mabie BC, Sibai BM. Magnesium sulfate in women with mild preeclampsia: a randomized controlled trial. Obstet Gynecol 2003;101:217-20.
12. Crowther CA, Hiller JE, Doyle LW. Magnesium sulfate for preventing preterm birth in threatened preterm labour (Cochrane Review). In: The Cochrane Library; Issue 3, Oxford: Update Software; 2003.
13. Crowther CA, Hiller JE, Doyle LW, Haslam RR, for the Australasian Collaborative Trial of Magnesium Sulfate (ACTO $Mgso_4$) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth. A randomized controlled trial. JAMA 2003;290:2669-76.
14. Lucas MJ, LeVeno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. N Engl J Med 1995;333:201-5.
15. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol 1984;148:951-63.
16. Richards A, Stather-Dunn L, Moodley J. Cardio-pulmonary arrest after the administration of magnesium sulfate. S Afr Med J 1985;67:145.
17. McCubbin JH, Sibai BM, Abdella TN, Anderson GD. Cardiopulmonary arrest due to acute maternal hypermagnesemia. Lancet 1981;ii:1058.
18. Bohman VR, Cotton DB. Supralethal magnesemia with patient survival. Obstet Gynecol 1990;76:984-6.

19. Mattar F, Sibai FM. Eclampsia VIII. Risk factors for maternal morbidity. Am J Obstet Gynecol 2000;182:307-12.
20. Katz VL, Farmer R, Kuller JA. Preeclampsia into eclampsia: toward a new paradigm. Am J Obstet Gynecol 2000;182: 1389-96.
21. Lopez-Llera MM. Complicated eclampsia. Fifteen years experience in a referral medical center. Am J Obstet Gynecol 1982;142: 28-35.
22. Adetoro OO. A sixteen year survey of maternal mortality associated with eclampsia in Ilorin, Nigeria. Int J Gynaecol Obstet 1989;30:117-21.
23. Obed SA, Wilson JB, Elkins TE. Eclampsia: 134 consecutive cases. Int J Gynaecol Obstet 1994;45:97-103.
24. Taner CE, Hakverdi AU, Aban M, Erden AC. Prevalence, management and outcome in eclampsia. Int J Gynaecol Obstet 1996;53:11-5.