Epidural Fever in Obstetric Patients: It's a Hot Topic

Laura Goetzl, MD, MPH

Traditionally, maternal fever ≥38°C during the course of labor has been attributed to ascending infection of the amniotic cavity or "chorioamnionitis." In the past, typical rates of chorioamnionitis ranged from 1% to 5%. However, in 1989, Fusi et al.[1] first reported a novel phenomenon, hyperthermia associated with epidural analgesia in parturients. This finding was unexpected given that peripheral vasodilation below the level of epidural blockade is typically associated with a slight decrease in core temperature in non-obstetric patients. In the decades that followed, multiple publications linked intrapartum epidural analgesia with increased rates of maternal fever. The cumulative risk of intrapartum fever in nulliparas receiving epidural analgesia has generally been reported to be between 11% and 33%.[2] Despite the now well-established relationship between epidural analgesia and maternal fever, controversy continues to rage over the etiology.

In this issue of *Anesthesia & Analgesia*, Sharma et al.[3] present the results of a well-designed, double-blind, placebo-controlled trial of prophylactic cefoxitin versus placebo to prevent epidural fever. The underlying premise of this investigation is 2-fold: first, epidural fever may be infectious in origin and second, there is potential merit in prevention. The study population consisted of nulliparous women at Parkland Hospital requesting epidural analgesia for labor pain. The study population was appropriate; nulliparous women are consistently at the highest risk of epidural fever due to longer duration of exposure to analgesia.[4] The choice of cefoxitin was reasonable given that broad-based prophylaxis was the goal. Although many institutions are now using lower concentration bupivacaine or ropivacaine boluses and patient-controlled techniques to initiate and maintain analgesia, the bupivacaine concentrations used in this study (0.25% for initiation and 0.125% for maintenance) likely represent those at the high end of the range currently used in clinical practice. Duration of exposure to epidural analgesia (median duration approximately 6 hours) was average or perhaps somewhat shorter than average for a nulliparous population. Maternal temperature was measured hourly ensuring uniform ascertainment of fever. Potential exposure to infection was modest, and most women labored rapidly and had between 4 and 6 vaginal examinations; despite this, the reported rate of intrapartum fever was surprisingly high at 38.5% in the entire group.

One potential reason for the higher than expected rates of fever was the method of temperature assessment. Tympanic devices using infrared technology to measure temperature can be subject to variability, especially in untrained users. Furthermore, maternal tympanic temperature does not correlate as well with fetal temperature as oral measurements. Despite this, tympanic temperature evaluation is common practice in many labor and delivery units while rates of intrapartum fever as high as that reported in this study are uncommon. There was no objective reason to believe that the individuals assessing temperature in this study were trained any differently than the individuals assessing temperature in other studies. In women who developed a fever and in whom serial temperature measurements were available, 77% remained persistently febrile, so temperature measurements were consistent in the majority of cases. Finally, the authors have used the same device in prior studies and have reported low rates of intrapartum fever in women who did not receive epidural analgesia. If afebrile women were misclassified as febrile in the current study, study results would be biased toward the null. However, even if only three-quarters of fevers in the study were genuine, a 29% rate of fever following antibiotic prophylaxis is not encouraging. Overall, there were no other significant methodological flaws that undermine the study findings.

Thus, the results of this study appear clear: prophylactic antibiotic treatment does not alter the subsequent rate of epidural fever to a degree that is statistically or clinically significant. This primary outcome provides very strong evidence against an infectious etiology for epidural fever in obstetric patients. Stated another way, there is no evidence to support an oft-stated hypothesis that epidural fever is an artifact of preferential selection of epidural analgesia by women with dysfunctional prolonged labors who are at subsequent risk for infectious chorioamnionitis. Nor is there any evidence that decreased pain with cervical examinations following epidural analgesia leads to frequent and indiscriminate obstetric evaluations that, in turn, cause ascending infection.

In some ways, these results are a relief for both providers and patients. Yancey et al.[5] elegantly demonstrated that introduction of an epidural analgesia service was associated with an immediate and abrupt 18-fold increase in the rate

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of intrapartum fever in nulliparous patients (from 0.6% to 11.0%). Considering the current quality and safety focus on hospital-acquired infections, any new intervention that was associated with these types of rates of infectious consequences would certainly raise eyebrows. Therefore, it is reassuring that the widespread preference for epidural analgesia in nulliparas in the United States is not associated with skyrocketing rates of intrapartum infection.

However, even if infection is excluded, intrapartum fever that affects up to 1 in every 3 first-time mothers with epidural analgesia has consequences. Some consequences, such as neonatal sepsis evaluations and increased antibiotic treatment, are largely short-term issues of cost and excess treatment; this in no way minimizes the maternal distress associated with sepsis evaluation or the rare complications of treatment. The more serious potential consequence is that noninfectious intrapartum fever in low-risk nulliparous patients has been associated with an increased risk of neonatal encephalopathy. In a large prospective cohort of low-risk nulliparous patients with an observed intrapartum fever rate of 6.9%, the rate of neonatal encephalopathy was 1.13% in infants born to febrile mothers, 1.58% in infants born with acidosis, and 0.12% in infants born with neither risk.[6,7] All neonates with encephalopathy were evaluated for infection, and no cases of sepsis were found. What is striking is that intrapartum fever and fetal acidosis were associated with surprisingly similar risks. A tremendous amount of effort is spent attempting to avoid fetal acidosis, including oxytocin safety protocols, continuous intrapartum fetal monitoring, and excess rates of cesarean delivery; in contrast, comparatively little effort has been spent on preventing intrauterine exposure to fever. Sharma et al.[3] may be on the right track with their premise that epidural-related fever could be worth preventing.

However, to effectively prevent epidural-related fever, we must understand its true mechanism. The current study by Sharma et al.[3] provides some tantalizing clues. Epidural-related fever was associated with neutrophilic placental inflammation, and levels of inflammation were not reduced with antibiotic prophylaxis. These findings support a previous report by Riley et al.[8] that demonstrated an association between intrapartum fever and noninfectious histologic placental chorioamnionitis (70.6% with fever vs 27.2% in afebrile group). The key question is what is the primary stimulus for the placental inflammation associated with epidural fever if not infection? The answer to this question is not currently known. In theory, epidural analgesia stimulates a primary inflammatory response either in the placenta or in the epidural space (followed by secondary placental inflammation). Since the phenomenon of hyperthermia following epidural analgesia appears to be unique to laboring patients, it is tempting to assume that placental inflammation is the primary etiology. However, Wang et al.[9] recently reported that low-dose epidural steroids can prevent or mitigate the increase in maternal temperature during epidural analgesia as well as decrease maternal inflammatory activation. This suggests that anti-inflammatory treatment limited to the epidural space may prevent subsequent peripheral and/or placental inflammation and that the epidural space may be the primary source of inflammation. The stimulus for the inflammation could be mechanical or drug related, but the reason why either would do so preferentially in obstetric patients is not known.

Overall, the current study by Sharma et al.[3] adds further strong evidence for a noninfectious inflammatory etiology for epidural fever. If we agree with the premise that epidural fever is worth preventing, these latest data should help focus new research efforts on interventions that are more likely to result in effective prevention. Potential interventions include agents that block the maternal inflammatory response to epidural analgesia without increasing maternal or fetal risks.

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A Randomized Trial of the Effects of Antibiotic Prophylaxis on Epidural-Related Fever in Labor

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BACKGROUND: It has been suggested that the development of maternal fever during epidural analgesia could be due to intrapartum infection. We investigated whether antibiotic prophylaxis before epidural placement decreases the rate of epidural-related fever.

METHODS: In this double-blind, placebo-controlled trial, 400 healthy nulliparous women requesting epidural analgesia were randomly assigned to receive either cefoxitin 2 g or placebo immediately preceding initiation of epidural labor analgesia. Maternal tympanic temperature was measured hourly, and intrapartum fever was defined as a maternal temperature of ≥38°C. Neonates born to women with fever were evaluated for possible sepsis, and available placentas were evaluated for the presence of neutrophilic inflammation. The primary outcome was maternal fever during epidural analgesia.

RESULTS: Thirty-eight percent of women in the cefoxitin group and 40% of women in the placebo group developed fever ($P = 0.68$). The risk difference (95% confidence interval) for fever ≥38°C during labor (antibiotic versus placebo) was −2.0% (−11.5 to 7.5), and for fever >39°C during labor was −1.5% (−4.7 to 1.7). Approximately half of each study group had placental neutrophilic inflammation, but administration of cefoxitin had no significant effect on any grade of neutrophilic inflammation. Fever developed significantly more often in the women with placental neutrophilic inflammation compared with those without such inflammation (73/158 vs 33/144, $P < 0.001$; risk difference 23% [95% confidence interval, 13.0–34.0]). There were no significant differences in any neonatal outcomes between the antibiotic and placebo study groups. Sepsis was not diagnosed in any of the infants. There were no neonatal deaths.

CONCLUSION: Fever during labor epidural analgesia is associated with placental inflammation, but fever and placental inflammation were not reduced with antibiotic prophylaxis. This finding suggests that infection is unlikely to be the cause in its development. (Anesth Analg 2014;118:604–10)

Epidural analgesia has emerged as a popular method of pain relief during labor during the latter half of the 20th century. Although epidural analgesia provides very effective pain relief during labor, its use may be associated with development of maternal fever (≥38°C) in >20% of women.[1] Consequences of maternal fever may include increased neonatal evaluations for sepsis, increased use of antibiotics, and prolonged hospital stay.[2–4] The precise mechanism of the development of maternal fever during epidural analgesia is unclear.[5] However, possible mechanisms include (1) increased metabolic expenditure during labor, (2) decrease in evaporative heat loss through hyperventilation as a result of pain relief, (3) thermoregulatory changes induced by epidural analgesia through peripheral sensory (autonomic) blockade, (4) direct central nervous system effects of local anesthetic drugs due to the release of cytokines,[6–8] (5) sweat gland paralysis resulting from neural blockade decreasing sweating and evaporative heat loss,[9] (6) noninfectious systemic inflammatory process,[10] and (7) intrapartum infection.[11]

Women who choose epidural analgesia may have prolonged and dysfunctional labor and hence may inherently be predisposed to infection of the amniotic cavity and fetus.[12–15] Usual organisms isolated in the amniotic fluid of patients with chorioamnionitis include a mixture of aerobes and anaerobes. We hypothesized that if intrapartum infection is one of the causes of maternal fever during epidural analgesia, then prophylactic administration of antibiotics might reduce the occurrence of such infection-related fever attributed to epidural analgesia. This randomized, double-blind trial in low risk women at term was performed to determine whether prophylactic antibiotic administration before the initiation of epidural analgesia decreases the rate of epidural analgesia-related fever.

METHODS

This randomized, double-blind, placebo-controlled study was developed by investigators from the Departments of Anesthesiology, Obstetrics and Gynecology, and Pathology at the University of Texas Southwestern Medical Center at Dallas. This study protocol was approved by the IRB at the University of Texas Southwestern Medical Center at Dallas, and was conducted between June 2002 and December 2005. This trial commenced and was completed before registration was required with ClinicalTrials.gov.

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Healthy nulliparous women presenting to Parkland Hospital with singleton cephalic gestations at term and in spontaneous labor (cervical dilation 4–6 cm with uterine contractions) and requesting epidural analgesia were offered participation in this study. Women giving written informed consent were randomly assigned to receive either cefoxitin 2 g or an identical appearing placebo (normal saline) immediately preceding placement of an epidural catheter. The randomization sequence was computer-derived in blocks of 20 subjects and placed in sealed opaque envelopes. The envelope was opened at the time of request of epidural analgesia immediately before antibiotic administration. The study drug was disbursed by the Parkland Hospital Investigational Drug Service. A follow-up dose of study drug was given at 6 hours after the first dose in undelivered women. Women who developed an intrapartum fever ≥38°C were treated with IV ampicillin 2 g every 6 hours plus IV gentamicin (1. 5 mg/kg) every 8 hours. This therapy was continued after delivery until the patient was afebrile for 24 hours. Cefoxitin has been safely used for prophylaxis against infection with gram-positive and gram-negative organisms in patients undergoing gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, and cesarean delivery.[16] Epidural analgesia was administered using a standardized method. A 500-mL bolus of lactated Ringer's solution was administered, followed by placement of an epidural catheter into the lumbar epidural space through a 17-gauge Tuohy needle. After a test dose of 3 mL of 1.5% lidocaine with epinephrine 1:200,000, analgesia was achieved with 3-mL increments of 0.25% bupivacaine, titrated to a bilateral T-10 sensory level. A continuous epidural infusion of 0.125% bupivacaine with fentanyl 2 μg/mL was infused at 8 to 10 mL/h to maintain a T-10 sensory level.

Our labor management approach encourages amniotomy in active labor when the fetal head is applied to the cervix. Pelvic examinations were performed approximately every 2 hours to evaluate the progress of labor. Oxytocin augmentation of labor was begun when the rate of cervical dilation was <1 cm/h, and a hypotonic contraction pattern was diagnosed using internal electronic fetal monitoring. Maternal tympanic temperature was measured by midwives or research nurses hourly using a Genius® thermometer (Sherwood Medical, St. Louis, MO). A study comparing various temperature measurement sites during cardiac surgery concluded that the tympanic temperature using Genius® tympanic thermometer reflects rapid changes in body temperature better than axillary or rectal temperature.[17] Intrapartum fever was defined as a maternal temperature of 38°C or higher. Neonates born to women with fever during labor were commonly evaluated for possible sepsis, which included a complete blood count and blood cultures, after which they were given antibiotics for 48 hours. Indications for a sepsis evaluation in neonates born to women without fever in labor included temperature instability, tachypnea, dusky spells, lethargy, or hypoglycemia. Neonates with suspected sepsis were empirically treated with antibiotics for 48 hours. This was the standard of practice during the interval of the study and was not part of the trial protocol.

Providers were asked to submit the placentas for histologic examination. Placentas were labeled with a study number at delivery and refrigerated immediately. A single senior pathologist blinded to study drug evaluated the placentas within 48 hours of delivery. The placenta was examined according to routine protocol. The following sections were submitted for each placenta: 2 sections of umbilical cord, 2 full-thickness sections of placental parenchyma, and a section of a membrane roll that included the point of membrane tear or "rupture." All sections were evaluated for the presence and severity of neutrophilic infiltrates in the extraplacental membranes or chorionic plate (acute chorioamnionitis). There are many ways to define the severity of acute chorioamnionitis. We graded acute chorioamnionitis using a simple scheme previously reported.[18,19] This scheme uses the intensity of the neutrophilic infiltrate in the area of greatest density on the free membranes or chorionic plate and categorizes the inflammation as mild, moderate, or severe. We also included "necrotizing chorioamnionitis" as a separate category, defined as inflammation with necrosis of the amnion and/or chorion.[19] We modified the designation of severity of inflammation of umbilical cord by reporting funisitis as neutrophilic inflammation involving Wharton's jelly and vasculitis by assigning categories based on the number of vessels involved by the inflammation. Similar to the extraplacental membranes, necrotizing funisitis required the presence of necrotizing neutrophilic inflammation involving Wharton's jelly.

Sample size was based on the incidence of intrapartum fever in a prior study of similar women conducted at our hospital.[1] We reported that 23% to 33% of women randomized to epidural analgesia developed fever during labor. An analysis based on a projected absolute reduction of fever with antibiotic treatment from 20% to 10% required 200 women enrolled in each study arm. This analysis used 80% power to detect a 2-tailed significance level $\alpha = 0.05$.

Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC). Data were analyzed on an intention-to-treat principle. Further analysis was performed according to the intended randomization for those deliveries in which placentas were available. We also compared histologic findings in the placentas and neonatal outcome in women who developed fever versus those who did not. Comparisons using Student *t* test or Wilcoxon rank sum test were assigned a priori under assumptions of statistical normality or not. Age, height, weight, birth weight, and temperature were assumed to satisfy statistical normality from prior experience as to the symmetry of their frequency distributions. Under the central limit theorem for sufficiently large sample sizes, such data satisfy the normality assumption for Student *t* test. Data such as duration of labor, duration of analgesia, length of membrane rupture, and cervical dilation at epidural placement which experience high degrees of asymmetry or positive skewness due to a zero lower bound and extreme possibilities were examined using the Wilcoxon rank sum test.

We further analyzed the fever outcome data for those with placentas available to determine the association between randomization arm and fever stratified by placental neutrophilic infiltration as well as the association between infiltration and fever stratified by randomization. This was accomplished using the Breslow-Day statistic to evaluate the difference in odds ratios between strata

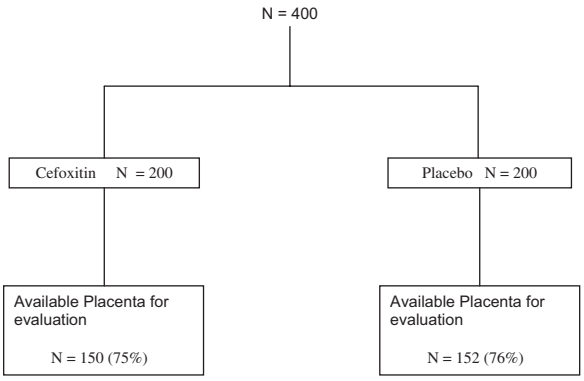

Figure 1. Women at term in labor, receiving epidural analgesia.

(interaction) and the Cochran-Mantel-Haenszel test for the association adjusting for the strata.

Risk differences are provided as the difference in the observed percentage and the corresponding 95% CIs of the difference, based on the normal approximation of the binomial distribution. Risk differences and CIs were estimated using a frequency procedure from SAS version 9.2 (PROC FREQ). A hyperbolic growth model of temperature versus hours is estimated with random effects models (hours being a random effect) for each of the 2 strata of patients, those who received cefoxitin and those who received placebo treatment. The treatment assignment was a fixed effect.

RESULTS

Four-hundred women were randomized in this study (Fig. 1). Maternal demographic characteristics are shown in Table 1. There were no significant differences between the study groups with the exception that there were significantly more African American women in the placebo than the cefoxitin arm.

A variety of labor characteristics were analyzed in relation to antibiotic or placebo study groups, (Table 2) and none was significantly different. The number of vaginal examinations during the epidural analgesia period was similar in both groups. Cesarean delivery was performed in 30 (15%) women randomized to cefoxitin and 31(15%) randomized to placebo ($P = 0.89$).

Approximately 40% of women in each study group developed fever ≥38°C during labor. The risk difference (95% confidence interval [CI]) for fever ≥38°C during labor (antibiotic versus placebo) was −2.0% (−11.5 to 7.5), and for fever >39°C during labor was −1.5% (−4.7 to 1.7). Figure 2 shows a hyperbolic growth model of epidural analgesia duration in hours versus tympanic temperature.

Histologic findings in the fetal membranes and placentas are summarized in Table 3 and 4. Placentas were available from 302 of the study cohort (Fig. 1). Administration of cefoxitin had no significant effect on any grade of neutrophilic infiltration. As shown in Figure 3, fever in women with neutrophilic inflammation was not reduced significantly by maternal cefoxitin prophylaxis (45% for cefoxitin and 48% for placebo, $P = 0.703$; risk difference 3% [95% CI,

Table 1. Maternal Demographic Characteristics

	Cefoxitin, *N* = 200	Placebo, *N* = 200	*P*
Characteristic			
Age, y	22 ± 4	22 ± 4	0.28
Height, in	158 ± 8	158 ± 8	0.88
Weight, lbs	75 ± 12	74 ± 13	0.45
Race/ethnicity			0.02
Hispanic	171 (86)	172 (86)	
African American	11 (6)	22 (11)	
Caucasian	6 (3)	2 (1)	
Other	12 (6)	4 (2)	
Temperature at epidural analgesia initiation, °C	36.6 ± 0.5	36.7 ± 0.5	0.30
Spontaneous rupture of membranes at epidural analgesia initiation	59 (30)	69 (35)	0.30
Cervical dilation at epidural analgesia initiation, cm	5 [4, 6]	4 [4, 6]	0.41

Data are presented as mean ± SD or *n* (%) or median [1st, 3rd quartiles].

Table 2. Labor Characteristics and Events

	Cefoxitin, *N* = 200	Placebo, *N* = 200	*P*
Labor characteristics			
First stage of labor, min	505 [270, 865]	560 [280, 900]	0.63
Second stage of labor, min	40 [25, 80]	50 [27, 91]	0.31
Duration of analgesia, min	353 [256, 491]	361 [225, 514]	0.73
Labor >10 h	27 (14)	32 (16)	0.48
Oxytocin augmentation after analgesia	68 (34)	76 (38)	0.41
Number of vaginal examinations	5 [4, 6]	5 [4, 6]	0.61
Length of membrane rupture, min	600 [408, 802]	552 [389, 812]	0.88
Maternal fever before delivery			
≥38°C	75 (38)	79 (40)	0.68
>38.5°C	19 (10)	23 (12)	0.51
>39°C	4 (2)	7 (4)	0.36

Data are presented as median [1st, 3rd quartiles] or *n* (%).
Duration of analgesia = interval from initiation of analgesia to delivery.

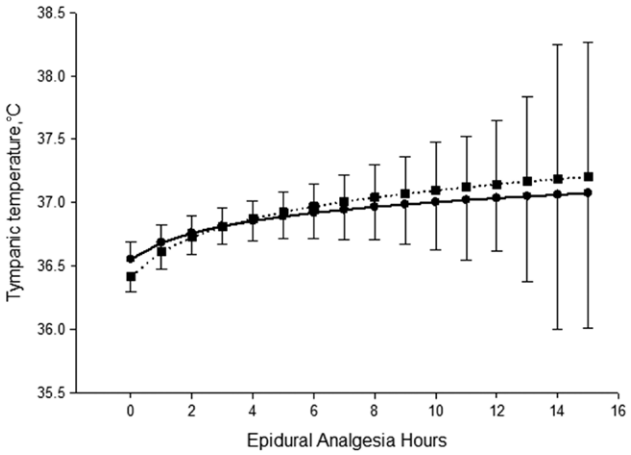

Figure 2. Tympanic membrane temperature (mean value) by hours. Squares and dotted line represent the cefoxitin group, and circles and solid line represent the placebo group. Error bars represent the SEM.

–13% to 19%]). Fever developed significantly more often in women with placental neutrophilic inflammation compared with those without such inflammation (73/158 (46%) vs 33/144 (23%), $P < 0.001$; risk difference 23.0% (95% CI, 13.0–34.0).

Infant outcomes in relation to maternal antibiotic treatment are summarized in Table 5. There were no significant differences in any outcomes between the antibiotic and placebo study groups. Sepsis, defined as a positive blood culture, was not diagnosed in any of the infants, and there were no neonatal deaths. Infant outcomes in relation to development of fever in the study cohort are summarized in Table 6. The percentage of infants with 1-minute Apgar scores ≤7 was significantly higher in the fever group compared with no fever group (risk difference 5.8% [95% CI, 0.8–10.9]) (Table 6). There were no significant differences in the percentage of infants with Apgar scores ≤7 at 5 minutes (risk difference 0.9% [95% CI, –1.1 to 2.9]). One infant in the febrile group was admitted to the intensive care unit due to suspected sepsis and low 1- and 5-minute Apgar scores with prolonged labor. There were no other significant differences in the infant outcome in the fever and no fever groups.

We further evaluated temperature trends after the first indication of fever in all 154 women who became febrile (≥38°C) during labor. In 33 (17%) women in the cefoxitin group and 38 (19%) women in the placebo group ($P = 0.61$), subsequent temperature readings after the first observed febrile reading continued to be ≥38°C throughout labor. Thirty-one (16%) women in the cefoxitin group and 31 (16%)

Table 3. Histologic Findings in the Placentas Available for Analysis

	Cefoxitin, *N* = 150	Placebo, *N* = 152	*P*
Placental neutrophilic inflammation	74 (49)	84 (55)	0.30
Vasculitis:			0.91
None	104 (69)	101 (66)	
Grade 1: One vessel of the UC	37 (25)	39 (25)	
Grade 2: Two vessels of the UC	2 (1)	6 (4)	
Grade 3: Three vessels of the UC	7 (5)	6 (4)	
Acute chorioamnionitis:			0.28
None	92 (61)	79 (52)	
Mild	42 (28)	53 (35)	
Moderate	13 (9)	13 (9)	
Severe	3 (2)	7 (5)	
Funisitis	18 (12)	21 (14)	0.64
Necrotizing funisitis	1 (1)	1 (1)	0.99
Necrotizing acute chorioamnionitis	3 (2)	3 (2)	0.99

Data are presented as *n* (%).Three hundred two placentas were analyzed.
UC = Umbilical cord; Funisitis = Neutrophilic inflammation of the Wharton's jelly. Necrotizing funisitis = Necrotizing neutrophilic inflammation of the Wharton's jelly; Necrotizing chorioamnionitis = Necrotizing neutrophilic inflammation of the placenta membranes.

Table 4. Histologic Findings in the Placentas Available (*N* = 302) for Analysis in Fever or No Fever Groups

	Fever, *N* = 106	No fever, *N* = 196	*P*
Placental neutrophilic inflammation	73(69)	85 (43)	<0.001
Vasculitis			<0.001
None	58 (55)	147 (75)	
Grade 1: One vessel of the UC	31 (29)	45 (23)	
Grade 2: Two vessels of the UC	7 (7)	1 (1)	
Grade 3: Three vessels of the UC	10 (9)	3 (2)	
Acute chorioamnionitis			<0.001
None	43 (41)	128 (65)	
Mild	42 (40)	53 (27)	
Moderate	14 (13)	12 (6)	
Severe	7 (7)	3 (2)	
Funisitis	24 (23)	15 (8)	<0.001
Necrotizing funisitis	2 (2)	0 (0)	0.054
Necrotizing acute chorioamnionitis	4 (4)	2 (1)	0.10

Data are presented as *n* (%).Three hundred two placentas were analyzed.
UC = Umbilical cord; Funisitis = Neutrophilic inflammation of the Wharton's jelly; Necrotizing funisitis = Necrotizing neutrophilic inflammation of the Wharton's jelly; Necrotizing chorioamnionitis = Necrotizing neutrophilic inflammation of the placenta membranes.

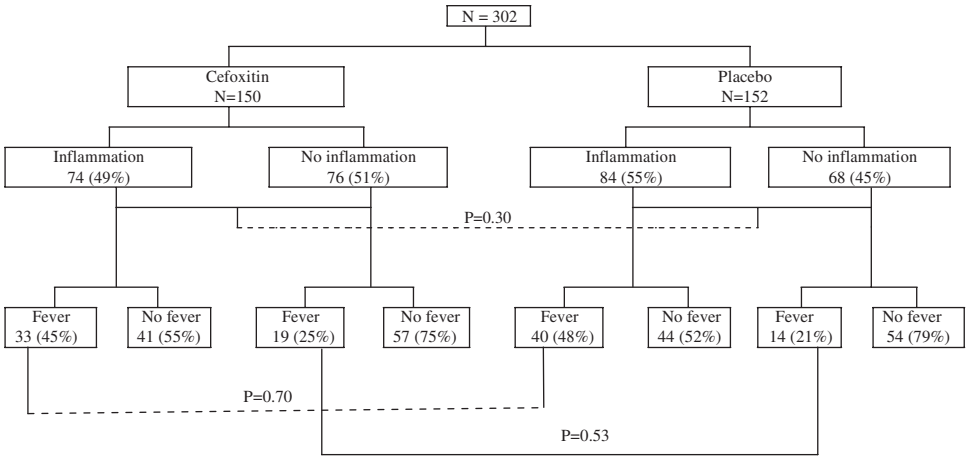

Figure 3. Histologic findings and incidence of fever (≥38°C) in women whose placentas were available for evaluation.

women in the placebo group (P = 0.79) developed fever immediately preceding delivery. Finally, 11 (6%) women in the cefoxitin group and 10 (5%) women in the placebo group (P = 0.72) had a temperature range of 37.5°C to 37.9°C after at least 1 febrile readings of ≥38°C.

DISCUSSION

Antibiotic prophylaxis with cefoxitin did not significantly reduce the rate of fever defined as temperature ≥38°C during labor in women given epidural analgesia. This was also true for fever >38.5°C. However, based on the 95% CIs between groups, if antibiotic prophylaxis made a difference in the rate of fever, it was a relatively small difference. Cefoxitin administration had no effect on any neonatal outcome including work-ups for sepsis. Neutrophilic infiltration of the placenta and membranes was found in approximately 50% of both study groups. Such infiltration was associated with maternal fever, but cefoxitin administration did not reduce the fever rate in women with placental infiltration. These findings suggest that maternal fever in women receiving labor epidural analgesia probably cannot be attributed to maternal infection. Such fever was not shown to significantly impact either maternal or neonatal outcome.

Riley et al.[10] in a recent observational study of labor epidural analgesia-related fever did not find evidence of a higher rate of infection using chorion–amnion culture among women who received epidural analgesia. In their study, despite the higher rate of fever in the epidural group (23% vs 6%), the prevalence of infection was the same in women with and without epidural analgesia (5% vs 4%). Also, the infection rate was similar in febrile (5.4%) and afebrile (4.3%) women. However, they found a higher rate of histologic acute chorioamnionitis in women with fever compared with women without fever.[10] The authors concluded that most epidural-related fever is associated with a noninfectious inflammation of the placenta. This result is similar to our study. However, we did not attempt to culture the placentas in our study. The incidence of fever was somewhat higher in this study than was reported in our previous studies and other studies.[1] This difference could be attributed to dysfunctional labor in some subjects. The Genius thermometer used in this study is better than other infrared systems.[17] However, considerable variability from reading to reading has been reported with infrared tympanic membrane thermometry, especially when used by unskilled practitioners.[20] The temperature in this study was recorded at a regular interval during labor by trained investigators, and Figure 2 shows a time-dependent increase in aural canal temperature in the study groups. Similar devices to measure aural canal temperature have also been used in

Table 5. Infant Outcomes

	Cefoxitin, *N* = 200	Placebo, *N* = 200	*P*
Infant outcomes			
Birthweight (g)	3410 ± 476	3396 ± 407	0.75
Meconium at delivery	12 (6)	14 (7)	0.69
Neonatal temperature at birth, °C			
Temperature >38°C	15 (8)	13 (7)	0.69
Temperature >40°C	0	0	
Apgar scores:			
≤7 at 1 min	10 (5)	12 (6)	0.66
≤3 at 1 min	4 (2)	1 (0.5)	0.18
≤7 at 5 min	0 (0)	3 (1.5)	0.08
<3 at 5 min	0 (0)	1 (0.5)	0.32
Umbilical artery blood:			
pH <7.0	0 (0)	1 (0.5)	0.31
Pco_2 ≥65 mm Hg	33 (21)	42 (30)	0.18
Neonatal sepsis work-up	83 (42)	91 (46)	0.42
Intensive care admission	0 (0)	1 (0.5)	0.32

Data are presented as mean ± SD or *n* (%).

Table 6. Infant Outcomes in Relation to Maternal Fever During Epidural Analgesia

	Fever, *N* = 154	No fever, *N* = 246	*P*
Apgar scores:			
≤7 at 1 min	14 (9)	8 (3)	0.013
≤3 at 1 min	1 (1)	4 (2)	0.39
<7 at 5 min	2 (1.3)	1 (0.4)	0.31
<3 at 5 min	0 (0)	1 (0)	0.43
Umbilical artery blood:			
pH <7.00	0 (0)	1 (0)	0.43
Pco_2 ≥65 mm Hg	25 (18)	50 (22)	0.34
Intensive care admission	1 (1)	0 (0)	0.21

Data are presented as *n* (%).

several noticeable studies evaluating fever during labor epidural analgesia.[21,22] Tympanic membrane thermometry eliminates the effects of oral intake and mouth breathing. However, we consider the use of infrared tympanic membrane thermometry in this study is a limitation of this study because significant variability in temperature measurement can occur even with skilled practitioners. Despite this limitation, the subsequent observation of fever after the first indication of fever (≥38°C) in women who became febrile during labor was not significantly different in the cefoxitin and placebo groups. Moreover, there were no significant differences in infant outcomes and histologic findings in the placentas in either group, which further supports the validity of temperature measurements in this study.

Some studies have found a strong association between maternal serum interleukin-6 levels and the development of fever during epidural analgesia.[6–8] It has been suggested that the maternal inflammatory response is a primary source for the development of fever.[7,8] Riley et al.[10] reported that women with high initial maternal serum interleukin-6 levels were twice as likely to have fever after epidural analgesia compared with women with lower levels. They hypothesized that women who have an activated cytokine system on admission may react differently to labor epidural analgesia and further activate the cytokines leading to fever.[10]

Goetzl et al.[21] administered steroid prophylaxis before epidural placement to reduce placental inflammation and thereby the rate of fever. They found that prophylactic treatment with steroids decreased the rate of fever by 90% but also increased neonatal bacteremia. Wang et al.[23] in their recent trial used epidural dexamethasone infusion with epidural analgesia. They concluded that epidural dexamethasone alleviates maternal temperature increase after epidural analgesia. In another placebo-controlled study, prophylactic use of acetaminophen during labor epidural analgesia did not prevent maternal fever.[22] It has also been hypothesized that an increased incidence of fever in women receiving epidural analgesia is due to the antipyretic effect of opioids in the nonepidural group. However, Gross et al.[24] did not find a significant difference in the rate of fever in women whose labor analgesia was managed with opioids versus no opioids.

Epidural-related fever remains a significant problem because these fevers inevitably result in neonatal work-ups for infection. In our study although sepsis was suspected in neonates born to women with fever, sepsis was not diagnosed in any of the infants. Mecredy et al.[25] in their literature review determined that 95% of asymptomatic, term neonates born to women with fever in labor have a benign course. They suggested that aggressive evaluation and management of these infants are unnecessary.

It is interesting to note that evaluation of neonates for possible sepsis has been reported with epidural analgesia in the absence of maternal fever. Lieberman et al.[26] found a 3-fold increase in the rate of sepsis evaluations in infants born to afebrile women who had received epidural analgesia during labor. They concluded that the use of epidural analgesia during labor is strongly associated with neonatal sepsis evaluations. In contrast, Philip et al.[13] reported that in the absence of maternal fever, epidural analgesia during labor has no bearing on the need for such neonatal management and therefore should not be considered a predictor per se for neonatal sepsis evaluations. These authors also concluded that association between epidural analgesia and maternal fever becomes apparent only in a small subset of women who are usually nulliparous and who experience prolonged labor.[13]

We were surprised by the results of our current study. The study was conceived with the expectation that fever associated with labor epidural analgesia was largely attributable to maternal bacterial infection and could therefore be prevented with prophylactic antibiotics. Clearly this was not the case in this trial. We thus conclude that epidural analgesia during labor is associated with fever which does not result from bacterial infection.

DISCLOSURES

Name: Shiv K. Sharma, MD, FRCA.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Shiv K. Sharma has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Beverly B. Rogers, MD.
Contribution: This author helped design and conduct the study and write the manuscript.
Attestation: Beverly B. Rogers has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Contribution: This author helped design and conduct the study.
Attestation: James M. Alexander has seen the original study data and approved the final manuscript.
Name: Donald D. McIntire, PhD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.

Attestation: Donald D. McIntire has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Kenneth J. Leveno has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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