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

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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 nulliparous women 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 broad-based prophylaxis. 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. 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. 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. 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. 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. 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. 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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REFERENCES