Association between Intrapartum Magnesium Administration and the Incidence of Maternal Fever

A Retrospective Cross-sectional Study

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ABSTRACT

Background: Intrapartum maternal fever is associated with several adverse neonatal outcomes. Intrapartum fever can be infectious or inflammatory in etiology. Increases in interleukin 6 and other inflammatory markers are associated with maternal fever. Magnesium has been shown to attenuate interleukin 6–mediated fever in animal models. We hypothesized that parturients exposed to intrapartum magnesium would have a lower incidence of fever than nonexposed parturients.

Methods: In this study, electronic medical record data from all deliveries at Northwestern Memorial Hospital (Chicago, Illinois) between 2007 and 2014 were evaluated. The primary outcome was intrapartum fever (temperature at or higher than 38.0°C). Factors associated with the development of maternal fever were evaluated using a multivariable logistic regression model. Propensity score matching was used to reduce potential bias from nonrandom selection of magnesium administration.

Results: Of the 58,541 women who met inclusion criteria, 5,924 (10.1%) developed intrapartum fever. Febrile parturients were more likely to be nulliparous, have used neuraxial analgesia, and have been delivered *via* cesarean section. The incidence of fever was lower in women exposed to magnesium (6.0%) than those who were not (10.2%). In multivariable logistic regression, women exposed to magnesium were less likely to develop a fever (adjusted odds ratio = 0.42 [95% CI, 0.31 to 0.58]). After propensity matching (N = 959 per group), the odds ratio of developing fever was lower in women who received magnesium therapy (odds ratio = 0.68 [95% CI, 0.48 to 0.98]).

Conclusions: Magnesium may play a protective role against the development of intrapartum fever. Future work should further explore the association between magnesium dosing and the incidence of maternal fever. **(Anesthesiology 2017; 127:942-52)**

MATERNAL fever, commonly defined as a temperature of 38.0°C or greater, complicates up to one third of all labors.[1] There are multiple infectious and noninfectious etiologies of intrapartum fever, and it is known that intrapartum fever is associated with several adverse neonatal outcomes, such as hypotonia, need for assisted ventilation, cardiopulmonary resuscitation, neonatal seizures, and cerebral palsy.[2–6] Pyrogenic cytokines, such as interleukin 6 (IL-6), mount an inflammatory response resulting in pyrexia. Several studies have demonstrated elevated levels of IL-6 in both inflammatory and infectious etiologies of maternal fever.[7–9]

Magnesium sulfate has been shown to confer protective effects on neonatal brains and is commonly used clinically to reduce the risk of moderate-to-severe cerebral palsy in preterm infants.[10–17] Although the mechanism of the neuroprotection of magnesium is not clear, in inflammatory models of neonatal brain injury it appears to be protective.[18,19] Because not all maternal fever is infectious in etiology and can be inflammatory,[20] magnesium may also have a role in maternal fever reduction. In a rat model, magnesium sulfate suppressed IL-6–induced increases in maternal temperature.[21] Moreover, in a small clinical study, when intravenous magnesium sulfate was used as a tocolytic agent in preterm laboring parturients, an associated decrease in maternal central core temperature was observed.[22]

What We Already Know about This Topic

- Intrapartum maternal fever is associated with adverse neonatal outcome. Magnesium attenuates interleukin 6–mediated fever in animal models.

What This Article Tells Us That Is New

- In a multivariable logistic regression, parturient women exposed to magnesium were less likely to develop fever.

The association between intrapartum magnesium sulfate administration and maternal fever has not been evaluated previously. The objective of this study was to evaluate whether maternal magnesium administration is associated with

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intrapartum maternal fever. We hypothesized that intrapartum exposure to magnesium therapy is associated with a lower incidence of maternal fever than no magnesium exposure.

Materials and Methods

The study was approved by the Northwestern University Institutional Review Board (Chicago, Illinois; STU00103617). Electronic medical record data were extracted using the Northwestern University Electronic Data Warehouse (EDW) for all deliveries at Northwestern Memorial Hospital between January 1, 2007, and September 1, 2014. The start date was selected based on the date on which electronic medical record data were available for labor analgesia. Patients were included if they were admitted to the labor and delivery unit with intent for labor resulting in vaginal delivery. Included patients also had a value recorded for the highest temperature in labor, a finite variable that is recorded by the nursing staff in a labor and summary form within the electronic medical record. Patients were excluded if the highest temperature in labor was recorded as lower than 35°C or higher than 40.6°C, because these temperatures were likely errantly entered. Patients were also excluded if a cesarean delivery was performed without antecedent labor (*e.g.*, scheduled cesarean deliveries). More than 5,000 records in the electronic medical record were manually evaluated to confirm data accuracy from the EDW.

In our hospital, baseline temperatures are routinely recorded on admission to the labor and delivery unit. Temperatures are assessed hourly by the nursing staff after rupture of membranes. Once a temperature of 38.0°C is reached, the obstetric provider is notified. A diagnosis of chorioamnionitis is made by the obstetric provider based on the patient's clinical presentation, as well as fetal heart rate tracing. This diagnosis may be made in the absence of clinical fever. The diagnosis of chorioamnionitis is recorded in the nursing summary form in the patient's record. Antipyretic use in the setting of fever is at the discretion of the obstetric provider. After a diagnosis of chorioamnionitis is made, the patient is started on an antibiotic regimen of ampicillin and gentamicin that continues through delivery.

Data extracted from the medical record included age, race or ethnicity, and body mass index. Admission obstetric data included gestational age, gravidity, parity, labor type (spontaneous *vs.* induced labor), group B streptococcus status (positive, negative, or unknown), and date and time of admission. Intrapartum data included method and time of membrane rupture (artificial *vs.* spontaneous), mode and time of delivery, indication for cesarean delivery (if applicable), diagnosis (and severity) of preeclampsia, use of prostaglandins for induction of labor, diagnosis of chorioamnionitis, and use of intrapartum magnesium during labor. The method and time for initiating labor analgesia (combined spinal–epidural analgesia or epidural analgesia) were recorded. Temperature-related data included the highest temperature in labor and the use of intrapartum antipyretics, antibiotics, and systemic opioids. Neonatal data included 1- and 5-min Apgar scores, pediatrician's presence at delivery (only called for anticipated need for pediatric evaluation at birth), need for neonatal resuscitation, umbilical cord blood gas values, and admission to the neonatal intensive care unit (NICU) and neonatal death. At Northwestern Memorial Hospital (Chicago, Illinois), labor nurses are responsible for assessment and care of healthy neonates. A pediatric hospitalist is the first-line pediatric provider at deliveries in which a higher level of neonatal evaluation and resuscitation is anticipated, such as those complicated by intrapartum fever or chorioamnionitis. A neonatologist is added to the pediatric team for very-high-risk neonates.

The following time intervals were calculated for each patient: duration of labor, time from admission to the highest temperature in labor, time between initiation of neuraxial labor analgesia to the highest temperature in labor, and time from rupture of membranes to highest temperature in labor. The *duration of labor* was defined as the time from admission to the labor and delivery suite until delivery.

Statistical Analysis

The primary outcome was *intrapartum maternal fever*, defined as a temperature of greater than or equal to 38.0°C any time between admission and delivery. Data were stratified by febrile status (febrile *vs.* afebrile). Normal distribution for continuous variables was determined using the Shapiro–Wilk test. Categorical data were compared using the chi-square test, and continuous data were compared using a two-tailed *t* test or the Kruskal–Wallis test if the data were not normally distributed. *Change in maternal temperature* was defined as the difference between admission temperature and the highest temperature in labor. Change in temperature was compared by neuraxial analgesia use. The time interval from the initiation of neuraxial labor analgesia to the highest temperature in labor was also evaluated among febrile women. Differences in the incidence of fever by year were evaluated using the test of trend. $P < 0.05$ was used to determine statistical significance.

A multivariable logistic regression model was estimated to evaluate the association between magnesium administration and maternal fever. Candidate independent variables were selected for model entry if their bivariate association with the dependent variable (maternal fever) resulted in a *P* value less than 0.1. Variables included in the final model included intrapartum magnesium therapy, race or ethnicity (white, Hispanic, black, or Asian), obesity (body mass index at or greater than 30 kg/m^2), nulliparity, preterm delivery (estimated gestational age less than or equal to 37 weeks), method of membrane rupture (spontaneous and artificial), use of prostaglandins for labor induction, use of neuraxial labor analgesia, diagnosis of preeclampsia, diagnosis of chorioamnionitis, cesarean delivery, group B streptococcus status, age at or greater than 35 yr, live birth, labor duration, and year of delivery.

A propensity score model was created to evaluate the association between magnesium administration (independent variable) and maternal fever (dependent variable). After a univariate analysis to identify factors associated with receiving magnesium, the propensity score model was created using variables significantly associated with receiving treatment. Although

chorioamnionitis and neuraxial analgesia were not significantly associated with magnesium use, they were included in the model to ensure balance in the subjects selected. Logistic regression was used to create a propensity score for each subject. Variables included in the model were white race, diagnosis of preeclampsia, duration of labor greater than 10 h (median labor time), preterm birth, spontaneous rupture of membranes, diagnosis of chorioamnionitis, group B streptococcus–positive status, use of neuraxial labor analgesia, antibiotic administration, systemic opioid administration, acetaminophen administration, cesarean delivery, admission to the NICU, and need for newborn resuscitation. Only cases with no missing data were used for propensity analysis. The data were then matched, using an optimal caliper method that defines the maximum width of the distance at 0.00125 in propensity scores between acceptable matches. Larger caliber size would lead to a larger number of potential matches, but the matched pairs would have a significant difference in at least one of the variables. The algorithm was able to match 959 magnesium therapy recipients with 959 corresponding nonusers. After testing the sample for balance on variables in the model, a single variable logistic regression model was created to test the association of magnesium and fever.[23,24] Results were consistent when a conditional logistic regression using matched pairs was used to analyze the sample (data not shown). The propensity score model was also constructed using labor duration as a continuous variable; however, more than 30% of the original sample could not be matched, with the number of matched pairs being reduced to 802.

A *post hoc* mediation analysis was performed to evaluate the effect of intrapartum magnesium therapy on neonatal outcomes among febrile patients using the code developed by Valeri and VanderWeele.[25] Fever was the exposure and magnesium therapy was the mediator. Admission to NICU was used as the adverse neonatal outcome, because it is a surrogate for multiple adverse neonatal events.

Data were analyzed using Stata SE (version 12, Stata Corp., USA). Propensity score analysis and mediation analysis were created using SAS (version 9.4, SAS Institute, USA).

Results

A total of 97,245 deliveries were identified by the initial EDW query. From this initial group, 33,485 were excluded because they did not have a highest temperature in labor recorded (fig. 1). The final sample consisted of 58,541 parturients, of whom 5,924 (10.1%) developed intrapartum fever. A total of 1,179 patients (2.0%) received intrapartum magnesium therapy. Patient demographics stratified by fever status (febrile or afebrile) are described in table 1. Labor characteristics and labor outcomes are shown in table 2.

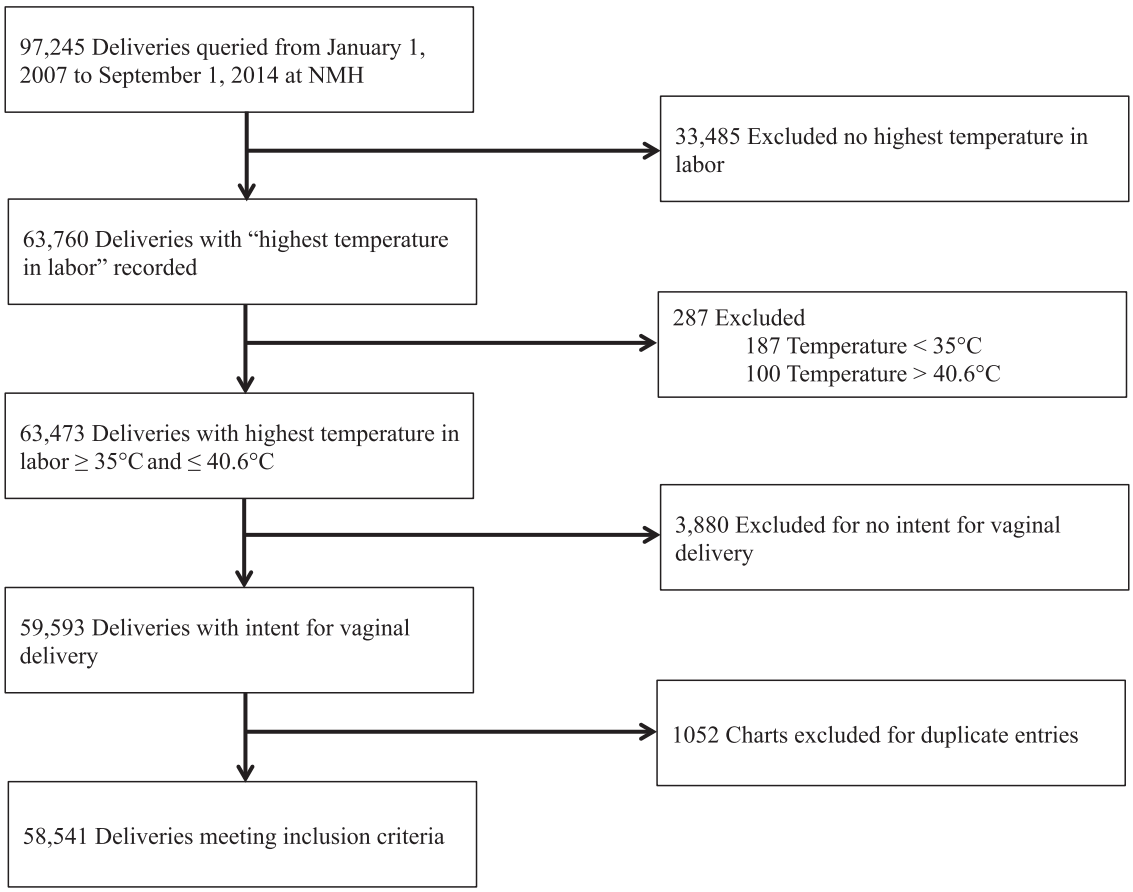

Fig. 1. Participant flowchart.

Table 1. Patient Demographics

	Febrile (n = 5,924)	Afebrile (n = 52,617)	*P* Value
Advanced maternal age, n (%)*	1,255 (21.2)	14,307 (27.2)	< 0.001
Race/ethnicity, n (%)			< 0.001
White	2,670 (45.1)	28,062 (53.3)	
Hispanic	1,128 (19.0.)	8,648 (16.4)	
Black	649 (10.9)	5,367 (10.2)	
Asian	507 (8.6)	3,014 (5.8)	
Other/declined	970 (16.4)	7,526 (14.3)	
BMI, n (%)			< 0.001
Nonobese (BMI < 30 kg/m^2)	2,916 (49.2)	30,005 (57.0)	
Obese (BMI ≥ 30 kg/m^2)	3,008 (50.8)	22,612 (43.0)	
Para, n (%)			< 0.001
Nulliparous	4,687 (79.1)	26,633 (50.6)	
Parous	1,237 (20.9)	25,984 (49.4)	
Estimated gestational age, n (%)†			< 0.001
Preterm (< 37 weeks)	409 (7.0)	4,641 (8.9)	
Term (≥ 37 weeks)	5,439 (93.0)	47,262 (91.1)	
No. of gestations, n (%)			0.14
Singleton	5,842 (98.6)	51,756 (98.4)	
Multiple gestation	82 (1.4)	861 (1.6)	

*Advanced maternal age defined as age ≥ 35 yr. †Gestational age data missing for 790 patients.
BMI = body mass index.

The median highest temperature in labor was 38.2°C (interquartile range [IQR], 38.1° to 38.5°C) in parturients who developed intrapartum fever compared with 37°C (IQR, 36.7° to 37.3°C) in parturients who did not develop intrapartum fever. Parturients who developed fever were more likely to be nulliparous, obese, have prolonged labors, have used neuraxial analgesia, and to have required cesarean delivery. Intrapartum maternal fever was less likely to

Table 2. Labor Description

	Febrile (n = 5,924)	Afebrile (n = 52,617)	*P* Value
Labor description, n (%)*			0.19
Spontaneous	4,028 (69.2)	35,095 (68.3)	
Induction	1,795 (30.8)	16,266 (31.7)	
Labor duration, median (interquartile range), h†	15.6 (11.3–21.5)	9.1 (5.8–13.8)	< 0.001
Membrane status, n (%)‡			< 0.001
Intact	392 (6.7)	4,267 (8.3)	
Artificial rupture of membranes	3,037 (52.3)	27,341 (53.2)	
Spontaneous rupture of membranes	2,383 (41.0)	19,824 (38.5)	
Group B streptococcus status, n (%)			< 0.001
Negative	3,899 (65.8)	32,729 (62.2)	
Positive	1,121 (18.9)	10,394 (19.8)	
Unknown	904 (15.3)	9,494 (18.0)	
Prostaglandin use, n (%)	147 (2.5)	456 (0.9)	< 0.001
Systemic opioid administration, n (%)	829 (14.0)	4,238 (8.1)	< 0.001
Neuraxial labor analgesia, n (%)	5,765 (97.3)	46,426 (88.2)	< 0.001
Preeclampsia, n (%)	213 (3.6)	2,923 (5.6)	< 0.001
Maximum recorded temperature in labor, median (interquartile range), °C	38.2 (38.1–38.5)	37 (36.7–37.3)	< 0.001
Magnesium administration, n (%)	71 (1.2)	1,108 (2.1)	< 0.001
Acetaminophen administration, n (%)	2,589 (43.7)	2,277 (4.3)	< 0.001
Chorioamnionitis, n (%)	3,208 (54.2)	369 (0.7)	< 0.001
Intrapartum antibiotic administration, n (%)	4,984 (84.1)	12,588 (23.9)	< 0.001
Mode of delivery, n (%)			< 0.001
Vaginal	4,008 (67.7)	46,265 (87.9)	
Cesarean	1,916 (32.3)	6,352 (12.1)	

*Labor description had 1,357 missing values (2.3%). †Labor duration had 6,542 missing values (11.2%). ‡Membrane status had 1,297 missing values (2.2%).

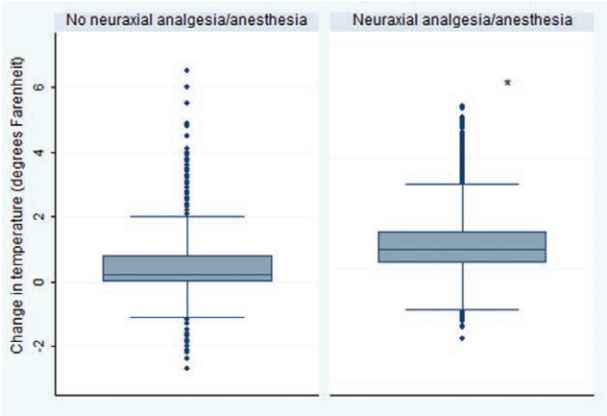

Fig. 2. Change in intrapartum temperature by neuraxial analgesia/anesthesia use. *P < 0.001.

occur in women with preterm labor, preeclampsia, and in those who received intrapartum magnesium sulfate therapy compared with those who did not. Change in intrapartum temperature as a function of neuraxial analgesia use is shown in figure 2.

Patients exposed to magnesium were more likely to be younger, black or Hispanic, obese, nulliparous, preterm, and have preeclampsia than women not exposed to magnesium (table 3). Labor characteristics also differed. In comparison with women not receiving magnesium, those who received intrapartum magnesium were more likely to have induced labor; require intrapartum antibiotics, acetaminophen, and systemic opioids; and deliver *via* cesarean (table 4). Magnesium exposure differed by year of the study, because guidelines for the treatment of preterm deliveries less than 32 weeks and preeclampsia guidelines both changed over this time period.[10,26]

The time interval from the initiation of neuraxial labor analgesia to the highest temperature in labor was evaluated among febrile women. Those patients who did not receive intrapartum magnesium achieved a febrile maximum temperature in labor 78 min earlier than the cohort receiving magnesium therapy (P = 0.004). Among febrile women who used neuraxial analgesia, magnesium administration was associated with an increased interval between epidural catheter placement and fever (8.5 h [IQR, 6.2 to 11.4 h] in the nonmagnesium group *vs.* 9.8 h [IQR, 7.4 to 16.9 h] in the magnesium-exposed group; P = 0.004).

Neonatal outcomes, including 1- and 5-min Apgar scores, differed between the febrile and afebrile cohorts

Table 3. Demographics Stratified by Magnesium Therapy

	Magnesium Therapy (n = 1,179), n (%)	No Magnesium (n = 57,362), n (%)	*P* Value
Advanced maternal age*	335 (28.4)	15,227 (26.6)	0.15
Race/ethnicity			< 0.001
White	486 (41.2)	30,246 (52.7)	
Hispanic	213 (18.1)	9,563 (16.7)	
Black	225 (19.1)	5,791 (10.1)	
Asian	42 (3.6)	3,479 (6.1)	
Other/declined	213 (18.1)	8,283 (14.4)	
BMI			< 0.001
Nonobese (BMI < 30 kg/m^2)	474 (40.2)	32,447 (56.6)	
Obese (BMI ≥ 30 kg/m^2)	705 (59.8)	24,915 (43.4)	
Parity			< 0.001
Nulliparous	811 (68.8)	30,509 (53.2)	
Parous	368 (31.2)	26,853 (46.8)	
Estimated gestational age†			< 0.001
Preterm (< 37 weeks)	615 (52.9)	4,435 (7.8)	
Term (≥ 37 weeks)	548 (47.1)	52,153 (92.2)	
No. of gestations			< 0.001
Singleton	1,081 (91.7)	56,517 (98.5)	
Multiple gestation	98 (8.3)	845 (1.5)	
Year of delivery			< 0.001
2006	1 (0.1)	35 (0.1)	
2007	192 (16.3)	6,650 (11.6)	
2008	228 (19.3)	6,585 (11.5)	
2009	112 (9.5)	7,062 (12.3)	
2010	137 (11.6)	7,250 (12.6)	
2011	122 (10.3)	8,022 (14.0)	
2012	147 (12.5)	8,098 (14.1)	
2013	147 (12.5)	7,974 (13.9)	
2014	93 (7.9)	5,687 (9.9)	

*Advanced maternal age defined as age ≥ 35 yr. †Gestational age data missing for 790 patients.
BMI = body mass index.

Table 4. Labor Description Stratified by Magnesium Therapy

	Magnesium Therapy (n = 1,179)	No Magnesium (n = 57,362)	*P* Value
Labor description, n (%)*			< 0.001
Spontaneous	441 (38.5)	38,682 (69.0)	
Induction	706 (61.5)	17,355 (31.0)	
Labor duration, median (interquartile range), h†	23.1 (12.7–44.9)	9.6 (6.1–14.5)	< 0.001
Membrane status, n (%)‡			< 0.001
Intact	113 (9.8)	4,546 (8.1)	
Artificial rupture of membranes	745 (64.9)	29,633 (52.8)	
Spontaneous rupture of membranes	290 (25.3)	21,917 (39.1)	
Group B streptococcus, n (%)			< 0.001
Negative	401 (34.0)	36,227 (63.2)	
Positive	138 (11.7)	11,377 (19.8)	
Unknown	640 (54.3)	9,758 (17.0)	
Prostaglandin use, n (%)	19 (1.6)	584 (1.0)	0.050
Systemic opioid administration, n (%)	346 (29.4)	4,721 (8.2)	< 0.001
Neuraxial labor analgesia, n (%)	1,050 (89.1)	51,141 (89.2)	0.92
Preeclampsia, n (%)	893 (75.7)	2,243 (3.9)	< 0.001
Maximum recorded temperature in labor, median (interquartile range), °C	37.0 (36.7–37.3)	37.0 (36.7–37.5)	< 0.001
Fever, n (%)	71 (6.0)	5,853 (10.2)	< 0.001
Acetaminophen administration, n (%)	420 (35.6)	4,446 (7.8)	< 0.001
Chorioamnionitis, n (%)	65 (5.5)	3,512 (6.1)	0.39
Intrapartum antibiotic administration, n (%)	611 (51.8)	16,961 (29.6)	< 0.001
Mode of delivery, n (%)			< 0.001
Vaginal	907 (76.9)	49,366 (86.1)	
Cesarean	272 (23.1)	7,996 (13.9)	
Pediatric support at delivery, n (%)§			< 0.001
No pediatrician	512 (43.4)	41,060 (71.6)	
Hospitalist	338 (28.7)	14,861 (25.9)	
Neonatologist	329 (27.9)	1,441 (2.5)	
Live birth, n (%)	1,164 (98.7)	57,087 (99.5)	< 0.001
Disposition of live-born neonate, n (%)‖			< 0.001
Remained with mother	708 (63.6)	51,854 (95.0)	
Live birth admitted to NICU	398 (35.8)	2,624 (4.8)	
Neonatal death	7 (0.6)	135 (0.2)	
Antepartum fetal demise, n (%)	15 (1.3)	275 (0.5)	< 0.001

*Labor description had 1,357 missing values (2.3%). †Labor duration had 6,542 missing values (11.2%). ‡Membrane status had 1,297 missing values (2.2%). §At Northwestern Memorial Hospital (Chicago, Illinois), labor nurses are responsible for assessment and care of healthy neonates. A pediatric hospitalist is the first-line pediatric provider at deliveries in which a higher level of neonatal evaluation and resuscitation is anticipated, such as those complicated by intrapartum fever or chorioamnionitis. A neonatologist is added to the pediatric team for very-high-risk neonates. ‖Disposition of live-born neonate had 2,525 missing values (4.3%).

NICU = neonatal intensive care unit.

(table 5). There was also a higher incidence of antepartum fetal demise, as well as neonatal death after delivery, in the febrile cohort. Neonates born to mothers with intrapartum fever were more likely to have a pediatric hospitalist present at delivery. Newborns born to mothers with intrapartum fever were also more likely to be acidemic and hypoxemic based on both arterial and venous cord blood gases than their counterparts born to afebrile mothers. Admission to the NICU was also more frequent in the neonates born to the febrile cohort. A mediation analysis was performed to assess whether disparities might exist in NICU admission among febrile and afebrile cohorts depending on exposure to intrapartum magnesium therapy; the indirect effect estimate for mediation of the sample was not significant, with a point estimate of 1.01 (95% CI, 0.99 to 1.03).

The results of the multivariable logistic regression model are presented in table 6. Intrapartum magnesium therapy was associated with lower odds of maternal fever (adjusted odds ratio [aOR] = 0.42 [95% CI, 0.31 to 0.58]). Factors associated with intrapartum fever included nulliparity, obesity, use of neuraxial labor analgesia, intrapartum administration of prostaglandins or systemic opioids, a diagnosis of chorioamnionitis, prolonged labor, and delivery *via* cesarean section.

Fifty-seven patients were missing at least one variable and could not be included in the propensity score analysis (*i.e.*, preterm status, acetaminophen administration, opioid administration, neuraxial anesthesia or analgesia use, rupture of membranes, admission to the NICU, and pediatrician present at delivery). Using a caliper method to set the

Table 5. Neonatal Outcomes

	Febrile (n = 5,925)	Afebrile (n = 52,617)	*P* Value
Apgar 1-min	8 (7 to 9)	9 (8 to 9)	< 0.001
Apgar 5-min	9 (9 to 9)	9 (9 to 9)	< 0.001
Pediatric support at delivery, n (%)*			< 0.001
No pediatrician	2,342 (39.5)	39,230 (74.6)	
Hospitalist	3,411 (57.6)	11,788 (22.4)	
Neonatologist	171 (2.9)	1,599 (3.0)	
Live birth, n (%)	5,833 (98.5)	52,418 (99.6)	< 0.001
Disposition of live-born neonate, n (%)†			< 0.001
Remained with mother	4,484 (81.1)	48,078 (95.8)	
Live birth admitted to NICU	1,012 (18.3)	2,010 (4.0)	
Neonatal death	33 (0.6)	109 (0.2)	
Antenatal fetal demise, n (%)	91 (1.5)	199 (0.4)	< 0.001
Umbilical artery blood gas median (interquartile range)			
pH	7.22 (7.17 to 7.26)	7.23 (7.17 to 7.27)	< 0.001
P_{CO_2}, mmHg	55 (49 to 61)	57 (51 to 64)	< 0.001
P_{O_2}, mmHg	18 (14 to 24)	20 (15 to 26)	< 0.001
HCO_3, mEq/l	22 (20 to 24)	24 (22 to 25)	< 0.001
Base deficit, mEq/l	–6 (–9 to –4)	–5 (–7 to –3)	< 0.001
Umbilical vein blood gas, median (interquartile range)			
pH	7.29 (7.24 to 7.32)	7.3 (7.26 to 7.33)	< 0.001
P_{CO_2}, mmHg	42 (39 to 47)	44 (40 to 48)	< 0.001
P_{O_2}, mmHg	27 (22 to 34)	30 (24 to 37)	< 0.001
HCO_3, mEq/l	20 (19 to 22)	22 (20 to 23)	< 0.001
Base deficit, mEq/l	–6 (–8 to –4)	–5 (–7 to –3)	< 0.001

*At Northwestern Memorial Hospital, labor nurses are responsible for assessment and care of healthy neonates. A pediatric hospitalist is the first-line pediatric provider at deliveries in which a higher level of neonatal evaluation and resuscitation is anticipated, such as those complicated by intrapartum fever or chorioamnionitis. A neonatologist is added to the pediatric team for very-high-risk neonates. †Disposition of live-born neonate had 2,525 missing values (4.3%).

NICU = neonatal intensive care unit.

maximum acceptable distance between score matches, 959 (85.5%) of 1,122 subjects were matched in a 1:1 fashion with a nonrecipient. Fisher exact tests were used to test the balance between study groups in each of the variables used in the propensity model; no comparison *P* values were less than 0.05 (table 7). Using the total sample of 1,918 subjects, the relationship between fever and magnesium was modeled using a logistic regression. Exposure to magnesium was associated with a lower incidence of fever (aOR, 0.68 [95% CI, 0.48 to 0.98]). Similar results were obtained when labor duration was modeled as a continuous variable (aOR, 0.57 [95% CI, 0.39 to 0.82]).

Discussion

The most important finding in this study was that exposure to intrapartum magnesium therapy is associated with a lower incidence of intrapartum fever compared with no magnesium therapy. To our knowledge, this study is the first to describe this negative association between maternal intrapartum magnesium therapy and intrapartum fever. This finding is significant because, in the United States, as many as 280,000 parturients may develop an intrapartum fever annually.[1] In addition to maternal morbidity associated with fever, there are fetal implications, including admission to the NICU and higher rates of neonatal death after delivery.[2–6] Although our study found that magnesium administration was associated with less maternal fever, it is important to understand whether fever-associated neonatal outcomes are mediated by magnesium exposure. We found that maternal fever was associated with more NICU admissions; however, exposure to magnesium did not appear to attenuate the association between fever and NICU admission. Although it is possible that magnesium administration may result in improved neonatal outcomes, our measure (NICU admission) lacked the sensitivity to detect these differences. Also, it is important to consider that maternal magnesium administration may have short-term negative consequences on the neonate itself (*e.g.*, more depressed babies).

Intrapartum fever during labor likely has multiple causes. Maternal fever may occur secondary to both intrauterine and extrauterine causes. Often the presumed infectious etiology of maternal fever is chorioamnionitis, although other bacterial and viral infections may cause fever. Higgins *et al.*[20] advocate for a more general descriptive term, intrauterine inflammation, infection, or both, coined the *triple I*. Noninfectious causes of maternal fever include the administration of medications that raise maternal temperature, such as prostaglandin E2 agents, elevated ambient temperature, and a fever related to the administration of neuraxial analgesia, often referred to as *epidural fever*.

Table 6. Variables Associated with Intrapartum Fever

Variable	Adjusted Odds Ratio (95% CI)
Magnesium therapy	0.42 (0.31–0.58)
Race/ethnicity	
White	Reference
Hispanic	1.31 (1.20–1.43)
Black	1.16 (1.05–1.29)
Asian	1.66 (1.48–1.86)
Other/declined	1.23 (1.14–1.33)
Obesity (BMI ≥ 30 kg/m^2)	1.27 (1.19–1.35)
Nulliparity	3.03 (2.82–3.27)
Preterm	0.52 (0.45–0.61)
Membrane status	
Intact	Reference
Spontaneous ROM	1.11 (0.98–1.25)
Artificial ROM	1.08 (0.96–1.22)
Prostaglandins used	1.48 (1.17–1.88)
Neuraxial labor analgesia	4.17 (3.48–5.02)
Systemic opioid administration	1.43 (1.30–1.58)
Preeclampsia	0.53 (0.45–0.64)
Cesarean delivery	2.34 (2.18–2.51)
Group B streptococcus status	
Negative	Reference
Positive	0.90 (0.84–0.98)
Unknown	0.85 (0.78–0.94)
Live birth	0.10 (0.07–0.14)
Age ≥ 35 yr	0.84 (0.78–0.90)
Labor duration	1.38 (1.33–1.43)
Year	
2006	Reference
2007	0.90 (0.10–7.93)
2008	0.79 (0.09–6.94)
2009	0.93 (0.11–8.14)
2010	0.95 (0.97–8.37)
2011	1.01 (0.11–8.87)
2012	0.88 (0.10–7.71)
2013	0.61 (0.07–5.39)
2014	0.68 (0.08–6.02)

BMI = body mass index; ROM = rupture of membrane.

Our results confirm that neuraxial analgesia is a risk factor for the development of intrapartum fever, even after adjusting for other confounders. The relationship between neuraxial labor analgesia and maternal fever was first described in 1987.[27] Since that time there have been a variety of studies, both observational and randomized, describing epidural fever.[5,28–31] Although the exact mechanism of epidural fever is poorly understood, it is currently believed to be related to an underlying systemic and/or regional inflammatory process, likely mediated by IL-6, without an underlying infectious etiology.[21,29] This noninfectious inflammation hypothesis was additionally supported by the work of Sharma *et al.*,[32] who performed a double-blind, placebo-controlled trial with prophylactic antibiotics before epidural catheter placement and showed no difference in the incidence of maternal hyperthermia or placental inflammation between groups.

Although there have been several studies investigating treatment options for epidural fever, to date none have yielded acceptable options. Administration of prophylactic acetaminophen does not prevent maternal temperature increase.[33] Goetzl *et al.*[34] found that high-dose methylprednisolone prevented maternal fever and resulted in lower levels of IL-6 compared with the control group, who did not receive methylprednisolone, but it was associated with an increased risk of neonatal bacteremia. Women who were randomly assigned to receive epidural dexamethasone at the time of initiation of epidural labor analgesia showed a trend toward less maternal fever, as well as lower levels of IL-6, but the study was underpowered and did not evaluate the neonatal consequences of maternally administered dexamethasone.[35]

How magnesium sulfate administration influences body temperature regulation is not completely understood. A variety of mechanisms are plausible. Magnesium-induced peripheral vasodilation is thought to accelerate the drop in core temperature observed in healthy volunteers in research experimental settings.[36] The shivering threshold decreased by 0.3°C without concomitant peripheral vasodilation, when healthy male volunteers received continuous intravenous magnesium infusion, underlying the importance of a magnesium central nervous system effect.[37] It is possible that a combination of a peripheral and a central nervous system magnesium effect contribute to the observed decrease in central core temperature in the parturient who receives intrapartum magnesium therapy. High magnesium dietary intake has been found to be associated with decreased systemic levels of inflammatory cytokines, such as IL-6, among 3,713 healthy postmenopausal women.[38] It is possible that magnesium blunts the systemic inflammatory cascade and attenuates the febrile response in the parturient, because intrapartum fever is commonly associated with increased plasmatic level of IL-6.[29] The protective effects of magnesium sulfate on the neonatal brain have been well demonstrated in rat models of inflammation[18,19] and in randomized trials in humans[39–41] and is currently used for its neuroprotective properties in preterm delivery.[10]

Our study further confirms other risk factors previously shown to be associated with the development of maternal fever; these include duration of labor and mode of delivery. Goetzl *et al.*[29] did not find the duration of labor to be predictive of maternal fever, instead concluding duration of epidural analgesia and duration of membrane rupture to be more predictive of maternal temperature. However, our study suggests that labor duration is associated with an increase in the occurrence of fever, a finding consistent with other reports in the literature.[5,30,31] In addition, our results suggest that women with intrapartum fever are more likely to deliver *via* cesarean section. Greenwell *et al.*[5] similarly demonstrated that febrile patients with epidural analgesia were more likely to undergo cesarean section or operative vaginal delivery.

It is important to consider the limitations of this study. The study was retrospective, thus we cannot exclude the possibility of errors in documentation or inaccuracy within the extracted data. In addition, the only temperature that was

Table 7. Propensity Scoring

	After Matching			
	Magnesium Therapy (n = 959)	No Magnesium (n = 959)	Standardized Mean Difference	*P* Value
Preeclampsia	75.7	72.8	–0.059	0.25
Admission to NICU	29.9	27.6	0.053	0.29
Labor >10 h	85.5	84.8	0.024	0.70
Newborn resuscitation*	24.8	24.8	0.007	> 0.99
Acetaminophen administration	30.2	27.3	0.069	0.17
Systemic opioid administration	28.1	24.9	0.074	0.13
Neuraxial labor analgesia	89.0	91.4	–0.081	0.08
SROM	27.6	29.0	–0.028	0.54
Chorioamnionitis	5.4	5.3	0.009	> 0.99
Antibiotic administration	48.1	49.4	–0.025	0.58
Group B streptococcus positive	12.5	12.7	–0.013	0.95
Cesarean delivery	23.3	23.0	0.010	0.91
White race	40.3	41.1	–0.004	0.71
Preterm	48.5	45.5	0.063	0.20

Data are presented as %.

*At Northwestern Memorial Hospital, labor nurses are responsible for assessment and care of healthy neonates. A pediatric hospitalist is the first-line pediatric provider at deliveries in which a higher level of neonatal evaluation and resuscitation is anticipated, such as those complicated by intrapartum fever or chorioamnionitis. A neonatologist is added to the pediatric team for very-high-risk neonates.

NICU = neonatal intensive care unit; SROM = spontaneous rupture of membranes.

used for analysis was the maximum temperature in labor. Although hourly temperatures are recorded during labor, these values are recorded on the fetal heart rate tracings. Data from the tracings are not available in the EDW, and therefore hourly temperatures and labor curves could not be evaluated. This precluded us from evaluating the interaction among the timing of fever development, magnesium therapy, and neuraxial analgesia, because we only had access to the highest temperature in labor and the time of its occurrence but not the time at which the patient initially became febrile. An additional limitation is that approximately 34.4% of cases were missing data on the maximum temperature, and we do not know whether these cases excluded from the analysis differed from the included cases. The duration of magnesium therapy and total dose of therapy were not evaluated; thus, we were unable to assess whether there is a dose-dependent effect on maternal temperature. Furthermore, given the retrospective nature of our data, we were unable to determine the mechanism of decreased maternal fever in patients receiving magnesium therapy.

An additional limitation is the definition of *fever* used for this study. Although the definition of fever as a temperature 38.0°C or greater may be considered conservative and broad, it is one of the most commonly used in clinical practice. Although Lieberman *et al.*[42] suggest that higher-grade fevers may be worse for neonatal outcomes, in human epidemiology studies even low-grade temperatures (*e.g.*, 37.5°C) are associated with adverse neonatal outcomes.[3] Additionally, there is reasonable evidence to suggest that the inflammation leading to hyperthermia and not the hyperthermia itself is culpable. In clinical practice, unexplained fever of 38.0°C is often considered clinical chorioamnionitis and is treated with antimicrobial therapy,[20] although the etiology is in fact not infectious.[43] Furthermore, clinical diagnosis of chorioamnionitis, per the Centers for Disease Control and Prevention guidelines, results in neonatal evaluation and treatment.[44]

Our data suggest that magnesium may play a protective role against the development of maternal fever. These findings should be validated in a prospective study to inform the use of magnesium as a potential intervention. Future work should evaluate the association between the duration of magnesium administration and the development of fever and the mechanism of this protective effect.

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Competing Interests

The authors declare no competing interests.

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Hiding from Santa Claus behind the curtain, four children populate a circular illustration that is suspended like a Christmas tree ornament on the cover of the December 28, 1889, issue of *Judge*, a weekly magazine of political satire. Dangling from the fireplace mantle are four Christmas stockings labeled with the names of St. Louis, Chicago, New York, and Washington—each a city hoping that Santa would fill that city's stocking with the job of hosting the Columbian Exposition. Signed "[Grant E.] Hamilton" by its political cartoonist, the illustration was captioned: "SUSPENSE! Which one will get the fair?" Eventually, Chicago won the bid for the 1893 Columbian Exposition. Once the Exposition was underway, Chicago's "Post-Graduate School of Anaesthesia" would hold classes weekday mornings but leave afternoons available for the postgraduate physicians and dentists to attend the world's fair. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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