Labor Epidural Analgesia and Maternal Fever

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Women in labor who receive epidural analgesia are more likely to experience hyperthermia and overt clinical fever. The gradual development of modest hyperthermia observed in laboring women with epidural analgesia is not seen in those electing other forms of analgesia or unmedicated labor. Clinical fever is also far more likely in women laboring with epidural analgesia. It is possible that the observed slow increase in mean temperature is an artifact of averaging the temperature curves of a small group of women who eventually develop fever with a larger group who remain afebrile throughout labor. Selection bias confounds the association between epidural analgesia and fever, because women at risk for fever—due to longer duration of ruptured membranes, longer labor, more frequent cervical examinations, and other interventions—are also more likely to select epidural analgesia. However, even randomized trials have confirmed a higher incidence of fever in epidural-exposed women, suggesting a causal relationship. The mechanisms of epidural-associated fever remain incompletely understood. Altered thermoregulation and an antipyretic effect of opioids given to women without epidural analgesia may explain part of the phenomenon, but the most likely etiology is inflammation, most commonly in the placenta and membranes (chorioamnionitis). The consequences of maternal fever are diverse. Obstetricians are more likely to intervene surgically in laboring women with fever, and neonatologists are more likely to evaluate neonates of febrile women for sepsis. More ominously, maternal inflammatory fever is associated with neonatal brain injury, manifest as cerebral palsy, encephalopathy, and learning deficits in later childhood. At present, there are no safe and effective means to inhibit epidural-associated fever. Future research should define the etiology of this fever and search for safe and effective interventions to prevent it and to inhibit its potential adverse effects on the neonatal brain. (Anesth Analg 2010;111:1467–75)

Fever in labor complicates up to one-third of deliveries. The etiologies of intrapartum fever are diverse and include maternal chorioamnionitis and other infections. In addition, epidural analgesia used for pain relief in labor is associated with mild maternal temperature increase and overt fever. Originally dismissed by obstetric anesthesiologists as a clinical curiosity of little consequence, epidural-associated hyperthermia may lead to significant maternal as well as fetal or neonatal adverse effects. This article reviews the phenomenon of epidural-associated fever, its etiology, its consequences to the mother and baby, and future strategies for minimizing these effects.

PHENOMENOLOGY

Epidural anesthesia administered for surgical anesthesia, including cesarean delivery,[1] typically results in hypothermia. The physiology of this effect is well characterized: sympathectomy-induced vasodilation produced by neuroblockade causes redistribution of body heat from the core to the periphery, where it is lost to the environment.[2] Conversely, laboring women who receive neuraxial analgesia experience, on average, an increase in temperature.

Observational investigations performed 2 decades ago demonstrated a gradual increase in temperature in laboring parturients with epidural analgesia not seen in those electing systemic opioid analgesia or no analgesia. Fusi et al.[3] compared the vaginal temperatures of 18 parturients who received epidural analgesia with those measured in 15 women who received IM meperidine and metoclopramide. Women self-selected their analgesia. The epidural groups showed an average increase in temperature of approximately 1°C over 7 hours, whereas the temperatures of the nonepidural group remained constant. No evidence of clinical infection was reported in any of the women. The authors suggested that epidural analgesia may cause an "imbalance between heat-producing and heat-dissipating mechanisms."

Vaginal temperature measurements might be affected by epidural analgesia-induced sympathectomy and vaginal mucosal vasodilation, although Fusi et al. showed excellent correlation between oral and vaginal temperatures. Tympanic membrane temperature should not be affected by the local vasodilation induced by epidural analgesia, and it may provide a more accurate assessment of core temperature. Camann et al.[4] studied the effect of epidural analgesia on maternal oral and tympanic membrane temperature measurements in 53 laboring women who self-selected IV nalbuphine or epidural analgesia. Women who requested epidural analgesia were randomized to receive either epidural bupivacaine only or epidural bupivacaine with fentanyl. The investigators found no differences in maternal temperature among the groups during the first 4 hours of the study. Beginning at 5 hours, the mean tympanic membrane temperature was significantly higher in both epidural groups when compared with the IV nalbuphine group (Fig. 1). As in the earlier study, the increase in temperature was slow, averaging <0.07°C per hour, with no difference between epidural groups. Several other investigators have documented similar patterns of slow,

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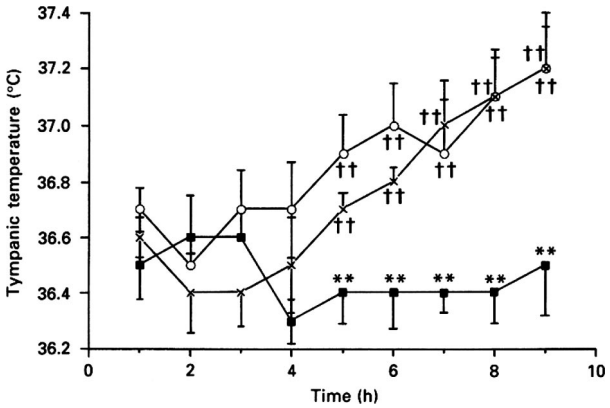

Figure 1. Tympanic membrane temperature in laboring women self-selecting different types of analgesia. Patients receiving epidural bupivacaine with fentanyl (open circles) or epidural bupivacaine only (crosses) experienced a gradual increase in temperature averaging 0.07°C/hour with no difference between groups. Patients receiving IV nalbuphine (■) had no temperature change during labor. $**P < 0.01$ for difference between opioid and epidural groups. $††P < 0.01$ for difference between baseline (pre-epidural) temperature. Reprinted with permission from Camann et al.[4]

modest temperature increase in women with epidural analgesia in comparison with those without it.[5–8]

An increased incidence of clinical fever, usually defined as core temperature >37.5°C or 38.0°C, in laboring women receiving epidural analgesia has also been observed (Table 1).[5,9–20] The incidence of clinical fever has varied strikingly, from 1% to 46%, likely reflecting differences in the populations studied. Evidence for a greater incidence of clinical fever in women with epidural analgesia comes from a variety of study designs, most commonly observational or retrospective studies, in which women self-select their analgesia.[5,10–13,19,20] These investigations can be influenced by selection bias; women who choose epidural analgesia may also be at risk for fever from infectious causes. Other evidence comes from before–after or natural experiment studies, in which epidural analgesia suddenly becomes available to a population in which it was previously unavailable.[9] Although women still self-select their analgesia in this study design, it is less likely that significant changes in patient characteristics (which might be associated with a higher risk of infection) would occur coincidentally with the increased use of epidural analgesia.

Finally, a few randomized controlled trials (RCTs) have compared women randomized to receive epidural or nonepidural analgesia techniques; these trials have also shown an increased incidence of fever in the epidural groups.[15–18] These trials should avoid the problem of selection bias and better isolate the effect of epidural analgesia. Unfortunately, even RCTs may suffer from bias in the obstetrical treatment of women, because the obstetrical caregivers are not blinded to the presence or absence of epidural analgesia. For example, women randomized to epidural groups may undergo an increased frequency of cervical examinations, artificial rupture of membranes, or use of oxytocin. In summary, evidence that epidural analgesia is associated with an increased incidence of clinical fever comes from a variety of sources. Although bias may complicate all study designs, it is likely a real phenomenon and not merely an artifact of selection bias.

The mean temperature of women with epidural analgesia is higher than that of women without epidural analgesia. Two investigations have concluded that the slow progressive increase observed in the epidural group may actually be an artifact caused by averaging the temperature curves of women who develop clinical fever with a larger cohort of those who remain afebrile (Fig. 2).[7,8] In an observational study of women self-selecting their analgesia, Goetzl et al.[7] found that the majority of women with epidural analgesia never had a temperature change, but a small cohort who developed overt fever >38°C experienced an increase of 0.33°C/hour immediately upon initiation of epidural blockade. The entire cohort showed, on average, a slow increase in temperature similar to that in the earlier studies. Similarly, our group found 2 distinct

Table 1. Incidence of Clinical Fever in Women with Labor Epidural Analgesia

Study	Design	Definition fever (°C)	Epidural group [% (*n*/*N*)]	Nonepidural group [% (*n*/*N*)]	*P* value
Lieberman[11]	Observational	>38	14.5 (152/1047)	1.0 (6/610)	<.001
Mayer[12]	Observational	≥37.8	20.4 (39/191)	2.1 (2/96)	<.001
Kaul[19]	Observational	>38	6.6 (61/922)	0 (0/255)	<.001
Dashe[20]	Observational[a]	≥38	46.3 (37/80)	26.1 (18/69)	.01
Vinson[5]	Observational	≥37.5	26.8 (11/41)	8.3 (3/36)	.05
		>38	14.6 (6/41)	0 (0/36)	.03
Herbst[13]	Observational	≥38	6.4 (44/683)	1.1 (28/2426)	<.001
Ploeckinger[10]	Observational	>38	1.6 (17/1056)	0.2 (11/6261)	<.005
Yancey[9]	Before–after study[b]	≥37.5	26.2 (150/572)	8.2 (41/498)	<.01
		≥38	11.0 (63/572)	0.6 (3/498)	<.01
Ramin[16]	RCT[c]	≥38	22.7 (98/432)	4.8 (21/437)	<.001
Sharma[17]	RCT[c,d]	≥38	33.2 (75/226)	6.9 (16/233)	<.001
Sharma[18]	RCT[e]	>38	23.9 (58/243)	6.2 (16/259)	<.0001
Lucas[15]	RCT[f]	≥38	20.4 (76/372)	7.1 (26/366)	<.001

RCT = randomized controlled trial.

[a] All patients had ruptured membranes >6 hours and included fever up to 6 hours postpartum.

[b] Comparison of 2 time periods, before and after introduction of on-demand labor epidural analgesia. 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.

[c] Fever reported for protocol-compliant women only.

[d] Data from this investigation were analyzed again in more detail by Philip et al.[14]

[e] Nulliparas only.

[f] Patients with pregnancy-induced hypertension; percentages recalculated from *n*/*N* reported in the original publication.

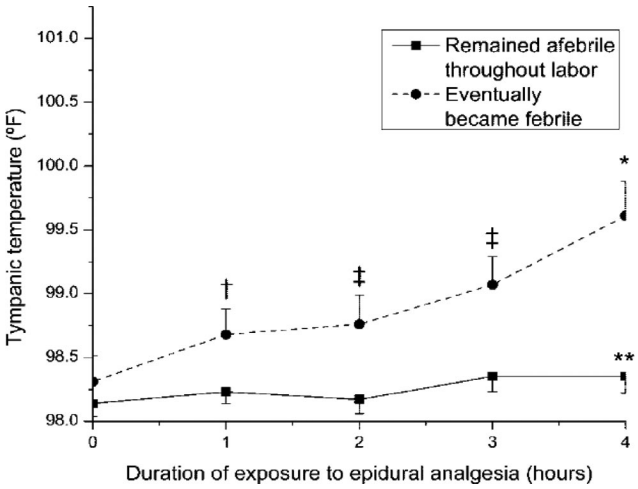

Figure 2. Temperature curves in labor in patients with epidural analgesia subdivided by whether or not the patient eventually developed fever >38°C. Two distinct patterns of temperature were observed: a group remaining afebrile throughout labor for whom temperature did not change over time, and a smaller group of eventually febrile patients, who showed an increase of 0.33°C/hour immediately after epidural initiation. $*P < 0.001$. ‡$P < 0.01$. †$P < 0.05$ for difference between eventually febrile and afebrile cohorts. $**P = 0.26$ for change over time in afebrile cohort. Reprinted with permission from Goetzl et al.[7]

populations of patients with epidural analgesia: a larger group of completely afebrile patients and a smaller group who eventually developed clinical fever. Temperatures were higher in the eventually febrile subset even before the initiation of neuroblockade, although still in the afebrile range.[8] This finding is potentially important. If the slow increase in mean temperature is really an averaging artifact, then an understanding of the nature of the relationship between epidural analgesia and overt fever is the key to understanding hyperthermia during labor in this subset of patients. If the increase in temperature is more universal, then a search for thermoregulatory or other mechanisms that do not produce clinical fever is indicated.

MECHANISMS

The mechanisms by which epidural analgesia produces maternal hyperthermia during labor remain unclear. Several explanations have been advanced; there is evidence to support the role of thermoregulatory factors, systemic opioid administration, and inflammation.

Thermoregulation

Fusi et al.[3] attributed maternal pyrexia in women with epidural analgesia to the high ambient temperature (24°C to 26°C) found in most British delivery rooms. However, this mechanism does not immediately explain the difference between patients electing epidural and nonepidural forms of analgesia. Moreover, subsequent investigators failed to find an association between ambient temperature and maternal[5] or fetal[21] temperature.

Alternatively, epidural analgesia may cause an imbalance between heat production and heat-dissipating mechanisms. Labor and delivery is physical exercise, and is probably thermogenic. Nineteenth-century physicians noted the tendency for laboring women to develop elevated temperature.[22] Marx and Loew[23] measured tympanic membrane temperature continuously in 11 women of mixed parity and various analgesic choices. They found increased temperature with each contraction, which they attributed to the muscular work of the uterus. They also found a progressive increase in temperature over time, averaging 1.5°C in nulliparous and 0.5°C in parous women, with no differences attributable to type of analgesia. Hagerdal et al.[24] measured oxygen consumption and minute ventilation in laboring women before and after institution of epidural analgesia and found an increase in both variables during contractions, in comparison with intervals between contractions. Epidural analgesia attenuated the increase in these variables, but did not eliminate it, implying that the work of uterine contraction caused a measurable increase in metabolic demand. Epidural analgesia may further increase thermogenesis because of the frequent incidence of shivering associated with its use among laboring women. Gleeson et al.[6] found that laboring patients who shivered after the administration of epidural analgesia developed pyrexia as early as 1 hour after initiation of the block, in comparison with >4 hours after initiation of the block in patients who did not shiver. Moreover, the maximum temperature was higher, and the incidence of clinical fever was 3 times more common in women who shivered.[6] Some shivering and sweating in labor is nonthermoregulatory, in that it is not preceded by changes in core temperature or vasomotor tone.[25] However, it is not clear whether shivering is a cause or an effect of increased temperature.

Simultaneously, epidural analgesia may alter normal heat-dissipating mechanisms. Decreased sweating and the lack of hyperventilation that follow the provision of effective epidural pain relief may predispose laboring women to pyrexia.[3,4,22] In volunteers, epidural neuroblockade raised the sweating threshold in response to radiant skin warming by 0.55°C and prevented sweating below the level of the block in some subjects.[26] As was noted above, epidural analgesia attenuates the increase in oxygen consumption and minute ventilation seen during contractions and expulsive efforts.[24] If hyperventilation dissipates heat in unmedicated parturients, decreased ventilation in the setting of increased energy expenditure may manifest as increased temperature in the laboring patient. Goodlin and Chapin[22] found a correlation between absence of sweating and hyperventilation with hyperthermia in 50 women who self-selected their analgesia and were not clinically suspected of infection. Those with no pain relief showed a progressive decrease in mean temperature until delivery, followed by a return to baseline within 1 hour postpartum. Those with effective pain relief with epidural analgesia, paracervical block, or systemic opioids showed no change or a slight increase in temperature until delivery.

Effect of Opioids

Opioids given to women without epidural analgesia might suppress fever that would otherwise have been apparent. In interleukin (IL)-2-induced fever in nonpregnant volunteers, epidural analgesia with ropivacaine with or without epidural fentanyl did not affect the magnitude of fever, but IV fentanyl markedly attenuated the increase in temperature.[27] In a small and likely underpowered study, Evron et

al.[28] showed a trend towards a slower and smaller increase in temperature in laboring women randomized to epidural ropivacaine plus IV remifentanil in comparison with those receiving epidural ropivacaine alone. Conversely, differences in nalbuphine use could not explain the difference in occurrence of fever between epidural and no-epidural groups in one large retrospective study.[29] Camann et al.[4] did not find a difference in temperature curves between women randomized to opioid-containing versus opioid-free epidural infusions. It appears that only μ-opioid agonists administered systemically have any significant effect on temperature in labor, and the impact is modest.

Inflammation

An emerging dominant view posits the role of maternal inflammation in the etiology of epidural-associated fever. Several lines of evidence support this view. First, most clinical studies describing epidural analgesia-associated fever have been nonrandomized comparisons of women who self-select their analgesia. Risk factors for fever during labor are similar to those associated with use of epidural analgesia, including nulliparity,[13] prolonged rupture of membranes,[5,13] and prolonged labor.[4,5,13,21] In addition, women requesting epidural analgesia are more likely to have higher temperature on admission,[13] chorioamnionitis,[13] and more frequent cervical examinations.[30]

Second, some studies have sought pathologic diagnoses of chorioamnionitis in women with epidural analgesia. Vallejo et al.[31] compared 3 groups of women who self-selected their analgesia: those without epidural analgesia and with clinical chorioamnionitis, those with epidural analgesia and without clinical chorioamnionitis, and those with both epidural analgesia and chorioamnionitis. The diagnosis of chorioamnionitis required both fever and clinical signs such as tachycardia, leukocytosis, uterine tenderness, or foul-smelling amniotic fluid, and was confirmed histologically. By definition, fever was universal in the infected women. However, the incidence of fever in uninfected women with epidural analgesia was only 1%. Dashe et al.[20] compared the placental pathology of 149 women who self-selected epidural or nonepidural analgesia. Fifty-four percent of the subjects received epidural analgesia, and this group developed a temperature of >38°C more frequently than did the group that did not receive epidural analgesia (46% vs. 26%). However, histologic evidence of placental inflammation was also more common among epidural-exposed women. In the absence of placental inflammation, the incidence of maternal fever was equivalent in the epidural exposed and unexposed patients (11% vs. 9%). Conversely, Evron et al.[32] were unable to demonstrate a difference in either fever or β-A activin staining in placental tissue between women randomized to epidural or IV analgesia. However, β-A activin is associated with chronic inflammatory conditions rather than with acute inflammation. Additionally, the difference in fever (31% vs. 11%) did not reach statistical significance because of insufficient power. These studies suggest that epidural-associated fever in women who select their analgesia is often accompanied by chorioamnionitis and placental inflammation.

A third line of evidence that inflammation is involved in maternal fever comes from studies attempting to suppress inflammation in labor. Goetzl et al.[33] randomized women with epidural analgesia to receive acetaminophen or placebo in labor. The incidence of temperature >38°C was identical in the 2 groups. However, elevated maternal serum and cord blood markers of inflammation (IL-6) were demonstrated in febrile women. IL-6 levels were higher at baseline in women who eventually developed fever, and levels increased with longer exposure to epidural analgesia. These observations suggest that women who develop fever may be experiencing an inflammatory process before the initiation of epidural analgesia and that epidural analgesia may enhance this inflammation. However, this conclusion is confounded by the fact that women who developed fever had other risk factors for infection and fever, including longer duration of ruptured membranes, more cervical examinations, and larger babies. More recently, the same group was able to suppress epidural-associated fever with high-dose maternal methylprednisolone (100 mg every 4 hours).[34] Cord blood IL-6 levels were also lower in steroid-treated patients, indicating suppression of inflammation. Unfortunately, neonatal bacteremia was significantly increased by steroid exposure, from 0% to 9%.[34]

Other studies have taken a different approach, randomizing patients to different types of neuraxial analgesia, with the hypothesis that variations in epidural exposure should affect the incidence of fever if the epidural is causal. Mantha et al.[35] randomized women to receive either bupivacaine 0.125% or ropivacaine 0.1%, both with fentanyl 2 mcg/mL, by either intermittent bolus injection or continuous infusion. They found a lower incidence of temperature ≥38°C in the intermittent group than in the continuous group at 4 hours (5% vs. 23%) but not thereafter. They proposed that "intermittent partial recovery of heat loss mechanisms between injections" might explain the difference. Conversely, Wong et al.[36] randomized 750 women to neuraxial (combined spinal–epidural technique) or systemic opioid analgesia, followed by epidural analgesia after 4 cm dilation. The spinal opioid group was exposed to neuraxial analgesia an average of 110 minutes longer than was the systemic group, but there was no difference in the duration of epidural analgesia. The mean maximal temperature in labor, a secondary outcome, was identical between the groups. Similar results were found by Ohel et al. among women randomized to receive epidural analgesia at a mean of 2.4 versus 4.6 cm cervical dilation, although the actual duration of epidural exposure was not reported.[37] Similarly, in an astonishingly large single-institution trial, Wang et al.[38] randomized 12,793 nulliparous women to early (1 cm dilation) versus later (≥4 cm) initiation of epidural analgesia with 0.125% ropivacaine with sufentanil 0.3 mcg/mL administrated via patient-controlled epidural analgesia with no basal infusion. The incidence of temperature >38°C, a secondary outcome, was not different in the 2 groups (9.3% vs. 9.6%), nor was the mean temperature "in labor" (37.4°C vs. 37.2°C). However, the early group was exposed to a median of 12.6 hours of epidural analgesia, in comparison with 4.8 hours in the later group. Together, these studies do not provide strong evidence that the technique or duration of epidural analgesia in a randomized, controlled setting has an important effect on the incidence of fever. These findings are in contrast to those of

observational studies, in which longer duration of epidural analgesia is associated with a greater risk of fever. The disparity in findings is likely due to selection bias: women self-selecting early epidural analgesia, and thus experiencing longer labors, may be at higher risk for fever.

The studies in the foregoing discussion did not randomize women to epidural analgesia or an alternative. Therefore the relationship between epidural analgesia and inflammation, particularly in the placenta, may be due to differences in obstetrical care or the course of labor rather than caused by the neuroblockade. However, such mechanisms do not readily explain a higher incidence of fever in women randomly receiving epidural analgesia in a clinical trial. Several RCTs have examined the incidence of fever, and each has found increased fever in the group randomized to epidural analgesia. Meta-analysis of the 3 most rigorous trials showed a relative risk of 3.67 [95% confidence interval (CI) 2.77, 4.86].[39] In a detailed reanalysis of one such trial, Philip et al.[14] confirmed an increased incidence of fever in women randomized to epidural analgesia. However, the association was confined to nulliparous patients. Febrile patients had longer labors, more internal fetal monitoring, and more oxytocin augmentation. This observation indicates that differential obstetrical management among epidural-exposed and nonexposed patients can potentially bias even RCTs. Conversely, the length of labor, use of oxytocin, and surgical amniotomy do not differ between the epidural and opioid arms of most RCTs.[39] These observations, together with the finding that type of neuraxial block may not affect the incidence of fever, suggest that it may indeed be the instrumentation of the epidural space, administration of epidural medications, or neuraxial blockade that contributes to inflammatory fever in laboring women.

CONSEQUENCES

Epidural analgesia-associated fever may have significant consequences for both the mother and the fetus/neonate. It can be difficult, however, to differentiate the effect of fever from that of the underlying cause, particularly when the clinical suspicion of chorioamnionitis or other infection is high.

Maternal Effects

Elevated temperature is associated with increased maternal heart rate, cardiac output, oxygen consumption, and catecholamine production. These physiologic effects are rarely deleterious to otherwise healthy mothers but are potentially deleterious in women with severe cardiac or pulmonary disease. Evidence has linked postcesarean fever to risk of uterine rupture during subsequent attempted vaginal birth.[40] Not surprisingly, shivering or shaking rigors[6,25,41] and antibiotic exposure[12,42] are far more common in febrile women. Frequently, maternal fever prompts changes in obstetrical management. Lieberman et al.[43] found a 2-fold higher incidence of operative vaginal as well as cesarean delivery in a retrospective analysis of nulliparous women who were afebrile at admission but developed a temperature of >99.5°F (37.5°C) during labor, in comparison with those who remained afebrile, even after controlling for birthweight, length of labor, and analgesic choice. It is unclear whether fever alters the labor pattern, which impacts obstetrical management, or whether the presence of fever alters the decision-making of obstetricians who may fear maternal or fetal complications of delaying delivery.

Fetal Effects

Effects of maternal fever on the fetus and newborn have stimulated considerable controversy. Similar to maternal effects, there are both direct effects of fever and indirect effects on neonatology practice.

The fetus depends on transfer of heat to the mother to avoid hyperthermia, so maternal fever can produce fetal hyperthermia. Early work by Morishima et al.[44] demonstrated detrimental maternal and fetal effects of radiantly warming pregnant baboons to a temperature of approximately 42°C (107°F). Maternal hemodynamic deterioration and occasional death were observed, as well as increased uterine activity, late decelerations, and fetal acidosis. The extreme hyperthermia produced in this study is of uncertain relevance to the clinical realm. However, Macaulay et al.[21] evaluated the effect of epidural analgesia on maternal oral, intrauterine, and fetal skin temperature during labor in humans. Women selected their own analgesia: 33 received epidural analgesia, and 24 received nitrous oxide, systemic opioids, or no analgesia. Maximum fetal skin temperature >38.0°C was seen in one third of patients in the epidural group but none in the nonepidural group. Three fetuses, all in the epidural group, developed estimated core temperatures of >40.0°C. Overall measures of neonatal well-being, including Apgar scores and umbilical blood gas and acid-base measurements, were unaffected by analgesic choice. Indeed, animal models of moderate hyperthermia have demonstrated minimal adverse fetal effects and even an increase in uterine bloodflow.[45,46]

Some direct adverse effects of maternal fever have been documented in the immediate postpartum period. Lieberman et al.[47] reviewed the records of 1218 nulliparous women who were afebrile on admission. Approximately 10% developed fever >100.4°F and 5% >101°F (38.0°C and 38.3°C, respectively). Nearly all febrile women had epidural analgesia. Moderate fever was associated with low fetal tone and 1-minute Apgar scores <7. Higher fever was associated with bag-mask ventilation at delivery and need for supplemental oxygen in the nursery, and weakly associated with neonatal seizures. In a case-control study, this group of investigators found that maternal fever was associated with unexplained neonatal seizures (odds ratio 3.4).[48] Similarly, Perlman found lower 5-minute Apgar scores and an increased need for cardiopulmonary resuscitation in the babies of febrile women.[49] A group from the same institution found that positive pressure ventilation for longer than 2 minutes, tracheal intubation, or Apgar score <6 at 5 minutes was associated with increased neonatal temperature in term infants born to mothers with chorioamnionitis.[50] Conversely, Locatelli et al. found an association between poor neonatal condition (5-minute Apgar <7 or umbilical arterial pH <7.0) and placental vascular pathology, but not maternal infection, in a large epidemiologic investigation of >27,000 deliveries.[51]

A more ominous prospect has recently commanded more attention than have these transient neonatal issues.

Over a half-century ago, Eastman and DeLeon noted an association between maternal chorioamnionitis and cerebral palsy.[52] Subsequent work has clearly related maternal intrapartum infection, whether diagnosed clinically or pathologically, to subsequent development of cerebral palsy.[53–56] Other devastating neonatal brain injuries, including neonatal encephalopathy, have also been linked to maternal fever and infection during parturition.[57] Even if not apparent at birth, cognitive deficits later in childhood appear related to maternal intrapartum infection. For example, Dammann et al. demonstrated that nonverbal intelligence scores <2 standard deviations below the age-adjusted mean are related to maternal fever at birth (odds ratio 3.8).[58] Schizophrenia,[59] autism,[60] and possibly even Parkinson's disease[61] may be related to maternal fever as well.

As with the etiology of fever in labor in general, the link between fever and neonatal brain injury appears to be inflammation.[62] Animal models of intrauterine infection produce white matter lesions in the fetal brains.[63] These lesions are blocked with anti-inflammatory cytokines, perhaps by blocking gliosis in affected areas.[64,65] In humans, the amniotic fluid of babies who develop cerebral palsy shows higher levels of inflammatory cytokines than does that of controls with normal brain development.[54] Importantly, Impey et al.'s work linking maternal fever to neonatal encephalopathy found neonatal sepsis to be rare among affected babies, which suggests that inflammation rather than infection per se may be the etiologic mechanism.[57,66] Noninflammatory hyperthermia may also damage the fetus. Epidemiologic investigations have shown an increase in neural-tube defects in the babies of women exposed to external heat sources in early pregnancy, such as hot tubs or saunas, with attributable risk comparable to the risk observed with febrile illness.[67] Spontaneous abortion earlier than 20 weeks' gestation is also associated in a frequency-dependent fashion with hot tub use.[68] In a rat model of inflammation-induced fetal brain injury (hypoxia plus lipopolysaccharide exposure), exposure of the newborn pups to ambient environment-induced hyperthermia worsened the brain inflammatory response.[69] Hyperthermia also enhanced the effect of hypoxic brain injury on behavioral and learning tasks in rats.[70] Together, these investigations suggest that elevated maternal temperature may harm the fetus, particularly the developing nervous system, and that inflammatory causes are likely responsible when the fever occurs in the intrapartum period. Hyperthermia itself may worsen injuries due to inflammatory or other causes.

Finally, the neonate may also be placed at risk indirectly as a result of the interventions triggered by the occurrence of maternal fever. Retrospective studies have demonstrated an association between epidural use, maternal fever, and fetal and neonatal evaluation for sepsis and subsequent antibiotic exposure.[11,12,71] These studies suggested that either overt (>38°C) or low-grade (>37.5°C) maternal fever often triggered neonatologists to evaluate the neonate for possible infection, though the incidence of actual sepsis was extremely low. Other retrospective investigations have yielded conflicting results, perhaps because the criteria used to trigger neonatal sepsis evaluation vary among neonatologists.[19] In a natural experiment study, Yancey et al.[9] found the incidence of fever increased 3- to 18-fold in a military hospital when epidural analgesia on demand was introduced, and use increased from 1% to 83% over a short period of time. There was a modest increase in the measurement of neonatal blood counts and blood cultures (relative risk of 1.5 to 1.7), but no difference in antibiotic treatment or other interventions. The authors contrasted their findings to those of earlier studies and attributed the difference to practice style in which maternal fever alone did not trigger sepsis evaluation. Trials randomizing women to epidural versus nonepidural analgesia have yielded inconsistent results. Philip et al.[14] found fever to be more common in women randomly assigned to epidural analgesia (15% vs. 4%); neonatal sepsis evaluation was more common in febrile than afebrile women (96% vs. 13%). However, within the febrile and afebrile cohorts, analgesic assignment was not associated with sepsis evaluation, suggesting that fever, not epidural analgesia per se, was the risk factor. Wang et al.[38] found no difference in sepsis evaluation or neonatal antibiotic treatment in women who received epidural analgesia early in labor rather than later. Together, the evidence suggests that neonatal sepsis evaluation may be increased by fever and epidural analgesia, though the effect varies with neonatology practice style.

PREVENTION AND TREATMENT

Comparatively little work has concentrated on efforts to prevent epidural-associated fever. In part, this is likely due to the uncertain etiology of fever. Moreover, the likelihood that some epidural-associated fever may be related to chorioamnionitis may make obstetricians reluctant to suppress it for fear that doing so may mask the appearance of an infection that could threaten both maternal and fetal well-being. Conversely, there is now widespread agreement that once fever is suspected to be infectious, it is prudent to begin antibiotic therapy intrapartum, rather than waiting for confirmation postpartum. Both maternal and fetal outcomes are improved when suspected chorioamnionitis is treated promptly before delivery with appropriate antibiotics.[72,73]

Acetaminophen does not appear to suppress fever in women with epidural analgesia. Goetzl et al.[74] randomized 42 initially afebrile (<37.5°C) women in labor to rectal acetaminophen, 650 mg every 4 hours, or placebo. The incidence of temperature >38.0°C or >37.4°C, mean maximal temperature, and temperature trend during labor did not differ between groups. In a small study that was likely underpowered, Evron et al.[28] also found no difference in maximal temperature or fever in women in labor randomized to epidural ropivacaine or ropivacaine and IV acetaminophen at an unspecified dose, though there was a trend toward higher temperature in the ropivacaine-only group. Together, these results support the premise that epidural-associated fever may be inflammatory in origin. Acetaminophen reduces the temperature of the hypothalamic thermoregulatory set point, which is increased by some febrile stimuli. However, it has weak anti-inflammatory activity. Alternatively, the dose and route of acetaminophen administered may not have been adequate to suppress fever. High-dose methylprednisolone, which presumably has a much stronger anti-inflammatory action, does suppress fever in women with labor epidural analgesia. However, it has the unacceptable side effect of causing

increased neonatal bacteremia,[34] and thus is unlikely to be useful clinically. Other anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), have not been evaluated for suppressing maternal fever.

As was noted earlier, systemic fentanyl weakly suppresses fever induced by IL-2 in volunteers, but there was no difference in the incidence of fever in women who received epidural analgesia with or without fentanyl.[27] A similar effect was seen with systemic alfentanil in volunteers.[75] Because meperidine markedly attenuates shivering, and does so by mechanisms at least partly distinct from its μ-opioid effect,[76] it potentially could have a role in suppression of epidural-associated fever. Although epidural opioids have generally not been found to suppress fever in labor, neuraxial morphine has been anecdotally associated with hypothermia,[77,78] which may point to a therapeutic use. These possibilities have not been studied, but the therapeutic effect of opioids in reducing fever in labor appears weak.

In animal models, a variety of interventions can attenuate the effect of experimental maternal inflammation on neonatal brain injury. These include *N*-acetylcysteine—which reduces white matter lesions and improves behavioral responses even if given after the inflammatory insult[79–81]—activated protein C,[82] erythropoietin,[83] and dietary zinc supplementation.[84] None of these maneuvers has been tested in humans (*N*-acetylcysteine is currently being studied in human RCTs). One study in premature human deliveries suggested that a complete course of antenatal steroids was protective against the association between chorioamnionitis and brain injury.[85] Other reasonable possible anti-inflammatory interventions may include NSAIDs, epidural steroids, IV steroids and prophylactic antibiotics (to prevent neonatal bacteremia), and statins. Maneuvers such as active cooling of the mother or fetus via amnioinfusion may also be worthy targets for future study. None of these interventions has been studied in parturients for this purpose.

CONCLUSIONS AND FUTURE DIRECTIONS

Women in labor with epidural analgesia experience a larger increase in temperature and more clinical fever than do women who receive other forms of analgesia. The impact of such hyperthermia ranges from discomfort in the mother to influence on the practice of obstetrics and neonatology, and possible direct detrimental effects on the newborn. There remain a number of areas of uncertainty that warrant further investigation:

1. The mechanism of fever is most likely inflammation, though some thermoregulatory effects may be at work as well. Although considerable evidence points to the placenta as the source of the inflammatory response, it is not clear whether the etiology is infectious or noninfectious, and why some women with fever and epidural analgesia do not have placental inflammation on histologic examination.
2. The more frequent occurrence of fever in women with epidural analgesia in randomized trials comparing it with nonepidural analgesia remains unexplained. If placental or other inflammatory processes are responsible, the mechanism by which epidural analgesia enhances either inflammation or the occurrence of fever remains obscure.
3. It is unknown whether there is a link between noninfectious fever and neonatal brain injury. Most animal models and human epidemiology point to infectious inflammation.
4. It is also unknown whether epidural-associated fever is related to neonatal brain injury in the absence of clinical infection.
5. Safe and effective methods for suppressing maternal fever in women with epidural analgesia have yet to be identified.
6. Safe and effective methods for suppressing neonatal brain injury in the setting of fever in humans have yet to be tested.

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