Intrapartum Temperature Elevation, Epidural Use, and Adverse Outcome in Term Infants

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KEY WORDS

maternal fever, epidural analgesia, pregnancy, labor, infant, neonatal outcome, neurologic, seizures

ABBREVIATIONS

CMH—Cochran Mantel Haenszel

IL—interleukin

www.pediatrics.org/cgi/doi/10.1542/peds.2010-2301

doi:10.1542/peds.2010-2301

Accepted for publication Sep 27, 2011

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

WHAT'S KNOWN ON THIS SUBJECT: Previous observational studies and randomized trials have reported an association between the use of epidural analgesia for pain relief in labor and intrapartum maternal fever. Studies have also reported an increase in adverse neonatal outcomes with intrapartum maternal fever.

WHAT THIS STUDY ADDS: Among low-risk women receiving epidural analgesia, intrapartum maternal temperature $>99.5^{\circ}\text{F}$ was associated with adverse neonatal outcomes, with the rate of adverse outcomes increasing directly with maximum maternal temperature. Without temperature elevation, epidural use was not associated with adverse neonatal outcomes.

abstract

OBJECTIVES: To examine the association of intrapartum temperature elevation with adverse neonatal outcome among low-risk women receiving epidural analgesia and evaluate the association of epidural with adverse neonatal outcome without temperature elevation.

METHODS: We studied all low-risk nulliparous women with singleton pregnancies ≥ 37 weeks delivering at our hospital during 2000, excluding pregnancies where infants had documented sepsis, meningitis, or a major congenital anomaly. Neonatal outcomes were compared between women receiving ($n = 1538$) and not receiving epidural analgesia ($n = 363$) in the absence of intrapartum temperature elevation ($\leq 99.5^{\circ}\text{F}$) and according to the level of intrapartum temperature elevation within the group receiving epidural ($n = 2784$). Logistic regression was used to evaluate neonatal outcome while controlling for confounders.

RESULTS: Maternal temperature $>100.4^{\circ}\text{F}$ developed during labor in 19.2% (535/2784) of women receiving epidural compared with 2.4% (10/425) not receiving epidural. In the absence of intrapartum temperature elevation ($\leq 99.5^{\circ}\text{F}$), no significant differences were observed in adverse neonatal outcomes between women receiving and not receiving epidural. Among women receiving epidural, a significant linear trend was observed between maximum maternal temperature and all neonatal outcomes examined including hypotonia, assisted ventilation, 1- and 5-min Apgar scores < 7 , and early-onset seizures. In regression analyses, infants born to women with fever $>101^{\circ}\text{F}$ had a two- to sixfold increased risk of all adverse outcomes examined.

CONCLUSIONS: The proportion of infants experiencing adverse outcomes increased with the degree of epidural-related maternal temperature elevation. Epidural use without temperature elevation was not associated with any of the adverse outcomes we studied. *Pediatrics* 2012;129:e447–e454

Approximately 4 million women give birth in the United States each year, and >60% receive intrapartum epidural analgesia.^{1,2} Although epidural analgesia is generally considered a safe and effective method of pain relief during labor, both randomized trials and observational studies consistently demonstrate an association between epidural and maternal fever during labor.^{3–8} In low-risk women at term, epidemiologic studies have shown that >90% of fever during labor is related to epidural use.^{8,9} Although the precise mechanism of epidural-related fever has not been fully elucidated, recent data demonstrate that the fever is not due to infection.¹⁰

Investigations of term pregnancies have reported an association of intrapartum maternal fever with signs of neurologic depression in neonates such as lower Apgar scores, hypotonia,⁹ the need for assisted ventilation or cardiopulmonary resuscitation,^{9,11} and a three- to fourfold increased rate of neonatal seizures.^{12–15} Of greater concern is increasing evidence supporting an association between chorioamnionitis, primarily diagnosed on the basis of intrapartum fever, with neonatal stroke in term infants¹⁶ and the development of motor impairment or cerebral palsy in early childhood.^{17,18}

The purpose of our study was to determine the impact of epidural-related temperature elevation on neonatal outcome and to evaluate whether epidural analgesia is associated with adverse neonatal outcomes in the absence of temperature elevation.

METHODS

We conducted a retrospective cohort study of all infants born at Brigham and Women's Hospital Boston during 2000. The study was approved by the Human Research Committee at Brigham and Women's Hospital.

During the study period, 3894 nulliparous women delivered at the hospital. For the current analysis, we limited the population to women with singleton, term pregnancies (≥ 37 weeks gestation) with the fetus in a vertex presentation, who had the spontaneous or induced onset of labor and gave birth to a live born infant weighing ≥ 2500 g ($n = 3483$). Because we wished to study a low-risk population, we also excluded women with pregestational or gestational diabetes ($n = 109$), active genital herpes infection, HIV, or active syphilis ($n = 52$) during pregnancy. In addition, because we were interested in epidural-related fever, we excluded women if maternal temperature was never recorded ($n = 22$) or was $> 99.5^\circ\text{F}$ at admission ($n = 36$), or if they had spinal anesthesia ($n = 14$). To study the effects of intrapartum fever in the absence of infant infection, we also excluded pregnancies in which the infant was diagnosed with documented sepsis, meningitis, pneumonia, congenital infections, or viral infections ($n = 5$). Finally, we excluded cases in which infants had conditions that might be associated with adverse neonatal outcomes independent of maternal fever such as neonatal abstinence syndrome ($n = 3$), central nervous system anomalies, inborn errors of metabolism, or major congenital malformations ($n = 33$).

Our final study population included 3209 mother-infant pairs, 2784 infants born to women who received and 425 born to women who did not receive epidural analgesia during labor. We first evaluated the association of epidural use ($n = 1538$ epidural, $n = 363$ no epidural) with adverse neonatal outcomes in the absence of intrapartum maternal temperature elevation ($\leq 99.5^\circ\text{F}$). In the second phase of the analysis, we compared neonatal outcomes according to the level of temperature elevation within the group of women receiving epidural ($n = 2784$).

We did not examine outcomes for infants born to febrile women not receiving epidural because the number of women with fever $> 100.4^\circ\text{F}$ but no epidural was very small ($n = 10$), precluding additional statistical analysis.

Relevant data were abstracted from maternal and infant medical records by trained medical record abstractors. In addition to using a standardized form, abstractors were provided with specific guidelines for capturing each data element. Fetal distress or nonreassuring fetal status was coded as present if diagnosed by a physician during labor. Highest intrapartum maternal temperature was classified into 4 categories: (1) $\leq 99.5^\circ\text{F}$, (2) 99.6°F to 100.4°F , (3) 100.5°F to 101°F , and (4) $> 101^\circ\text{F}$. Maternal fever was defined as a maximum intrapartum temperature $> 100.4^\circ\text{F}$; maternal temperature elevation was defined as a maximum temperature $> 99.5^\circ\text{F}$. Most maternal temperatures were recorded orally; axillary temperatures were increased by 1°F for comparability.^{19,20} Laboratory data on potential markers of infection such as complete blood counts and blood cultures obtained as part of clinical care were obtained from institutional laboratory databases.

The following neonatal outcomes were evaluated immediately after delivery: transitional hypotonia ≤ 15 minutes (responding to stimulation); hypotonia lasting > 15 minutes (either recurring or not responding to stimulation); Apgar score < 7 at 1 and 5 minutes, and assisted ventilation (defined as positive pressure ventilation, bag and mask resuscitation, intubation, or chest compressions).

We also evaluated the occurrence of early-onset seizures (defined as seizures within the first 48 hours of life). The diagnosis of seizure was made by review of neonatal medical records by a neonatologist who confirmed the case only if observed by 2 people, including an attending neonatologist, or if the

diagnosis was based on EEG or made by a neurologist. A pediatric neurologist blind to the characteristics of labor and occurrence of intrapartum fever determined the specific brain injury for infants with seizures based on results of MRI and/or computed tomography scan. If an infant had multiple neuroimaging studies performed during their initial hospitalization, results of the last imaging was used.

STATISTICAL ANALYSIS

Demographic, pregnancy, intrapartum, and neonatal characteristics were compared using χ^2 tests or Fisher exact test for categorical variables. Continuous variables were compared by using Student *t* tests for normally distributed data and the Wilcoxon rank-sum test for nonparametric variables. When >2 groups were compared, analysis of variance was used for normally distributed variables and the Kruskal-Wallis test for nonparametric variables. A two-sided *P* value $< .05$ was considered statistically significant. To compare neonatal outcomes in infants of women without temperature elevation (maximum intrapartum temperature $\leq 99.5^\circ\text{F}$) according to epidural use, we performed multiple logistic regression analyses controlling for potential confounders. The Cochran-Mantel-Haenszel (CMH) summary χ^2 with 1 degree of freedom was employed to examine trends in the proportion of infants with adverse outcome across the 4 categories of intrapartum maternal temperature. Multiple logistic regression analyses were used to examine the association of maternal temperature elevation and neonatal outcomes, controlling for maternal age, infant birth weight, length of labor, and method of delivery (spontaneous vaginal delivery, cesarean section, and operative vaginal delivery) and expressed as odds ratios and 95% confidence intervals. Intrapartum temperature was modeled as

3 indicator variables (99.6°F – 100.4°F , 100.5°F – 101°F , and $>101^\circ\text{F}$) with women $\leq 99.5^\circ\text{F}$ as the referent group. Statistical analyses were performed by using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Of the 3209 low-risk nulliparous women in our population, 2784 (86.8%) received epidural analgesia for pain relief during labor, whereas 425 (13.2%) did not. Overall, 1246 (44.8%) women receiving epidural and 62 (14.6%) not receiving epidural developed a temperature $>99.5^\circ\text{F}$ after admission for delivery ($P < .0001$). Maternal fever $>100.4^\circ\text{F}$ developed during labor in 19.2% (535/2784) of women receiving epidural compared with 2.4% (10/425) of women not receiving epidural ($P < .0001$).

Comparison Among Women Without Temperature Elevation According to Epidural Use

To evaluate the effect of epidural in the absence of temperature elevation, we compared neonatal outcomes in women without temperature elevation (maximum intrapartum temperature $\leq 99.5^\circ\text{F}$)

according to epidural use (Table 1). Among women without temperature elevation, those receiving epidural were slightly older, less likely to receive welfare, and had larger infants and longer labors than women not receiving epidural. Women with epidural were also more likely to have Pitocin administered for induction or augmentation of labor and had higher rates of cesarean and operative vaginal delivery.

Among women without temperature elevation, the proportion of infants with hypotonia, low Apgar scores, the need for assisted ventilation immediately after delivery, and early-onset seizures was similar for women receiving and not receiving epidural (Table 2). In addition, no association with these adverse outcomes was noted in a multiple logistic regression model that adjusted for confounders such as maternal age, birth weight, length of labor, and method of delivery.

Comparison Among Women With Epidural According to Maximum Temperature

We then examined adverse neonatal outcomes among women receiving

TABLE 1 Demographic and Pregnancy Characteristics of Women Without Temperature Elevation ($\leq 99.5^\circ\text{F}$) According to Epidural Use

	No Epidural Analgesia (<i>n</i> = 363)	Epidural Analgesia (<i>n</i> = 1538)	<i>P</i>
	<i>n</i> (%)	<i>n</i> (%)	
Demographic characteristics			
Mean maternal age in years ($\pm$ SD)	27.0 (± 6.6)	29.4 (± 5.9)	$<.0001$
Welfare recipient	98 (27.0)	203 (13.2)	$<.0001$
Smoked or quit during pregnancy	22 (6.1)	99 (6.4)	.8
Pregnancy and labor characteristics			
Mean birth wt in grams ($\pm$ SD)	3339 (± 395)	3421 (± 434)	.0006
Median length of labor in hours (range)	6.4 (0.2–31.1)	11 (0.9–60.4)	$<.0001^a$
Premature rupture of membranes	119 (32.8)	457 (29.7)	.3
Use of Pitocin	104 (28.7)	1113 (72.4)	$<.0001$
Fetal distress	29 (8.0)	204 (13.3)	.006 ^b
Delivery			
Spontaneous vaginal delivery	310 (85.4)	1033 (67.2)	$<.0001$
Cesarean delivery	39 (10.7)	220 (14.3)	
Forceps	1 (0.3)	88 (5.7)	
Vacuum	13 (3.6)	197 (12.8)	

Based on χ^2 for categorical variables and student *t*-test for continuous variables.

^a Wilcoxon rank-sum test for nonparametric data.

^b Fetal distress or nonreassuring fetal status diagnosed by physician.

TABLE 2 Multiple Logistic Regression for Neonatal Outcomes According to Epidural Use Among Women Without Temperature Elevation ($\leq 99.5^{\circ}\text{F}$)

	No Epidural Analgesia (<i>n</i> = 363)	Epidural Analgesia (<i>n</i> = 1538)		<i>P</i>
	<i>n</i> (%)	<i>n</i> (%)	OR (95% CI) ^a	
Hypotonia (transitional)	39 (10.7)	166 (10.8)	0.7 (0.5–1.0)	.08
Hypotonia (>15 min)	0 (0)	9 (0.6)	NC	.9
Assisted ventilation	9 (2.5)	68 (4.4)	1.3 (0.6–2.7)	.5
1-min Apgar <7	24 (6.6)	98 (6.4)	0.8 (0.5–1.3)	.3
5-min Apgar <7	2 (0.6)	5 (0.3)	0.2 (0.04–1.6)	.1
Early-onset neonatal seizures	0 (0)	2 (0.1)	NC	.9

Referent group is women without temperature elevation ($\leq 99.5^{\circ}\text{F}$) and no epidural analgesia. One infant missing in the epidural analgesia group (*N* = 1537) for hypotonia (transitional and >15 min) and Apgar <7 (1 and 5 min). CI, confidence interval; NC, not calculable for this subgroup because there were no cases in the no-epidural analgesia group; OR, odds ratio.

^a Adjusted for maternal age, infant birth wt, length of labor, and method of delivery in a logistic regression model.

TABLE 3 Demographic and Pregnancy Characteristics of the Study Population

	Epidural Analgesia				<i>P</i>
	≤99.5°F (<i>n</i> = 1538)	99.6°F–100.4°F (<i>n</i> = 711)	100.5°F–101°F (<i>n</i> = 297)	>101°F (<i>n</i> = 238)	
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Demographic characteristics					
Mean maternal age in years (± SD)	29.4 (±5.9)	30.1 (±5.2)	30.6 (±5.7)	30.1 (±5.5)	.001
Welfare recipient	203 (13.2)	82 (11.5)	33 (11.1)	26 (10.9)	.5
Smoker	99 (6.4)	38 (5.3)	20 (6.7)	11 (4.6)	.5
Pregnancy and labor characteristics					
Mean birth wt in grams (± SD)	3421 (±434)	3548 (±423)	3568 (±403)	3578 (±383)	<.0001
Median length of labor in hours (range)	11 (0.9–60.4)	14.2 (3.2–52.7)	15.4 (3.6–45.0)	16.3 (5.8–57.2)	<.0001 ^a
Premature rupture of membranes	457 (29.7)	223 (31.4)	97 (32.7)	61 (25.9)	.3
Use of Pitocin	1113 (72.4)	583 (82.0)	258 (86.9)	207 (87.0)	<.0001
Fetal distress	204 (13.3)	89 (12.5)	38 (12.8)	41 (17.2)	.3 ^b
Delivery					
Spontaneous vaginal delivery	1033 (67.2)	411 (57.8)	157 (52.9)	100 (42.0)	<.0001
Cesarean delivery	220 (14.3)	125 (17.6)	72 (24.2)	72 (30.3)	
Forceps	88 (5.7)	54 (7.6)	24 (8.1)	17 (7.1)	
Vacuum	197 (12.8)	121 (17.0)	44 (14.8)	49 (20.6)	

P values refer to comparisons across the 4 groups. Based on χ^2 for categorical variables and analysis of variance for continuous variables.

^a Kruskal-Wallis test for nonparametric variables.

^b Fetal distress or nonreassuring fetal status diagnosed by physician.

epidural analgesia according to the maximum level of maternal temperature elevation during labor. Among women receiving an epidural, the maximum level of temperature elevation was >101 $^{\circ}\text{F}$ for 238 (8.6%) women, 100.5 $^{\circ}\text{F}$ to 101 $^{\circ}\text{F}$ for 297 (10.7%) women, 99.6 $^{\circ}\text{F}$ to 100.4 $^{\circ}\text{F}$ for 711 (25.5%) women, and $\leq 99.5^{\circ}\text{F}$ for 1538 (55.2%) women. Compared with women whose maximum temperature was $\leq 99.5^{\circ}\text{F}$, those who developed a temperature $\geq 99.6^{\circ}\text{F}$ were somewhat older, had larger infants, and

had longer labors (Table 3). In addition, women with a temperature $\geq 99.6^{\circ}\text{F}$ were far more likely than women whose temperature was $\leq 99.5^{\circ}\text{F}$ to have been delivered by cesarean section or to have required an operative vaginal delivery by vacuum extraction.

Adverse neonatal outcomes increased with maximum maternal intrapartum temperature (Fig 1). The proportion of infants with transitional hypotonia increased from 10.8% when maternal temperature was $\leq 99.5^{\circ}\text{F}$ to 25.2%

with fever >101 $^{\circ}\text{F}$ (CMH χ^2 , $P < .0001$; Table 4). Similarly, the proportion of infants with hypotonia lasting >15 minutes increased from 0.6% when maternal temperature was $\leq 99.5^{\circ}\text{F}$ to 2.5% with fever >101 $^{\circ}\text{F}$ (CMH χ^2 , $P = .0005$). The number of infants requiring substantial resuscitation measures at delivery increased from 4.4% when maternal with a maximum temperature $\leq 99.5^{\circ}\text{F}$ to 12.2% when maternal fever was >101 $^{\circ}\text{F}$ (CMH χ^2 , $P < .0001$).

The proportion of infants with Apgar scores <7 at 1 minute increased from 6.4% when maternal temperature was $\leq 99.5^{\circ}\text{F}$ to 13.5% with fever >101 $^{\circ}\text{F}$ (CMH χ^2 , $P < .0001$), and this same pattern was observed at 5 minutes of life for Apgar scores <7, with an increase from 0.3% to 2.1% (CMH χ^2 , $P = .0007$). Despite the fact that the number of infants with early-onset seizures in our sample was relatively small (*n* = 8), we observed a significant increase in the proportion of infants with seizures, from 0.1% when the mother's temperature was $\leq 99.5^{\circ}\text{F}$ to 1.3% with fever >101 $^{\circ}\text{F}$ (CMH χ^2 , $P = .008$).

Multiple logistic regression analyses controlling for maternal age, infant birth weight, length of labor, and method of delivery demonstrated that maternal temperature of 99.6 $^{\circ}\text{F}$ to 100.4 $^{\circ}\text{F}$ was associated with an almost twofold increase in the risk of both transitional hypotonia and 1-minute Apgar score <7 compared with infants whose mothers had a maximum temperature of $\leq 99.5^{\circ}\text{F}$ (Table 4). Infants of women who developed maternal fever 100.5 $^{\circ}\text{F}$ to 101 $^{\circ}\text{F}$ were twice as likely to experience transitional hypotonia after delivery, 3 times more likely have hypotonia >15 minutes, and almost twice as likely to have a 1-minute Apgar score <7 as infants of women without temperature elevation (Table 4).

Maternal fever exceeding 101 $^{\circ}\text{F}$ was associated with a twofold increase in

FIGURE 1

Occurrence of neonatal outcomes according to maximum intrapartum temperature among women who used epidural analgesia.

TABLE 4 Multiple Logistic Regression for Neonatal Outcomes According to Maximum Maternal Temperature

	Epidural Analgesia							
	≤99.5°F (n = 1538)	99.6°F–100.4°F (n = 711)	OR (95% CI) ^a		100.5°F–101°F (n = 297)	OR (95% CI) ^a		>101°F (n = 238)
	n (%)	n (%)			n (%)			n (%)
Hypotonia (transitional)	166 (10.8)	135 (19.0)	1.8	(1.4–2.3)	64 (21.6)	1.9	(1.4–2.7)	60 (25.2)
Hypotonia (>15 min)	9 (0.6)	9 (1.3)	1.9	(0.7–4.9)	7 (2.4)	3.3	(1.2–9.2)	6 (2.5)
Assisted ventilation	68 (4.4)	48 (6.8)	1.3	(0.9–1.9)	24 (8.1)	1.5	(0.9–2.4)	29 (12.2)
1-min Apgar <7	98 (6.4)	78 (11.0)	1.6	(1.2–2.2)	37 (12.5)	1.7	(1.2–2.6)	32 (13.5)
5-min Apgar <7	5 (0.3)	5 (0.7)	1.8	(0.5–6.5)	4 (1.4)	3.3	(0.8–12.6)	5 (2.1)
Early-onset neonatal seizures	2 (0.1)	2 (0.3)	1.7	(0.2–12.6)	1 (0.3)	1.7	(0.1–19.3)	3 (1.3)

Referent group is women with maximum maternal temperature ≤99.5°F (n = 1538). One infant missing in the ≤99.5°F temperature group (n = 1537) for hypotonia (transitional and >15 min) and Apgar <7 (1 and 5 min). CI, confidence interval; OR, odds ratio.

^a Adjusted for maternal age, infant birth wt, length of labor, and method of delivery in a logistic regression model.

the risk of transitional hypotonia, a threefold increased risk of hypotonia lasting >15 minutes, and a twofold increased risk for assisted ventilation. A fever >101°F was also associated with a twofold increased risk of a low Apgar score at 1 minute and an almost fivefold increase in the risk of having an Apgar score <7 at 5 minutes of life (Table 4).

Infants of mothers with fever >101°F were also 6.5 times more likely to have

a seizure compared with infants of mothers with a maximum temperature ≤99.5°F. All 8 seizure cases occurred between 12 and 46 hours (mean = 29 hours, SD ±11.2) after birth. Neuroimaging indicated that 1 infant had hypoxic-ischemic encephalopathy, 3 infants had intracranial hemorrhage, and 4 infants had a cerebral infarction. Of the 8 infants with neonatal seizures, maternal intrapartum fever >100.4°F was present in 3 of 4 infants with

cerebral infarction and 1 of 3 infants with intracranial hemorrhage. The 1 infant with hypoxic-ischemic encephalopathy was born to a mother whose maximum intrapartum temperature was ≤99.5°F.

DISCUSSION

This study and others^{8,9,12} showing an increase in adverse outcomes among infants of febrile mothers in the absence of demonstrated infection suggest that increased maternal temperature,

regardless of etiology, may have implications for the fetus. In our population of low-risk nulliparous women, elevated intrapartum maternal temperature ($>99.5^{\circ}\text{F}$) among women receiving epidural analgesia was associated with a higher risk of adverse neonatal outcomes such as hypotonia, the need for assisted ventilation, low 1- and 5-minute Apgar scores, and early-onset neonatal seizures. Our data indicated a trend, with a statistically significant increase in the occurrence of these adverse outcomes with increasing maximum maternal temperature (Fig 1). After adjusting for potentially confounding factors, high maternal fever $>101^{\circ}\text{F}$ was associated with a two- to sixfold increase in the occurrence of all adverse neonatal outcomes examined. Our estimates were conservative because length of labor was included as a potential confounder in our models. These findings are consistent with previous results from our institution^{9,12} and another study examining this issue.¹³ In contrast, we found no increase in adverse neonatal outcomes between women receiving and not receiving epidural in the absence of maternal temperature elevation, suggesting that epidural analgesia without accompanying maternal fever does not have an immediate effect on neonatal status.

A meta-analysis²¹ reported that labor epidural analgesia was not associated with an increase in adverse neonatal outcomes. However, the authors did not examine whether adverse effects may have occurred more often among the subset of women who were febrile. Because approximately 15% to 20% of women become febrile, even a relatively large increase in adverse outcomes in that subgroup might not be detectable in an analysis of the overall population of women receiving epidural. Our finding of an increase in unexplained seizures among infants of women with fever $>101^{\circ}\text{F}$ is of concern. Although the

findings were based on a relatively small number of seizures ($n = 8$), it is consistent with other studies reporting an association of intrapartum maternal fever with neonatal encephalopathy.^{13,15} We also previously reported an association of unexplained seizures with epidural-related fever in a different population.^{9,12} Studies hypothesizing an association between neonatal encephalopathy or seizures and intrapartum maternal fever have assumed the fever resulted from infection such as chorioamnionitis.^{14,15,17} However, data suggest that among women delivering at term, most fever is related to epidural use rather than infection.^{8–10,22} In their study of low-risk women, Impey et al¹³ found a positive blood culture in only 1 of 16 infants (6.3%) with neonatal encephalopathy.

We also observed that 3 of 4 infants diagnosed with cerebral infarction were born to febrile mothers. Although not statistically significant, possibly because of small numbers, this finding is consistent with recent evidence suggesting an association between maternal fever and neonatal stroke in term infants.¹⁶ However, in that study, maternal fever was viewed by the authors as a marker for infection. This study did not consider the possibility that maternal fever was not the result of infection but rather related to the use of epidural. Term infants with stroke, specifically perinatal arterial stroke, are at higher risk of long-term neurologic impairment during childhood,^{16,23} as are neonates with seizures or encephalopathy.^{17,24} Previous studies have demonstrated that clinical chorioamnionitis, primarily diagnosed by the presence of intrapartum fever, is associated with a four- to ninefold increased risk of cerebral palsy in term infants.^{17,18} If confirmed, these findings suggest that exposure to intrapartum fever may not only increase the risk of adverse effects at birth but could

potentially contribute to the development of long-term neurologic morbidity.

The exact mechanism through which epidural analgesia causes maternal fever and the mechanism through which the fever might increase the risk of adverse neonatal outcomes remains unclear. Our recent work,¹⁰ as well that of others,^{25–27} suggests an inflammatory response accompanying epidural-related fever. Studies have linked epidural use with elevated maternal serum levels of interleukin (IL)-6²⁵ and a higher monocyte production of IL-1 β and IL-6 in the newborn.²⁶ Goetzl et al²⁷ found that in the absence of neonatal infection, intrapartum epidural-related fever was associated with elevation of both maternal and fetal serum levels of IL-6 compared with women receiving epidural who did not develop fever. Cytokines released in response to inflammation or infection can act as mediators of neurologic injury and have been linked to neonatal encephalopathy and brain damage in newborns.^{28–30} Although available data suggest that epidural-related fever is associated with an inflammatory response, it is not yet clear whether control of the fever after it occurs would ameliorate the adverse neonatal outcomes we observed.

Because core fetal temperature in utero is approximately 0.5°C to 0.9°C higher than maternal temperature,^{31–33} the fetus may be exposed to higher temperatures than suggested by the degree of maternal temperature elevation. Previous animal studies have shown even small elevations in brain temperature before or during ischemia can increase the magnitude of brain injury and neuronal cell death in the fetus.^{34–36}

There are several limitations in our study. In our low risk population, there were few women not receiving epidural who developed fever ($n = 10$) precluding meaningful analysis of that group. We are therefore not able to comment

on the effects epidural-related fever compared with fever that occurs in the absence of epidural use.

In addition, the more frequent presence of pediatricians in the delivery room when a woman develops fever could have resulted in an increased use of resuscitative measures or assignment of lower Apgar scores. We addressed this potential bias by evaluating more serious resuscitative measures (positive pressure ventilation, bag and mask resuscitation, intubation, or chest compressions) because we believed such measures would have been used by pediatricians only when clearly necessary, and comparably applied regardless of maternal temperature status. We also evaluated 5-minute Apgar scores <7 and hypotonia lasting >15 minutes, which also represented more serious indicators of depression at birth. The higher rate of adverse outcomes among the infants of women whose maximum temperature was between 99.6 and 100.4°F, deliveries at which pediatricians would not be present, suggests the presence of pediatricians at the deliveries of febrile women is not responsible for the results we report.

Also, although we excluded infants with documented infection, one must consider the possibility that neonatal infection undiagnosed due to intrapartum maternal treatment with antibiotics

contributed to the increase in adverse neonatal outcomes we observed. Our institution follows Centers for Disease Control guidelines^{37,38} for evaluation and treatment of neonatal sepsis. All infants born to mothers with intrapartum fever >100.4°F were evaluated for sepsis, as were infants with additional risk factors such as fetal tachycardia or rupture of membranes ≥18 hours. Among the 3209 infants in our sample, 2.2% (17 of 760) were treated with antibiotics for 3 to 7 days and 0.7% (5 of 760) for 7 days or more. Although it is plausible that some of these cases represent “presumed culture negative infection,” exclusion of these cases did not substantially alter the associations we noted.

Finally, it is plausible that in some cases undetected maternal intrapartum infection was responsible for the adverse outcomes we observed. To minimize the possibility of including women with preexisting infection, we excluded women with temperatures >99.5°F at admission. In addition, it is important to note that 20% of infants born to mothers receiving epidural analgesia experienced ≥1 adverse outcomes. Given the expected low rate of infection in low-risk infants (1–5 in 1000),^{39,40} it seems unlikely that infection is responsible for our findings of adverse outcomes.

CONCLUSIONS

Our study indicates that even moderate elevation in maternal temperature among low-risk nulliparous women who received epidural analgesia is an independent predictor of adverse neonatal outcome in term infants. The proportion of infants experiencing adverse outcomes increased directly with the degree of maternal temperature elevation. Epidural use in the absence of elevated temperature was not associated with any of the adverse outcomes we studied. Although many of the specific outcomes we found associated with elevated maternal temperature may be transient, it is possible that particularly the increase in early-onset neonatal seizures could have implications for longer-term health of the infant.

ACKNOWLEDGMENTS

This research was supported in part by a Predoctoral Individual Ruth L. Kirschstein National Research Service Award from the Eunice Kennedy Shriver National Institute of Child Health and Human Development grant 1F31HD046408-01A1 to Dr Greenwell.

We thank the Center for Clinical and Epidemiologic Research at Brigham and Women's Hospital, Manuel Chinchilla, MA, and the entire research team.

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