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ORIGINAL ARTICLE

Effect of magnesium sulfate exposure on term neonates

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Objective: To compare neonatal intensive care unit and special care unit (NICU) admission rates between term neonates exposed to antenatal magnesium sulfate (MS) and those unexposed.

Study Design: We performed a retrospective cohort study of all singleton neonates ⩾37 weeks born to women with pre-eclampsia from August 2006 to July 2008. Cases were defined by antenatal exposure to MS and controls by absence of MS exposure. The primary outcome was NICU admission. Data were analyzed via univariable and multivariable regression analyses.

Result: In all, 28 (14.7%) out of 190 MS-exposed neonates ⩾37 weeks were admitted to the NICU, compared with 4 (5.4%) of 74 non-exposed neonates ($P = 0.04$). This association persisted after controlling for potential confounding variables including severe pre-eclampsia and cesarean delivery (AOR 3.69, 1.13 to 11.99). NICU admission was associated in a dose-dependent relationship with total hours and mean dose of MS exposure. Number needed to harm with MS was 11 per NICU admission. Among neonates admitted to the NICU, MS-exposed were more likely to require fluid and nutritional support than unexposed neonates (60.7 vs 0%, $P = 0.04$), and trended toward more frequent requirement for respiratory support and greater length of stay.

Conclusion: In term neonates, MS exposure may be associated independently with NICU admission in a dose-dependent relationship. Requirements for fluid and nutritional support are common in this group, likely due to feeding difficulties in exposed neonates. Assessment of acute care needs among all neonates exposed to MS for maternal eclampsia prophylaxis should be considered.
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Introduction

Magnesium sulfate is one of the most commonly prescribed intravenous medications in obstetric medicine.[1–4] Frequent antenatal indications for MS include tocolysis in the setting of preterm labor, maternal eclampsia prophylaxis and fetal neuroprotection in the setting of impending preterm delivery.[1–8] MS, a smooth muscle relaxant, has well-described short-term maternal side effects and toxicities ranging from nausea to respiratory depression, and, on occasion, maternal death.[5–7]

The potential for neonatal side effects from *in-utero* MS exposure has been explored in several recent publications. Lyell *et al*.[9] compared MS with nifedipine for preterm labor tocolysis, and demonstrated that preterm neonates exposed to magnesium were more likely to be admitted to the neonatal intensive care unit (NICU) and had twice the length of stay compared with those exposed to nifedipine, despite a similar birth weight and gestational age at delivery. Magnesium-exposed neonates had increased need for respiratory assistance and feeding difficulties compared with those exposed to nifedipine.[10]

These findings were unexpected, and led to a pilot study by our group to examine rates of NICU admission in a cohort of neonates exposed to MS for maternal eclampsia prophylaxis at 35 weeks and beyond.[11] We found a 20% rate of intensive care unit admission in this term and late-preterm cohort, a dose-dependent relationship between degree of MS exposure and intensive care admission, and common need for fluid and nutritional support. Though suggestive of an association between MS exposure and increased neonatal acute care needs, limitations of this pilot study included lack of a control group and inclusion of both late preterm and term neonates.

Based on this earlier work, the current investigation was undertaken to compare term neonates exposed to MS with those unexposed, in the setting of maternal pre-eclampsia. Our aim was to determine if MS exposure was associated independently with requirement for medical care beyond that available in the well-baby nursery (WBN).

Methods

We conducted a retrospective cohort study of newborns ⩾37 weeks at Lucile Packard Children's Hospital at Stanford. All singleton

deliveries between August 2006 and July 2008 with a coded diagnosis of maternal pre-eclampsia were identified. Maternal charts were reviewed to confirm the diagnosis of preeclampsia, and to identify whether women received MS for eclampsia prophylaxis immediately preceding delivery. Cases were neonates born to women with preeclampsia who received MS before delivery (MS-exposed). Controls were neonates born to women with preeclampsia who did not receive MS before delivery (non-exposed). Thus all neonates were exposed to maternal preeclampsia, but only cases were exposed to MS while controls were unexposed. A subset of previously described cases from our pilot study of MS-exposed term and late-preterm neonates was used to generate the cases for the current study.[11] Only newborns $\geqslant 37$ weeks from the pilot study were used as cases in the current study. Our earlier study lacked a control group of non-exposed neonates; thus the non-exposed neonates in our current study have not been described previously. The timeframe of the pilot study and current study was the same, and all cases from the earlier subset meeting inclusion criteria for our current study were analyzed.

For the present study, we reviewed all charts to confirm the pre-eclampsia diagnosis, and to determine whether neonates required neonatal intensive care (NICU) admission (level II or greater). Mild pre-eclampsia was defined as new onset hypertension with systolic blood pressure $\geqslant 140$ mm Hg and/or diastolic blood pressure $\geqslant 90$ mm Hg and proteinuria $\geqslant 1+$ on dipstick, urine protein to creatinine ratio (UPC) of $\geqslant 0.3$, or total proteinuria of $\geqslant 300$ mg in a 24-h collection period. Severe pre-eclampsia was defined as meeting the above criteria plus at least one of the following: systolic blood pressure $\geqslant 160$ mm Hg or diastolic blood pressure $\geqslant 105$ mm Hg, urine protein to creatinine ratio of $\geqslant 5$, or $\geqslant 5$ g of protein in a 24-h urine collection, or evidence of end organ involvement. Pre-eclampsia was considered to be superimposed if pre-existing hypertension was complicated by new onset or suddenly worsening proteinuria, sudden increase in blood pressure, or other associated features in accordance with American College of Obstetricians and Gynecologists definitions.[12]

The primary outcome was NICU admission, either at birth or at any time before discharge from the hospital. In our institution, neonates requiring a level of support greater than that administered in the WBN are admitted to one of two units including a transitional level II unit and a neonatal unit that provides level II, III and III+ care as required. For the purposes of this study, admission to the neonatal care unit providing level II care or greater was deemed a NICU admission. Criteria for level II NICU admission include: suspected sepsis requiring monitoring and treatment; respiratory symptoms anticipated to be transient and not requiring positive pressure; hyperbilirubinemia requiring intravenous (IV) hydration in addition to phototherapy; symptomatic polycythemia; hypoglycemia requiring IV treatment; feeding difficulty with or without need for gavage; and symptoms or potential for narcotic withdrawal. Criteria for level III admission include need for 1:1 nursing, multi-system failure, need for positive pressure ventilation, surgical care, multiple anomalies, congenital heart disease and need for isolation. Admission to any of our nursery locations is determined at an attending level. Neonates were considered WBN patients only if they remained in the care of the WBN throughout the entire hospital stay. Multiple gestations were excluded from analysis, as were neonates who met any antenatal criteria for automatic NICU admission including a clinical diagnosis of maternal chorioamnionitis and major fetal anomalies requiring immediate evaluation.

Maternal and neonatal variables, abstracted using a standardized data collection sheet, were analyzed to determine associations with NICU admission. Gestational age was determined by best obstetric estimate, which included ultrasound. A standard MS infusion protocol is utilized in our institution, consisting of a 4-g bolus of intravenous MS over 20 to 30 min followed by $2\,g\,h^{-1}$. The decision to administer MS to women with pre-eclampsia was per the discretion of the attending physician, including teaching and private practitioners, as per routine practice at our institution. Total dose of MS administered before delivery for each patient was calculated from review of medication infusion records. Postpartum MS was not included in the calculation of MS exposure. Length of labor data was abstracted from standard nursing documentation in the medical record, with onset of labor defined by regular painful contractions with documented cervical change.

NICU variables abstracted included admission and discharge diagnoses, length of stay and type of treatment administered. NICU admission and discharge diagnoses were abstracted as entered into the medical record by the treating physicians, who included resident physicians, neonatology fellows and supervising faculty members. Suspected neonatal hypermagnesemia was defined clinically by NICU treating physicians based on evidence of hypotonia, respiratory depression and poor gastrointestinal motility. Serum magnesium levels were checked in all neonates who had clinical signs of hypermagnesemia based on these criteria. Neonatal respiratory support was defined as use of oxygen supplementation by any means, including nasal cannula, continuous positive airway pressure, or intubation. Fluid/nutritional support was defined as need for any intravenous fluids or nutritional supplementation.

Data was tested for normality by Shapiro–Wilk test. Categorical data was analyzed via chi-squared and Fisher's exact tests, and non-parametric data via Kruskal–Wallis. Multivariable logistic regression analysis was used to control for potential confounding variables. Dose–response curves were generated from the logistic regression models. STATA version 7 software (StataCorp — College Station, TX, USA) was used for all analyses. An alpha of <0.05 was considered to be significant. The Institutional Review Board at Stanford University Medical Center approved this study.

Table 1 Demographic and baseline characteristics

	MS-exposed (n = *190*)	*Non-exposed* (n = *74*)	P-*value*
Gestational age, weeks (mean/s.d.)	38.9 (± 1.3)	39.0 (± 1.2)	0.6
Maternal age, years (mean/s.d.)	27.7 (± 7.7)	29 (± 7.4)	0.2
Maternal race (n/%)			0.6
White	32 (16.8%)	14 (18.9%)	
Black	9 (4.7%)	2 (2.7%)	
Latina	118 (62.1%)	40 (54.1%)	
Asian	17 (8.9%)	11 (14.9%)	
Native American/Pacific islander	10 (5.3%)	4 (5.4%)	
Other	4 (2.1%)	3 (4.1%)	
Public insurance (*n*/%)	142 (74.7%)	44 (59.4%)	0.02
Teaching physician (*n*/%)	169 (88.9%)	55 (74.3%)	0.003
Maternal comorbidities			
Chronic hypertension (*n*/%)	28 (14.7%)	3 (4.1%)	0.02
Other comorbidities (*n*/%)[a]	31 (16.3%)	14 (8.9%)	0.6
Severe pre-eclampsia (*n*/%)	41 (21.6%)	8 (10.8%)	0.05

Abbreviation: MS, magnesium sulfate.
[a]Includes insulin-requiring diabetes mellitus.

Table 2 Labor, delivery and neonatal characteristics

	MS-exposed (n = *190*)	*Non-exposed* (n = *74*)	P-*value*
Induction of labor (*n*/%)	157 (82.6%)	25 (33.8%)	<0.001
Induction of labor for PIH (*n*/%)	145 (92.4%)	19 (76%)	0.01
Length of labor, hours (median/IQR)	8.5 (4.8–14.6)	6.9 (4.4–9.9)	0.2
Anesthesia/analgesia			0.5
None	18 (9.5%)	11 (14.9%)	
Regional	171 (90%)	62 (83.8%)	
General endotracheal	1 (0.5%)	1 (1.4%)	
IV narcotics within 1 h of delivery	6 (3.2%)	2 (2.7%)	
Method of delivery n (%)			0.004
Spontaneous vaginal delivery	136 (71.6%)	37 (50%)	
Forceps assisted vaginal delivery	3 (1.6%)	1 (1.4%)	
Vacuum assisted vaginal delivery	7 (3.7%)	2 (2.7%)	
Cesarean delivery	44 (23.2%)	34 (46%)	<0.001[a]
Scheduled cesarean (*n*/%)[b]	4 (9.1%)	20 (58.8%)	0.007
Unscheduled cesarean (n/%)[b]	40 (90.9%)	14 (41.2%)	
Non-reassuring fetal status[c]	3 (7.5%)	5 (35.7%)	
Failed progress in labor[c]	34 (85%)	6 (42.9%)	
Other[c]	3 (7.5%)	3 (21/4%)	
Meconium-stained AF (*n*/%)	29 (15.3%)	11 (14.9%)	0.9
Shoulder dystocia (*n*/%)	9 (4.7%)	1 (1.4%)	0.2
Neonatal male gender (*n*/%)	96 (50.5%)	37 (50%)	0.9
Birth weight (mean/s.d.)	3.3 (± 0.6)kg	3.26 (± 0.5)kg	0.6
1 min Apgar score (median/IQR)	8 (8–9)	8 (8–9)	0.3
Neonatal comorbidities (n/%)	21 (11.1%)	7 (9.5%)	0.7
IUGR	1 (0.5%)	1 (1.4%)	
LGA	9 (4.7%)	4 (5.4%)	
Other comorbidities	12 (6.3%)	2 (2.7%)	
NICU admission (*n*/%)	28 (14.7%)	4 (5.1%)	0.04

Abbreviations: AF, amniotic fluid; IQR, interquartile range; IUGR, intrauterine growth restriction; IV, intravenous; LGA, large for gestational age; MS, magnesium sulfate; NICU, neonatal intensive care unit; PIH, pregnancy-induced hypertension.
[a]Comparing cesarean delivery with any vaginal delivery.
[b]Calculated for those delivered by cesarean.
[c]Calculated for those delivered by unscheduled cesarean.

Results

During the 2-year study period, 328 neonates $\geqslant$37 weeks' gestation with maternal charts coded for pre-eclampsia were identified. Of these, 22 neonates were excluded because maternal pre-eclampsia diagnosis could not be confirmed, 28 owing to maternal chorioamnionitis, 6 owing to major fetal anomalies and 8 owing to twin gestation. The remaining 264 neonates were included in the final analysis. There were 190 cases (78%) exposed to MS antenatally and 74 controls (22%) non-exposed.

Among the 74 controls, reasons for non-exposure included non-use of MS due to explicitly-stated physician preference in 23 (31.1%), pre-eclampsia diagnosed immediately before or after delivery in 22 (29.8%) and undocumented indication in 29 (39.2%). Among the MS-exposed group, mean total dose was 23.3 ± 17.4 g (range 4 to 120 g), and mean total length of exposure was 10.2 ± 8.9 h (range 0.5 to 56 h). Mean maternal peak serum creatinine was 0.73 ± 0.22 mg dl^{-1} in the MS-exposed group and 0.68 ± 0.14 in the non-exposed group ($P = 0.08$).

Maternal demographics were similar between groups, except that more women in the MS-exposed group had severe pre-eclampsia (Table 1). More women had induction of labor in the MS-exposed group (Table 2). Length of labor and analgesia/anesthesia use did not differ between groups. Cesarean delivery was more frequent in the non-exposed group, with a high percentage of scheduled cesareans in that group (Table 2). Rates of meconium-stained amniotic fluid, shoulder dystocia, LGA, IUGR, birth weight and Apgar scores were similar between groups (Table 2). Umbilical cord blood gases were available for 93 neonates (35.2%), and differences were seen only in arterial pH (7.18 MS-exposed, 7.21 non-exposed, $P = 0.05$) and arterial base excess (5.9 MS-exposed, 4 non-exposed, $P = 0.002$).

NICU admission rate was greater in the MS-exposed group, 28 out of 190 (14.7%) vs 4 out of 74 (5.1%) in the non-exposed group ($P = 0.04$, Table 2). This corresponds to a number needed to harm 11 (95% CI 6 to 40) neonates exposed to MS per one NICU admission. Among neonates admitted to the NICU, over half were initially admitted to the WBN, with a wide range of intervals between birth and NICU admission (Table 3). The most frequent primary admission diagnosis in the MS-exposed group was respiratory distress, and in the non-exposed group was suspected sepsis. Median length of NICU stay did not differ between groups

Table 3 NICU characteristics

	MS-exposed (n = *28/190*)	*Non-exposed* (n = *4/74*)	P-*value*
Initial admission			0.6
NICU (*n*/%)	13 (46.4%)	1 (25%)	
WBN (*n*/%)	15 (53.6%)	3 (75%)	
Birth to NICU admission time, hours[a]			
Range	0.66–72	1–120	
Median/IQR	15.2 (5.6–28)	24 (12.5–72)	
Primary admit diagnosis (n/%)			0.06
Respiratory distress	10 (35.7%)	0	
Rule out sepsis	2 (7.1%)	3 (75%)	
Hypotonia	6 (21.4%)	0	
Hypothermia	1 (3.6%)	0	
LBW	1 (3.6%)	0	
Hyperbilirubinemia	2 (7.1%)	0	
Hypermagnesemia	2 (7.1%)	0	
Other	4 (14.3%)[b]	1 (25%)[c]	
NICU length of stay, days (Median/IQR)	5 (3–7)	3 (2.5–4)	0.4
Treatments needed			
Respiratory	11 (39.3%)	1 (25%)	>0.99
Fluids/nutritional support	17 (60.7%)	0	0.04
Antibiotics	16 (57.1%)	3 (75%)	0.6
Phototherapy	6 (21.4%)	0	0.6

Abbreviations: IQR, interquartile range; LBW, low birth weight; MS, magnesium sulfate; NICU, neonatal intensive care unit; WBN, well-baby nursery.
[a]Calculated for those whose initial admission was to the WBN (well-baby nursery).
[b]Other = Subgaleal bleed, evaluation of abdominal mass, seizures, hypoglycemia.
[c]Other = Aplasia cutis.

(Table 3). A total of 60% of MS-exposed neonates received fluid and nutritional support in the NICU compared with none of the non-exposed neonates (Table 3). Three quarters of the MS-exposed neonates admitted to the NICU had serum total magnesium levels drawn, with a mean peak level of $4.1 \pm 1.6\,\mathrm{mg\,dl^{-1}}$.

In all, 12 of the 28 MS-exposed neonates admitted to the NICU had admission and/or discharge diagnoses of hypermagnesemia. Neonates in the MS-exposed NICU cohort with this diagnosis had similar requirements for respiratory support (50 vs 31%, $P = 0.2$) and phototherapy (8 vs 31%, $P = 0.2$) compared with those with other diagnoses, however fewer received antibiotics (33 vs 75%, $P = 0.03$) and more required fluid and nutritional support (91.7 vs 61.3%, $P = 0.004$) compared with those without a diagnosis of hypermagnesemia. All peak serum total magnesium levels in neonates with clinically suspected hypermagnesemia were $>2.4\,\mathrm{mEq\,l^{-1}}$ (upper limit of normal in our institution), with a linear relationship between degree of MS exposure and peak serum level (data not shown).

In multivariable regression analysis, MS exposure was significantly associated with NICU admission after controlling for potential confounding variables including gestational age, public insurance, birth weight, cesarean delivery, chronic hypertension and severe pre-eclampsia (AOR 3.69, 95% CI 1.13 to 11.99).

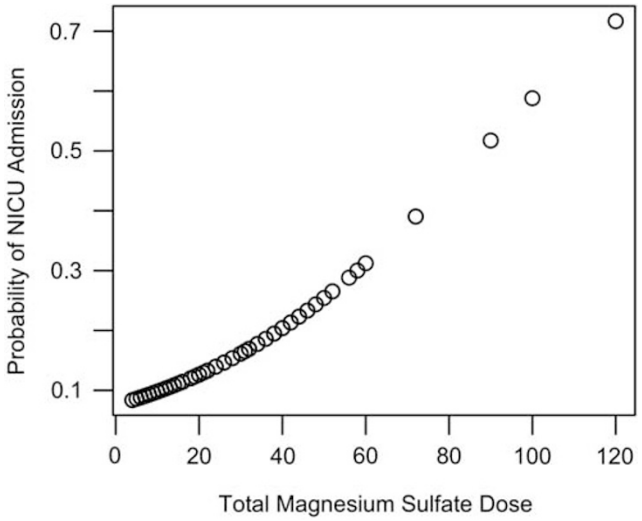

Figure 1 Probability of NICU admission by total magnesium sulfate exposure dose. Dose shown is total grams of magnesium sulfate administered antenatally. NICU, neonatal intensive care unit.

When analyzed by MS exposure thresholds chosen in an exploratory fashion, of the 190 neonates in the MS-exposed group, 132 were exposed for <12 h and 58 for $\geqslant 12$ h. This corresponded to a total dose of $\geqslant 30$ g vs <30 g. A total of 15 of the 58 (25.9%) exposed for >12 h were admitted to the NICU compared with 13 of the 132 (9.8%) exposed for $\leqslant 12$ h ($P = 0.004$). The number needed to harm with MS exposure >12 h compared with non-exposure was 5 (95% CI 3 to 12) per one NICU admission, and was 7 (95% CI 4 to 27) per one NICU admission compared with MS exposure $\leqslant 12$ h. In multivariable analysis, the adjusted odds ratio of NICU admission was 2.54 (95% CI 1.05 to 6.18) for exposure >12 h compared with $\leqslant 12$ h. Logistic regression of total magnesium dose (Figure 1) and total hours of exposure (Figure 2), demonstrated an increasing probability of NICU admission with increasing degree of exposure, across all exposure thresholds.

Discussion

We identified an association between antenatal MS exposure and NICU admission among otherwise-healthy term neonates of preeclamptic women, in a dose–response manner, and which persisted after controlling for potential confounding variables. As a smooth muscle relaxant that easily crosses the placenta, maternal MS administration can depress neonatal respiratory and gastrointestinal tone, as suggested by our findings. Neonates exposed to MS had a variety of acute care needs, most

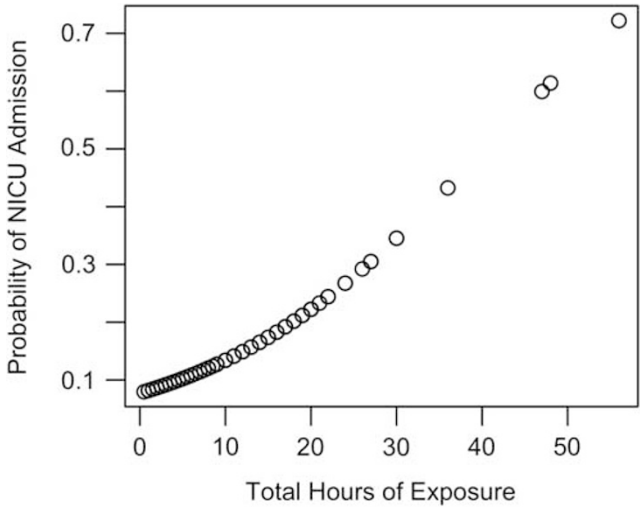

Figure 2 Probability of NICU admission by total hours of magnesium sulfate exposure. Hours shown is total number of hours of exposure antenatally. NICU, neonatal intensive care unit.

commonly the requirement for fluid and nutritional support that likely resulted from poor feeding due to gastrointestinal dysmotility.

Acute neonatal effects of MS among term neonates have been relatively understudied and deserve attention. Most of the existing literature has focused on long-term risks and benefits of neonatal MS exposure for preterm labor tocolysis,[1,4–8,13–16] where prematurity has a significant role in outcomes. In trials of MS for eclampsia prophylaxis, neonatal outcomes examined are frequently limited to major neonatal morbidities among term combined with preterm neonates. For example, the Magpie study of MS for eclampsia prophylaxis examined major neonatal morbidities only.[15] The study identified an overall 39% rate NICU admission in both the magnesium and placebo groups with 20% of neonates born <34 weeks, suggesting that both prematurity and other co-morbid conditions may lead to NICU admission.[15] Negative effects of MS on neonatal adaptation were potentially masked by the larger influence of prematurity in this and similar trials.[13–16] Further, beyond NICU admission rate and Apgar scores, acute care needs were not reported. Studies that have examined short-term care needs of MS-exposed neonates due to eclampsia prophylaxis have yielded mixed results, likely owing to heterogeneous study populations, designs and magnesium infusion protocols.[17–22] Most recently, Riaz *et al*.[22] compared 26 MS-exposed neonates of preeclamptic mothers with 26 non-exposed neonates without preeclamptic mothers at $\geqslant 34$ weeks. Their findings of increased NICU admission and delayed feeding in the MS-exposed group are compatible with our results, although they did not reach statistical significance potentially owing to small sample size.

Preeclampsia itself, inherent to any cohort of this nature, potentially influences neonatal adaptation. Our earlier work identified a 20% NICU admission rate among neonates $\geqslant 35$ weeks exposed to MS, in a dose-dependent manner, but was limited by the lack of a control group to account for the influence of preeclampsia.[11] The use of a control group in our current study, namely unexposed neonates of preeclamptic women, allowed us to identify an independent relationship between MS exposure and neonatal acute care needs. The dose–response relationship we demonstrate is consistent with an emerging appreciation for a therapeutic window in the use of MS,[1] and suggests a threshold effect for neonatal transition that may be useful to consider in future studies on neonatal impact of MS protocols.

There were more scheduled cesareans in the non-exposed group. We hypothesize that providers of women diagnosed with preeclampsia at the time of scheduled cesarean withheld MS until after delivery. Given the association between unlabored cesarean and neonatal respiratory morbidity,[23,24] the higher percentage of scheduled cesarean deliveries in the non-exposed group would potentially increase the NICU admission rate among controls. That we demonstrate significantly more NICU admissions in the MS-exposed group despite fewer unlabored cesareans adds strength to our findings. Finally, the decision to admit to the NICU may have been influenced by a number of uncontrolled factors, such as level of experience of the delivery room provider, but such variation should be found equally among both groups. The decision to admit a newborn to a NICU bed is undertaken at the attending level (experienced hospitalists and/or neonatologists) in our institution, ensuring a level of uniformity in admission criteria.

Strengths of our study, compared with previous work, are a relatively large sample size, a standard MS infusion protocol, focus on specific treatments required in the NICU and exclusion of preterm infants. The confounding impact of prematurity was eliminated in our analysis, revealing a level of MS-related compromise in term neonates that has not previously been noted.

Limitations of our study include other potential unaccounted-for influences on neonatal acute care needs. While our groups were matched for preeclampsia, the MS-exposed group contained more women with severe preeclampsia, as would be expected, and some women met preeclampsia criteria before delivery vs others, postpartum. We controlled for severity of preeclampsia in multivariable analysis, but some influence may remain as we did not adjust for the timing of the preeclampsia diagnosis.[25] Other inherent differences between our groups, such as payor status, induction of labor vs scheduled cesarean, and provider characteristics including propensity to administer or to withhold MS for eclampsia prophylaxis may have contributed to neonatal outcomes in subtle ways. However, we limited the impact of these factors by controlling for demographic differences, demonstrating comparable lengths of labor and excluding neonates exposed to chorioamnionitis.

This study has implications for women with pre-eclampsia and care of their neonates. In our institution, newborns of MS-exposed

women are not routinely evaluated for potential hypermagnesemia, nor are those exposed beyond a dose threshold routinely checked for hypermagnesemia. Earlier studies have reported a lack of correlation between clinically significant symptoms of hypermagnesemia and magnesium levels in neonatal umbilical cord blood.[18,21] Based on our findings, the degree of maternal MS exposure alone may be an appropriate indicator of the need to evaluate a neonate for potential clinical hypermagnesemia.

Given the relatively low number needed to harm with MS exposure to result in one NICU admission, all neonates exposed to MS in the immediate antenatal period should be considered at risk for increased acute care needs, with the level of risk proportional to the degree of exposure. Routine assessment of these needs among all neonates exposed to MS for eclampsia prophylaxis should be considered. Further prospective study of optimal protocols for postnatal evaluation and care of MS-exposed neonates is warranted.

Conflict of interest

The authors declare no conflict of interest.

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