The Association Between Epidural Labor Analgesia and Maternal Fever

Katherine W. Arendt, MDa,*, B. Scott Segal, MD, MHCMb

KEYWORDS

- Labor
- Hyperthermia
- Intrapartum fever
- Maternal temperature
- Epidural analgesia

KEY POINTS

- Observational, retrospective, before-and-after, and randomized controlled trials that randomize to intravenous opioid or epidural analgesia indicate that epidural analgesia is associated with maternal fever.
- Criticisms of the studies demonstrating an association between epidural and fever include selection bias, bias in obstetric practice, crossover and protocol violation, and the potential that systemic mu-opioid agonists mitigate an inflammatory febrile response.
- Randomized controlled trials that randomize to epidural analgesia initiated in early versus late labor indicate that the patients who get an early epidural are not more likely to develop a fever. The absence of a “dose-effect” for the association between epidurals and fever is puzzling, but leads some to believe that there may be “trigger effect.”
- Previously, it was thought that all women who had epidural analgesia had a gradual elevation of core body temperature. The current thinking is that only about 20% of those that receive epidural labor analgesia develop a fever and the remaining women have no increase in core body temperature with labor.
- A recent observational study evaluated the temperature slope of parturients throughout labor before and after the initiation of labor analgesia. They excluded any woman who developed a fever and therefore did not study the population affected by the phenomenon.
- Neonatal consequences of maternal fever in labor may involve low fetal tone, lower Apgar scores, assisted ventilation, tracheal intubation, cardiopulmonary resuscitation, supplemental oxygen requirements in the nursery, early onset neonatal seizures, and a greater likelihood of receiving a neonatal septic evaluation and antibiotic treatment.

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a Department of Anesthesiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA; b Department of Anesthesiology, Tufts Medical Center, Tufts University School of Medicine, 800 Washington Street, Mailbox 298, Boston, MA 02111, USA
* Corresponding author.
E-mail address: arendt.katherine@mayo.edu

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INTRODUCTION

In 1989, Gleeson and colleagues described a greater elevation of body temperature in women laboring with epidural analgesia than those without. Subsequently, a large body of research has been produced examining the relationship between epidural labor analgesia and maternal hyperthermia. This article focuses on the current literature associating epidural labor analgesia with fever organized by research methodology (Table 1) and discusses the criticisms of these studies (Box 1). Described are the proposed mechanisms, the consequences, and previous attempts to block or treat epidural-associated fever. Finally, the next steps for obstetricians and anesthesiologists in preventing the potential harmful effects of epidural-associated fever are discussed.

PROSPECTIVE OBSERVATIONAL AND RETROSPECTIVE STUDIES

Prospective observational trials in which women self-select their analgesia illustrate that women with epidural analgesia experience a higher incidence of fever or a modest elevation in temperature compared with women who select systemic opioids. Fusi and colleagues compared 18 women who selected epidural analgesia with 15 women who selected intramuscular meperidine and metoclopramide. Although the vaginal temperatures of the nonepidural group remained unchanged throughout labor, the average vaginal temperature of the epidural group increased by 0.14°C over 7 hours. Camann and colleagues also showed that women who selected epidural labor analgesia (randomized to infusions with or without epidural fentanyl) instead of intravenous nalbuphine had an increase in tympanic temperature of 0.07°C per hour on average. This study confirmed that the increased incidence of fever as observed by Fusi and colleagues was not an artifact of measuring temperature vaginally. Interestingly, the temperature increase began after 5 hours of epidural analgesia and there was no difference between the groups that did or did not receive epidural fentanyl.

Retrospective analyses also indicate that women who labor with epidural analgesia compared with those that do not are more likely to experience clinical fever, defined as a temperature greater than 37.8°C or 38°C. The data in many of these studies are quite dramatic. For example, Kaul and colleagues prospectively collected data for a quality improvement database and found that 61 out of 922 primiparous women who received epidural labor analgesia developed a fever of greater than 38°C, compared
<table>
<thead>
<tr>
<th>Study Author, Year</th>
<th>Design</th>
<th>Fever Definition (°C)</th>
<th>Epidural Group (% [n/N])</th>
<th>Nonepidural Group (% [n/N])</th>
<th>P Value</th>
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<tr>
<td>Vinson et al,64 1993</td>
<td>Observational</td>
<td>≥37.5</td>
<td>26.8 (11/41)</td>
<td>8.3 (3/36)</td>
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<td>≥38</td>
<td>6.4 (44/683)</td>
<td>1.1 (28/2426)</td>
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<td>1.6 (17/1056)</td>
<td>0.2 (11/6261)</td>
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<td>Ramin et al,13 1995</td>
<td>RCT⁰</td>
<td>≥38</td>
<td>22.7 (98/432)</td>
<td>4.8 (21/437)</td>
<td>&lt;.001</td>
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<tr>
<td>Lieberman et al,⁸ 1997</td>
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<td>14.5 (152/1047)</td>
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<tr>
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<td>20.4 (39/191)</td>
<td>2.1 (2/96)</td>
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<td>23.9 (58/243)</td>
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<td>≥37.5</td>
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<td>11.0 (63/572)</td>
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<td>0.8 (4/480)</td>
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<tr>
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<td>19.2 (535/2784)</td>
<td>2.4 (10/425)</td>
<td>&lt;.0001</td>
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Abbreviation: RCT, randomized controlled trial.

⁰ Fever reported for protocol-compliant women only.

¹ All patients had ruptured membranes more than 6 hours and included fever up to 6 hours postpartum.

⁰ Patients with pregnancy-induced hypertension; percentages recalculated from n/N reported in the original publication.

⁴ Epidural group reported as “after” period, in which 83% of women received epidural analgesia; nonepidural group reported as “before” period, in which 1% received epidural analgesia.

⁵ Patients with combined-spinal or nonpharmacologic analgesia.

Modified from Segal S. Labor epidural analgesia and maternal fever. Anesth Analg 2010;111:1467–75; with permission.
with none of the 255 nonepidural nulliparous women \((P = .000)\). Also, Herbst and colleagues\(^7\) performed a retrospective case-control study in which 44 (61.1\%) of the 72 women who developed a fever had epidural analgesia, whereas only 639 (21\%) of the 3037 women who were afebrile had an epidural \((P < .001)\).

Frolich and colleagues\(^9\) recently performed an observational study in which they reported the time-temperature slope of 81 parturients selecting epidural analgesia in labor. The change in temperature over time was calculated before and after initiation of epidural analgesia. Although a longer duration of rupture of membranes and elevated body mass index was associated with a more positive temperature trend, epidural analgesia was not. The authors suggest this observation exonerates epidural labor analgesia as a cause of intrapartum fever. However, it seems that

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**Box 1\
Criticisms of epidural fever studies**

- **Artifact of averaging**
  - The epidural group in observational studies and randomized controlled trials (RCTs) may contain a small group of women who develop higher fever than those without epidurals and a larger group of women who do not develop fever at all.

- **Selection bias**
  - Women who have longer labors are more likely to get chorioamnionitis (and therefore a fever) and are more likely to request an epidural.
  - Women with subclinical chorioamnionitis or placental infection may be more likely to select epidural analgesia for labor.

- **Crossover and dropout**
  - Some RCTs have high rates of women leaving a nonepidural group and receiving epidural analgesia. These women more commonly have complicated labors.
  - Some RCTs have high rates of women dropping out of the epidural group because of rapid, uncomplicated vaginal deliveries. This reduces uncomplicated labors in the epidural group.

- **Unknown temperature effects of intravenous opioids**
  - Most studies randomize to epidural or intravenous opioid labor analgesia. There are no studies randomizing women to unmedicated childbirth. It seems that intravenous opioids may have antipyretic effects.

- **Obstetric management bias**
  - It is impossible to mask the obstetrician or other providers to the presence or absence of an epidural.
  - Women randomized to epidural groups may have increased frequency of cervical examinations, use of oxytocin, or artificial rupture of membranes, which may increase their temperature.

- **Temperature measurement flaws**
  - Women without epidurals are more likely to hyperventilate during labor, artificially cooling an oral temperature measurement.
  - Vaginal temperature measurements involve measuring below the level of the sympathectomy, which could falsely increase temperature measurements in women with epidural analgesia.
women with “chorioamnionitis” (defined as temperature $>38^\circ\text{C}$) were excluded from analysis.

Excluding the population of women who develop clinical fever is a serious limitation. Previous studies have shown that the overall increase in temperature demonstrated in groups of women who labor with epidurals may be an “averaging artifact.” There seems to be a small group (about 20%) of women with an elevated inflammatory state who have a significant increase in temperature when laboring with an epidural. When the temperatures of these women are averaged with the remaining cohort, most of whom have no change in temperature, a gradual increase in temperature is demonstrated for all women laboring with epidural analgesia. However, because Frolich and colleagues excluded the small subset of women who eventually develop clinical fever, they may have excluded the group who explain the entire effect of epidural analgesia on temperature. Thus, the authors may have simply confirmed the lack of an effect of epidural analgesia on temperature among the large proportion of women who remain clinically afebrile throughout labor, as previously shown. Any further work in evaluation of the association between fever and epidural labor analgesia needs to focus on this approximately 20% of women who eventually do become febrile.

The data from observational and retrospective studies are clear: women who choose epidural analgesia are more likely to develop intrapartum fever. There is no need to perform further retrospective or observational studies comparing maternal temperature in labor of women who do or do not choose epidural labor analgesia. It is possible that the reason why these women choose epidural analgesia may be the reason that they are experiencing fever. Women who have clinical or subclinical chorioamnionitis or, perhaps more generally, an elevated inflammatory state may experience greater labor pain (and greater labor pain earlier in labor) and are therefore more likely to request epidural analgesia. Therefore, because of selection bias one should not presume that epidural labor analgesia causes maternal fever from these retrospective and observational data, no matter how dramatic the differences observed between the epidural and nonepidural groups.

**BEFORE-AND-AFTER STUDY**

A single before-and-after study evaluated maternal temperature within a cohort of term nulliparous patients before and then after the implementation of a continuous epidural analgesia service. In this retrospective cohort analysis, the frequency of epidural analgesia increased from 1% to 83% in approximately 1 year, and the incidence of a temperature of greater than $38^\circ\text{C}$ was 3 (0.6%) out of 498 before and 63 (11%) out of 572 after the implementation (relative risk, 18.2; 95% confidence interval, 7–86; $P<.001$). The overall maximum intrapartum temperature was $98.6^\circ\text{F} \pm 0.7^\circ\text{F}$ versus $99^\circ\text{F} \pm 1.1^\circ\text{F}$ ($P<.01$). Because other factors may have also changed during the period of introduction of epidural analgesia, the authors attempted to account for any bias by reporting no significant differences in the frequency of artificial rupture of membranes (55.5% vs 57.2%); the number of vaginal examinations in labor; and the length of first stage of labor (14.3 vs 13.6 hours). Of note, there was a significant difference in the length of second stage of labor (0.7 vs 1.1 hours; $P<.01$). This study design is beneficial in that it is not complicated by crossover between groups as the RCTs demonstrate. Furthermore, although women in the “after” group self-select their analgesia, their temperatures are compared with the women in the “before” group who did not self-select. As a result, selection bias is more limited than in retrospective or observational studies.
RANDOMIZED CONTROLLED TRIALS: EPIDURAL ANALGESIA VERSUS INTRAVENOUS OPIOIDS

Multiple randomized controlled trials (RCTs) have been performed that consistently illustrate the presence of epidural-associated fever. Here, women are randomized to receive epidural or nonepidural analgesia. Ramin and colleagues\textsuperscript{13} randomized 1330 women of mixed parity to epidural analgesia or intravenous meperidine. Unfortunately, the trial was analyzed on a protocol-compliant basis only, excluding one-third of subjects who did not receive the randomized analgesia. Nonetheless, 98 (23\%) of 432 subjects who received epidural analgesia developed fever greater than 38°C, compared with 21 (5\%) of 437 in the meperidine group ($P<$ .001).

Sharma and colleagues,\textsuperscript{14,15} from the same institution, were able to avoid such a high rate of crossover in two consecutive studies, which were analyzed on an intention-to-treat basis. In the first,\textsuperscript{14} they randomized 715 women of mixed parity to either epidural analgesia or intravenous meperidine. Of the 358 women randomized to epidural analgesia, 243 received epidural analgesia, and 115 did not, with 78 women progressing too rapidly to receive the block. Of the 357 women randomized to intravenous meperidine, 259 followed protocol and 98 did not with 73 receiving no analgesia because of rapid delivery, 20 refusing analgesia, and 5 women requesting epidural analgesia because of inadequate analgesia from the meperidine. Of the 243 women in the epidural group, 58 (24\%) developed a fever of 38°C or greater. Of the 259 women in the meperidine group, 16 (6\%) developed fever ($P<$ .0001). In a subsequent study,\textsuperscript{15} they randomized 459 nulliparous women in spontaneous labor to epidural or intravenous meperidine. Of the 226 randomized to epidural analgesia, 214 followed protocol. Of the 233 randomized to meperidine, 207 followed protocol, with 14 women crossing over to epidural analgesia because of inadequate pain relief. Of the 226 women randomized to epidural analgesia, 75 (33\%) developed a fever of 38°C or greater, whereas only 16 (7\%) of the intravenous meperidine group became febrile ($P<$ .001).

Lucas and colleagues\textsuperscript{16} published an RCT that showed no significant differences in length of the first stage of labor, no significant differences in oxytocin augmentation, and little crossover. Here, 372 women with pregnancy-induced hypertension were randomized to epidural analgesia and 366 to intravenous meperidine and promethazine. Only three women in the meperidine group crossed over. However, there were overall 51 protocol violations in the epidural group and 26 in the meperidine group. An intent-to-treat analysis found that 76 (22\%) of those randomized to the epidural group developed an intrapartum fever, compared with only 26 (8\%) of those in the meperidine group ($P<$ .001).

All of these RCTs are criticized because obstetric providers cannot be truly masked to whether a parturient is laboring with or without epidural analgesia. Therefore, bias is likely present. Both of the studies performed by Sharma and colleagues\textsuperscript{14,15} report a higher rate of oxytocin augmentation in the epidural groups (33\% vs 15\%, $P<$ .0001\%; 45\% vs 34\%, $P = .01$). Both report a longer interval from the initiation of epidural analgesia to the discovery of complete cervical dilation (260.3 ± 188 vs 199 ± 171 minutes, $P<$ .001; 302 ± 189 vs 261 ± 188 minutes, $P = .03$). Further obstetric management questions remain, such as the potential differences in the frequency of cervical examinations in patients laboring with an epidural compared with those without epidural analgesia, or the allowance of women comfortable enough with an epidural to delay pushing after complete cervical dilation. This could lead to increased likelihood of fever from causes other than epidural analgesia and make the RCT study design in which women are randomized to epidural or nonepidural analgesia suboptimal in studying the presence of epidural-associated fever.
Finally, as discussed later, a few studies have indicated that systemic mu-opioid agonists may suppress fever.\textsuperscript{17,18} Therefore, RCTs may suffer from some bias when comparing an epidural analgesia group with a systemic opioid analgesia group. There are no studies that compare epidural analgesia with no analgesia whatsoever, and it would be difficult and perhaps unethical to carry out such a study.

**RANDOMIZED CONTROLLED TRIALS: EARLY VERSUS LATE EPIDURAL ANALGESIA**

When women are randomized to receive epidural analgesia early or later in labor, no difference in temperatures is observed. Wong and colleagues\textsuperscript{19} randomized 750 women to either early combined spinal epidural with intrathecal opioid (N = 366), or systemic hydromorphone analgesia and delayed combined spinal epidural placement (N = 362). The maximal oral temperature of both groups was 37.3 ± 0.5 (\(P = .06\)). A similar result was observed by the same group in induced labor in nulliparous women (incidence of fever >38°C, 12.7% in the early group vs 10.3% in the late group; \(P = .32\)).\textsuperscript{20} Likewise, Wang and colleagues\textsuperscript{21} randomized 12,793 nulliparous women to early epidural analgesia (N = 6394) or systemic meperidine and delayed epidural analgesia until cervical dilation was at least 4 cm (N = 6399). The median duration of epidural analgesia was 12.6 hours in the early epidural group and 4.8 hours in the delayed-epidural group and the overall length of labor was not significantly different between the groups. The average oral temperature during labor was not different at 37.4°C ± 0.4°C versus 37.2°C ± 0.3°C (\(P = .52\)).

In a different type of design, Wang and colleagues\textsuperscript{22} randomized women to receive combined spinal epidural labor analgesia with 2 mg bupivacaine and 20 μg fentanyl and either immediate epidural analgesia (N = 26) or delayed epidural analgesia after the return of pain (N = 28). Three patients (11.5%) in the immediate epidural group developed a temperature greater than 38°C, whereas only two patients (7.1%) in the delayed epidural group developed a temperature greater than 38°C. This difference was not significant (\(P = .66\)). Because a previous study reported that intermittent epidural boluses resulted in a lesser incidence of maternal fever compared with continuous infusion epidural analgesia,\textsuperscript{23} it seemed that a similar result would follow in the study by Wang and coworkers, although it was admittedly underpowered.

Taken together, the RCTs that randomize women to epidural analgesia initiated in early versus late labor indicate that patients who have a longer duration of epidural analgesia are not more likely to develop a fever. The absence of a “dose-effect” for the association between epidurals and fever leads some to suggest that there may be a “trigger effect.” In this view, epidural analgesia interacts with an inflammatory state in susceptible women to initiate a febrile response shortly after the block is begun.

**PROPOSED MECHANISMS**

It is important to address the proposed mechanisms of this phenomenon if it is to be possible to avoid or appropriately treat hyperthermia with epidural labor analgesia. Unlike nonlaboring patients who receive epidural anesthesia and experience heat loss because of well-understood redistribution of heat from the core to the periphery,\textsuperscript{24,25} the observational, before-and-after, and randomized controlled studies discussed previously illustrate that some women in labor who receive epidural analgesia experience an elevation of core body temperature. The proposed theories behind this observation are as follows:

- High ambient temperatures in delivery rooms.\textsuperscript{2}
A decrease in heat-dissipating hyperventilation with effective pain relief.\textsuperscript{26}

Altered thermoregulation,\textsuperscript{27} which may involve an elevated sweating threshold below the level of the block\textsuperscript{28} or an increased likelihood of heat-producing shivering.\textsuperscript{1}

A difference in the patient population requesting epidurals such that they are more likely to have subclinical chorioamnionitis at presentation, or more likely to have longer labors requiring multiple interventions, increasing the risk of chorioamnionitis throughout labor.\textsuperscript{7,29}

A difference in obstetric management in women with effective analgesia, such as increased use of oxytocin, or more frequent cervical examinations.\textsuperscript{30}

Antipyretic effects of systemic opioid analgesia, the group to which patients who do not receive epidural analgesia are randomized in RCTs.\textsuperscript{17}

An exaggerated noninfectious inflammatory response by proinflammatory cytokines in women laboring with an epidural.\textsuperscript{31–37}

One theory is that epidural analgesia does not increase temperature, but systemic mu-opioid agonists may decrease the incidence of fever. Negishi and colleagues\textsuperscript{17} induced fever by intravenous interleukin (IL)-2 in eight nonpregnant subjects on 4 separate days each randomized to one of the following four groups on different days: (1) a control day with no opioid or epidural, (2) epidural analgesia with ropivacaine, (3) epidural analgesia with ropivacaine and 2 $\mu$g/mL fentanyl, or (4) intravenous fentanyl halved the pyrogenic response to the IL-2 injection compared with the control day, whereas epidural ropivacaine with and without fentanyl did not inhibit fever. Although this phenomenon was not present in a large retrospective review using the opioid agonist-antagonist nalbuphine,\textsuperscript{38} the clinical effects of systemic mu-agonists is a question that remains unanswered, and potentially undermines the value of RCTs that involve groups that receive systemic opioid agonists, such as meperidine.

The most intriguing mechanism of epidural-induced fever involves the theory that the fever is not infectious in origin but is associated with an inflammatory state.\textsuperscript{32–37} Riley and colleagues\textsuperscript{37} compared the rate of placental infection and the degree of maternal inflammatory response in women with and without epidural labor analgesia. Similar, but very low, rates of placental infection as measured by placental cultures and polymerase chain reaction analysis were present in the epidural and nonepidural groups (4.7\% vs 4\%; $P>$.99). However, fever was more common in the epidural group (22.7\% vs 5\%; $P = .009$), and the risk of fever in those women laboring with epidurals was greater in women who presented with elevated IL-6 levels at admission (relative risk, 2.3; 95\% confidence interval, 1.2–4.4). Experts believe that “these data support a non-infectious inflammatory theory for explaining epidural-associated maternal fever among women with an ‘activated’ immune system.”\textsuperscript{39} Other studies have shown that women who develop an epidural-associated fever do so immediately,\textsuperscript{10} almost as if they are primed or activated to do so. This theory is also supported by studies that have shown the overall gradual increase in temperature demonstrated in groups of women who labor with epidurals\textsuperscript{3,12} may be an “averaging artifact.”\textsuperscript{10,11} There seems to be a small group of women with elevated inflammatory states who have a significant increase in temperature when laboring with an epidural.\textsuperscript{10,11} The “averaging artifact” occurs when the temperatures of these women are averaged with the remaining cohort (most of whom have no change in temperature). A resultant gradual increase in temperature is demonstrated for all women laboring with epidural analgesia.
Kozlov\textsuperscript{40} recently proposed a role for the TRPV1 receptor (also known as the capsaicin receptor). The author hypothesized that local anesthetics act as agonists/antagonists at this receptor and that antagonist actions may cause hyperthermia through changes in thermoregulation and that agonist action may cause release of IL-6 and other inflammatory cytokines, which are known to cause fever. Much work needs to be done to investigate the possibility and the exact role of a potential receptor in the spine that could link the association between labor epidural and fever.

Some evidence does suggest thermoregulatory and other mechanisms of epidural-associated fever. Most evidence, however, supports the potential involvement of noninfectious inflammation. It is possible that women with elevated inflammatory states are more likely to get epidurals because of greater pain in labor. Whether epidural labor analgesia actually causes or induces an elevation of a maternal inflammatory state has not yet been entirely determined. There are no simple animal models of epidural labor analgesia, and thus evidence is indirect. It is most likely that an epidural interacts with a pre-existing inflammatory state and as a result unveils fever that may not have otherwise been observed.\textsuperscript{37}

**CONSEQUENCES**

The observation that epidural labor analgesia may be associated with an elevation of maternal core body temperature was once dismissed as a physiologic curiosity. The consequences, however, are potentially dire. The development of maternal fever is debatably associated with indirect clinical effects, such as increasing a woman’s likelihood of receiving intrapartum antibiotics and undergoing a cesarean or assisted vaginal delivery,\textsuperscript{41} and the neonate’s likelihood of receiving a neonatal septic evaluation and antibiotic treatment.\textsuperscript{8} The latter association, however, is not consistent and seems to be related to neonatal practice style.\textsuperscript{6}

Most ominously, however, maternal fever results in fetal hyperthermia. Although some studies show no differences in neonatal well-being (Apgar scores, umbilical cord gas, and acid-base measurements) with fetuses born greater than 38°C,\textsuperscript{42} most indicate that intrapartum maternal fever is associated with a poor neonatal condition, including low fetal tone, lower Apgar scores, bag mask ventilation, tracheal intubation, cardiopulmonary resuscitation, supplemental oxygen requirements in the nursery, and neonatal seizure.\textsuperscript{43–46} Most recently, Greenwell and colleagues\textsuperscript{47} found that the rate of neonatal adverse outcomes increased directly with maximum maternal temperature in low-risk women receiving epidural labor analgesia. Compared with women with a maximum temperature of 37.5°C or less, babies born to mothers with temperatures greater than 38°C were more likely to have early onset neonatal seizures (adjusted odds ratio, 6.5); 5-minute Apgar score less than 7 (adjusted odds ratio, 4.8); prolonged neonatal hypotonia greater than 15 minutes (adjusted odds ratio, 3.1); and require assisted ventilation (adjusted odds ratio, 2.1).

The current theory that epidural fever is associated with an elevated maternal inflammatory state is worrisome. Recent animal studies indicate that intrauterine inflammation results in fetal brain inflammation and neurotoxicity.\textsuperscript{48} Even more worrisome, one animal model that induced only subclinical placental inflammation still caused fetal brain injury.\textsuperscript{49} Historically, the association between intrapartum infection and cerebral palsy has been well established.\textsuperscript{50–54} The destructive contribution of the inflammatory state alone is debatably significant,\textsuperscript{52} as is the destructive contribution of the hyperthermic state alone.\textsuperscript{55–58}
TREATMENT

Goetzl\textsuperscript{59} has stated that “obstetricians and anesthesiologists should partner in elucidating the mechanism of epidural fever and in developing effective mechanism-based interventions rather than seeking to discourage epidural analgesia.” Unfortunately, all attempts to date have been unsuccessful or impractical. Goetzl’s group attempted such an approach, randomizing 42 afebrile women requesting epidural analgesia to receive 650 mg of rectal acetaminophen or placebo. They found no differences in the incidence of fever, the mean maximal temperature, or the change in temperature over time.\textsuperscript{60} This result is not surprising given the weak anti-inflammatory effect of acetaminophen. Evron and colleagues\textsuperscript{18} randomized laboring women to receive intravenous remifentanil only (N = 44); epidural ropivacaine only (N = 50); intravenous remifentanil and epidural ropivacaine (N = 49); or epidural ropivacaine with intravenous acetaminophen (N = 49). Although there was a significantly lesser maximal increase from baseline temperature in the remifentanil-only group (P = .013), no other significant differences in temperature change were found. The acetaminophen group had an insignificantly reduced incidence of hyperthermia than the epidural ropivacaine-only group (4 [8\%] of 49 vs 7 [14\%] of 15), and the epidural ropivacaine and remifentanil group had an insignificantly reduced incidence compared with the epidural ropivacaine-only group (4 [8\%] of 49 vs 7 [14\%] of 15). It is likely that this study was underpowered to detect these differences and that intravenous opioid and intravenous acetaminophen could have a therapeutic benefit alone, or in combination, in preventing epidural-associated fever.

Goetzl and colleagues\textsuperscript{61} did successfully prevent fever associated with epidural analgesia with systemic maternal steroids. At the time of epidural placement, women were randomized to placebo (N = 100), intravenous 25-mg methylprednisolone every 8 hours (N = 50), or 100 mg every 4 hours (N = 49). Fever occurred in 22 (21.8\%), 17 (34\%), and 1 (2\%) of the placebo, low-dose steroid, and high-dose steroid groups, respectively. High-dose steroids decreased the incidence of epidural-associated fever by 90\% (P<.001). However, neonatal bacteremia was present in none of the placebo group, one (2.1\%) of the low-dose group, but four (9.3\%) of the high-dose group (P = .005). This complication renders this therapy impractical clinically but supports the inflammatory nature of epidural-associated fever.

Preliminary work on the potential differing effects on the incidence of fever of various types of epidural local anesthesia (0.08\% ropivacaine vs 0.06\% levobupivacaine) reveals the potential for a series of studies to find the least pyrogenic labor epidural cocktail.\textsuperscript{62} Goetzl\textsuperscript{59} believes that proactive labor management that shortens labor may also play a role in reduction of intrapartum fever. Epidural dexamethasone also shows some promise of potential benefit. Wang and colleagues\textsuperscript{63} randomized women to epidural solutions with or without 0.2 mg/mL dexamethasone. They found that the group receiving the epidural solution without dexamethasone had an increase in maternal temperature and IL-6 levels, whereas the epidural dexamethasone group did not. There was, however, no difference in the incidence of fever between the groups. The appropriate epidural dexamethasone dose and the therapy’s potential effects on neonatal bacteremia require further study.

SUMMARY

Epidural analgesia is strongly associated with maternal intrapartum fever, and the effect does not seem to be merely attributable to selection bias. The most likely mechanism involves noninfectious inflammation, although the pathophysiology is incompletely understood. The direct effects of maternal fever are significant but, as
yet, not definitely linked to epidural-caused fever. The next steps in studying this association and the clinical consequences of it involve delineating the mechanism of the noninfectious inflammatory state and exactly how epidurals cause it; examining whether epidural-triggered noninfectious inflammation is as harmful to the neonate as other causes of maternal fever; and finally determining how safely to block, or at least minimize, this febrile response.

REFERENCES


