Epidural-related maternal fever: incidence, pathophysiology, outcomes, and management

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Epidural-related maternal fever affects 15% to 25% of patients who receive a labor epidural. Two meta-analyses demonstrated that epidural-related maternal fever is a clinical phenomenon, which is unlikely to be caused by selection bias. All commonly used neuraxial techniques, local anesthetics with or without opioids, and maintenance regimens are associated with epidural-related maternal fever, however, the impact of each component is unknown. Two major theories surrounding epidural-related maternal fever development have been proposed. First, labor epidural analgesia may lead to the development of hyperthermia through a sterile (noninfectious) inflammatory process. This process may involve reduced activation of caspase-1 (a protease involved in cell apoptosis and activation of proinflammatory pathways) secondary to bupivacaine, which impairs the release of the antipyrogenic cytokine, interleukin-1-receptor antagonist, from circulating leucocytes. Detailed mechanistic processes of epidural-related maternal fever remain to be determined. Second, thermoregulatory mechanisms secondary to neuraxial blockade have been proposed, which may also contribute to epidural-related maternal fever development. Currently, there is no prophylactic strategy that can safely prevent epidural-related maternal fever from occurring nor can it easily be distinguished clinically from other causes of intrapartum fever, such as chorioamnionitis. Because intrapartum fever (of any etiology) is associated with adverse outcomes for both the mother and baby, it is important that all parturients who develop intrapartum fever are investigated and treated appropriately, irrespective of labor epidural utilization. Institution of treatment with appropriate antimicrobial therapy is recommended if an infectious cause of fever is suspected. There is currently insufficient evidence to warrant a change in recommendations regarding provision of labor epidural analgesia and the benefits of good quality labor analgesia must continue to be reiterated to expectant mothers.

Key words: epidural fever, epidural-related maternal fever, fever, intrapartum fever

Introduction

Epidural analgesia remains the gold standard for treating labor pain with a proven track record of safety for both the mother and baby worldwide. Although utilization of labor epidural analgesia varies among institutions, approximately 60% of women in the United States are estimated to receive epidural analgesia for vaginal delivery.[1] Epidural-related maternal fever (ERMF) was first described in 1989 by Fusi et al[2] in a study in which it was reported that laboring women who received epidural analgesia were more likely to experience a rise in core temperature (1°C over 7 hours) than those who received intramuscular meperidine for labor analgesia without any evidence of clinical infection among the participants. The finding was a paradoxical phenomenon: one expects that the blockade of sympathetic nerves induced by epidural anesthesia will cause vasodilation and heat loss through radiation as seen with cesarean delivery, however, laboring patients who received epidural analgesia with lower doses of neuraxial (spinal or epidural) drugs were noted to have a rise in body. ERMF is a phenomenon that seems to be unique to laboring parturients. The absence of ERMF in the nonpregnant surgical population may be partly attributable to the inhibition of fever by inhaled anesthetic agents and opioids.[3,4] Furthermore, labor induces an inflammatory state, which is demonstrated by increased levels of circulating inflammatory cytokines such as interleukin-6 (IL-6) and IL-10, the levels of which increase at a greater rate in laboring patients than in nonlaboring patients.[5]

Although most women receiving epidural analgesia do not experience ERMF, the subset of those who do tend to exhibit signs of temperature increase within 1 to 2 hours of epidural placement and are more likely to have higher levels of underlying inflammatory markers. This supports an immune-mediated instead of a thermoregulatory-mediated etiology of ERMF. Although studies continue to confirm the findings of Fusi et al,[2] ERMF was considered an enigma of little clinical concern. However, over the past 3 decades, research has suggested that ERMF could lead to adverse maternal and neonatal outcomes. This narrative review summarizes the key studies that

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investigated ERMF and discusses the incidence, pathophysiology outcomes, and management strategies associated with this phenomenon.

Incidence of epidural-related maternal fever

The incidence of ERMF varies greatly in the literature, ranging from 1.6%[6] to 46%,[7] but typically, this phenomenon occurs in 15% to 25%[8] of patients who receive a labor epidural (Table 1).[6,7,9−22,24−41] The wide variation in the reported incidence can be attributed to differences in the study design, study populations, and definitions used for fever. In the United States, the recommended definition of intrapartum fever is a maternal oral temperature of >39°C on a single occasion or 2 oral temperature readings of 38°C to 38.9°C 30 minutes apart.[42] In contrast, the United Kingdom guidelines define intrapartum fever as a maternal temperature ≥38°C on a single occasion or 2 temperature readings ≥37.5°C 1 hour apart.[43] Most studies that investigated ERMF used a maternal oral temperature of ≥38°C on a single occasion as the definition for intrapartum fever (Table 1). When the threshold for fever is changed from >37.5°C to ≥38°C for a study population, there is a notable fall in the incidence of ERMF, but it is important to note that a substantial risk for developing ERMF remains.[16,25]

Early studies reporting an association between labor epidural analgesia and maternal fever were observational in nature (retrospective and prospective studies) with patients selecting the mode of analgesia (epidural or nonepidural). These studies were criticized for selection bias and confounding factors, which may have contributed to the findings—it was inferred that patients who had obstetrical risk factors for intrapartum fever (nulliparity, induction of labor, duration of labor, higher IL-6 level on admission, group B *Streptococcus* positive, and higher likelihood of needing operative delivery) were the patients who were more likely to elect for labor epidural analgesia. However, subsequent studies that controlled for confounding factors through statistical analyses continued to report an association between epidural analgesia and intrapartum fever.[21,38] Findings from a landmark natural study, which evaluated the incidence of intrapartum fever before and after introduction of a labor epidural service, suggests that epidural analgesia is an independent risk factor for intrapartum fever.[44] In this study, when epidural analgesia use increased from 1% to 83% among the population, a corresponding increase in the incidence of intrapartum fever from 0.6% to 11% was noted. Likewise, multiple randomized controlled trials (RCTs) have been performed and consistently demonstrated that women who received labor epidural analgesia were at increased risk for developing intrapartum fever. Two recent meta-analyses combined the results from previous observational studies and RCTs to evaluate the relationship between labor epidural analgesia and intrapartum fever.[45,46] Morton et al[45] found that patients who received an epidural had an overall odds ratio (OR) of 5.26 (95% confidence interval [CI], 4.98−5.56) for developing intrapartum fever. When a subgroup analysis of only the RCTs was performed, the OR was 4.21 (95% CI, 3.49−5.09) with minimal heterogeneity. Another meta-analysis of RCTs conducted by Jansen et al[46] also found that women who received labor epidural analgesia had a relative risk of 3.54 (95% CI, 2.61−4.81) for developing intrapartum fever.[46] The findings of these meta-analyses demonstrated a causal link between epidural analgesia and intrapartum fever, suggesting that ERMF is a clinical phenomenon unlikely to be a product of selection bias.

Clinical presentation

Although obstetrical risk factors for developing intrapartum fever are well known, there is limited research that has identified specific risk factors for ERMF. Women who experience ERMF exhibit a slow, insidious rise in maternal temperature, and the original study by Fusi et al[2] reported this to occur at a rate of 0.15°C/h. Goetzl et al[47] corroborated these findings, showing that women who develop ERMF experience an immediate rise in temperature after neuraxial analgesia has been commenced, followed by an increase over time at a rate of 0.18°C/h. Overall, the majority of studies have reported that ERMF occurs within 6 hours of commencing labor epidural analgesia.[8] Several studies have therefore suggested that the development of ERMF is dependent on the duration of labor and exposure to epidural analgesia drugs.[15,18,21,24,32,38,41,48−52] However, other studies reported an increased prevalence of ERMF among parturients receiving labor epidural analgesia even after controlling for the duration of labor in statistical analyses.[14,20,25] Parity may be associated with the likelihood of development of ERMF, however, results from studies are conflicting (Table 1), and this warrants further research. Furthermore, several RCTs investigating early vs late epidural placement during labor have concluded that the timing of epidural placement has no impact on the incidence of maternal fever,[53−55] however, it should be noted that the epidural exposure times between early and late groups within these studies were all <1 hour. The possible lack of a dose- or duration-dependent effect on ERMF has led some authors to postulate a trigger effect, which stimulates the underlying processes of ERMF to occur. Most of the published studies have evaluated maternal temperatures until time of delivery. Gonen et al[49] reported that 90% of ERMF cases that have been observed during labor resolved within a few hours of delivery,[49] however, more studies exploring the postpartum clinical course of ERMF are needed because this may help to differentiate it from other causes of intrapartum fever.

Choice of neuraxial analgesia

Mode of neuraxial analgesia

Conventional epidural remains the most popular neuraxial technique for labor analgesia in the United States, however, modifications of the technique, such as the combined spinal epidural (CSE) and dural puncture epidural (DPE), are gaining popularity. Currently, there are no RCTs comparing the effect of conventional epidural, CSE, or DPE techniques on ERMF incidence. De Orange

TABLE 1
Summary of studies that investigated the association between epidural analgesia and maternal fever

Observational studies

Study	Year	Study design	Country	Definition of maternal fever	Parity	Drugs and doses		Were patients with possible intraamniotic infection excluded from study?	Incidence of fever		
						Epidural	Nonepidural		Epidural % (n/N)	Nonepidural % (n/N)	*P* value or OR or AOR or ARR
Agakidis et al[9]	2011	Retrospective observational	Scotland	≥38°C axillary	Mixed[a]	Conventional epidural. 0.125% bupivacaine+2 μg/mL fentanyl, loading dose 15 mL, followed by CEI 8–12 mL/h	Drugs and doses not stated	Y, based on clinical features (foul smelling amniotic fluid, ↑ WCC, ↑ CRP)	11.3 (54/480)	0.8 (4/480)	<.0001
Baheri et al[10]	2013	Prospective observational	Belgium	≥37.5°C site not stated	Mixed[b]	Conventional Epidural. 0.16% ropivacaine+sufentanil 0.8 μg/mL, loading dose max 15 mL, followed by CEI+ PCEA (4 mL/h basal with 4 mL q15 min)	None	Y, diagnosis criteria not described	31.1 (28/90)	8.9 (8/90)	<.001
Curtin et al[11]	2015	Retrospective cohort (secondary analysis)	United States	≥38°C tympanic	Mixed[c]	Conventional Epidural. lidocaine+epinephrine test dose, followed by 20 mg bupivacaine+100 μg fentanyl bolus, followed by CEI 8.75 mg+28 μg fentanyl/h	Drugs and doses not stated	N, but ALL placentas histologically examined. Epidural analgesia and intraamniotic infection found to be independent predictors for fever	37 (180/487)	7.1 (11/154)	<.001
Dashe et al[7]	1999	Prospective cohort	United States	≥38°C site not stated	Mixed[d]	Conventional Epidural. Test dose 3 mL lidocaine and epinephrine. 0.25% bupivacaine 3 mL increments to achieve T10, followed by CEI 0.125% bupivacaine 8–10 mL/h	IV meperidine. 50–100 mg every 2 h	N, but ALL placentas histologically examined. ERMF found to occur in the presence of placental inflammation	46 (37/80)	26 (18/69)	.01

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del Arroyo et al[12]	2019	Prospective cohort	United Kingdom	≥38°C oral	Mixed[a]	Conventional Epidural. 0.1% bupivacaine with 2 μg/mL fentanyl 15 mL initially, followed by PCEA 0.1% bupivacaine with 2 μg/mL fentanyl 8 mL bolus, lockout 20 min	inhaled N_2O/O_2 mixture, IM diamorphine 7.5 mg prn	N, but women with known infection/ pyrexia and antibiotics were excluded	13.2 (5/38)	0 (0/15)	n/a
Greenwell et al[13]	2012	Retrospective cohort	United States	≥38°C oral	Nulliparous	Not stated	Drugs and doses not stated	N	19.2 (535/ 2784)	2.4 (10/425)	<.0001
Gross et al[14]	2002	Cohort (RCT secondary analysis)	United States	≥38°C site not stated	Nulliparous	Conventional Epidural. 0.25% bupivacaine 12–16 mL bolus to achieve T10, followed by CEI 0.125% bupivacaine with 2 μg/mL fentanyl 8–10 mL/h	1. Control group: no medication 2. IV nalbuphine 10 mg followed by IM nalbuphine every 3–4 h	N	17 (46/278)	1 (2/170)	<.0001
Herbst et al[15]	1995	Retrospective case control	Sweden	≥38°C oral	Mixed[e]	1989–1992: 0.25% bupivacaine 5–8 mL bolus doses. After 1993: 0.125% bupivacaine 5–8 mL with 10 μg sufentanil, followed by 0.125% 8 mL bolus as needed	Meperidine (dose and route not stated)	N	6.4 (44/683)	1.1 (28/2426)	<.001
Jia et al[16]	2021	Retrospective cohort (propensity matched)	China	≥37.5°C site not stated	Mixed[a]	Drugs and doses not stated	Drugs and doses not stated	N, but incidence of intraamniotic infection was a secondary outcome: epidural (7.4%) vs non- epidural (1.8%); ARR 2.98	15.4 (2379/ 15401)	3.8 (577/ 15401)	ARR, 3.37 (3.05 –3.72)

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Kaul et al[17]	2001	Retrospective cohort	United States	≥38°C site not stated	Nulliparous	Conventional Epidural. lidocaine+epinephrine test dose, followed by 0.25% bupivacaine or 0.2% ropivacaine 10 mL, followed by CEI 0.125% bupivacaine with 2 μg/mL fentanyl 10–12 mL/h or 0.1 ropivacaine + 2 μg/mL fentanyl 10–12 mL/h	IV Nalbuphine 5–10 mg or IV butorphanol 2 mg as needed	N	6.6 (61/922)	0 (0/255)	<.001
Lieberman et al[18]	1997	Prospective observational	United States	≥38°C site not stated	Nulliparous	Drugs and doses not stated	Drugs and doses not stated	N	14.5 (152/1047)	1.0 (6/610)	<.001
Lin et al[19]	2021	Retrospective cohort	China	≥38°C, site not stated	Nulliparous	Conventional Epidural. 0.1% ropivacaine+3 μg/mL sufentanil 8–10 mL loading dose, followed by CEI 8 mL/h same infusion, PCEA 5 mL bolus if needed	Drugs and doses not stated	N	23.3 (401/1722)	8.5 (98/1154)	<.001
Mayer et al[20]	1997	Retrospective observational	United States	≥37.8°C oral	Nulliparous	Conventional Epidural. Epidural only group (n=97), IV opioid and epidural group (n=94) Drugs and doses not stated	IV opioid. Drugs and doses not stated	N, but 10 patients had culture/pathology evidence of intraamniotic infection: 50% of these patients had no fever, 9 had an epidural, 1 did not	20.4 (39/191)	2.1 (2/96)	<.001

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						Epidural	Nonepidural		Epidural % (n/N)	Nonepidural % (n/N)	*P* value or OR or AOR or ARR
Ploeckinger et al[6]	1995	Retrospective observational	Austria	≥38°C axillary	Mixed[a]	Conventional Epidural. 0.25% bupivacaine with 15 μg epinephrine test dose, followed by 0.25% bupivacaine 10 mL. From 1989, 0.025 mg/mL bupivacaine, 2.5 μg/mL fentanyl with 0.0125 μg/mL epinephrine at 10–12 mL/h	IM Tramadol 100 mg or 75 mg meperidine every 2 h	N	1.6 (17/1056)	0.2 (11/6261)	<.005
Reilly and Oppenheimer[21]	2005	Retrospective case control	Canada	≥38°C or 2≥37.5°C oral	Mixed[c]	Drugs and doses not stated	Drugs and doses not stated	N, but 41 placentas reviewed for histology/culture. 26/41 had evidence of intraamniotic infection, but epidural use in this subgroup not reported	1.42 (156/10999)	0.09 (5/5484)	AOR, 5.5 (4.0–7.0)
Riley et al[22]	2011	Prospective observational	United States	≥38°C oral	Nulliparous	CSE (35/191) or epidural. Drugs and doses not stated	Drugs and doses not stated	N, but ALL placentas underwent histology + culture: 9/200 had evidence of infection. No difference between epidural and non-epidural groups	22.7 (34/150)	6 (3/50)	.009

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						Epidural	Nonepidural		Epidural % (n/N)	Nonepidural % (n/N)	*P* value or OR or AOR or ARR
Seiler et al[23]	2022	Retrospective case control	United States	≥38°C, site not stated	Mixed[e]	CSE/ Conventional Epidural/ DPE. CEI 0.0625% bupivacaine+2 μg/mL fentanyl+PCEA 5 mL, lockout 10 min. Transitioned to PIEB in 2015, 10 mL every hour of same mixture+PCEA 5 mL, lockout 10 min, max 30 mL/h	Spinal catheter. 1.25 mg bupivacaine+4 −15 μg fentanyl, followed by 0.0625% bupivacaine+2 μg/mL fentanyl CSI 2−4 mL/ h+patient bolus 1 mL lockout 30 min	N, but patients presenting with fever excluded	11.1 (18/162)	9.9 (8/81)	.83
Törnell et al[24]	2015	Retrospective cohort	Sweden	Not defined	Mixed[a]	Drugs and doses not stated	Drugs and doses not stated	N	1.42 (1838/ 129451)	0.24 (395/ 164878)	Not stated
Vinson et al[25]	1993	Retrospective and prospective cohort	United States	≥37.5°C tympanic, ≥38°C tympanic	Mixed[f]	Conventional Epidural. Test dose lidocaine. Bupivacaine bolus followed by infusion 10−14 mg/h with sufentanil 10−20 μg/h	Meperidine (dose and route not stated) Nalbuphine (dose and route not stated)	N	26.8 (11/41). 14.6 (6/41)	8.3 (3/36) 0 (0/36)	0.05−0.03
Ward et al[26]	2020	Retrospective cohort	United States	≥38°C, site not stated	Mixed[g]	Drugs and doses not stated	Drugs and doses not stated	N	12 (2103/ 16917)	3 (446/17454)	<.001
Wassen et al[27]	2014	Case- control	The Nether lands	≥38°C site not stated	Mixed[g]	Conventional Epidural. 0.125% ropivacaine+1 μg/mL sufentanil 2 mL test dose followed by 8 mL loading dose, and CEI 7−10 mL/h of same infusion.	Not known	N	11.6 (172/453)	1.8 (61/453)	<.001
White et al[28]	2017	Retrospective cohort	United States	Not defined	Mixed[g]	Drugs and doses not stated	Drugs and doses not stated	N	2.2 (3782/ 173324)	0.4 (362/ 88133)	OR, 5.4 (4.9−6.0)

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						Epidural	Nonepidural		Epidural % (n/N)	Nonepidural % (n/N)	*P* value or OR or AOR or ARR
Yin et al[29]	2019	Retrospective cohort	China	≥37.5°C oral	Mixed[g]	Conventional Epidural.0.1% ropivacaine+2–5 μg/mL sufentanil 4–10 mL loading dose, followed by CEI 5 mL/h same infusion, PCEA 5 mL lockout 15 min	Drugs and doses not stated	N	25.1 (93/371)	6.7 (9/135)	<.001

Randomized controlled trials

Study	Year	Study design	Country	Definition of maternal fever	Parity	Drugs and doses		Were patients with possible intraamniotic infection excluded from study?	Incidence of fever		
						Epidural	Nonepidural		Epidural % (n/N)	Nonepidural % (n/N)	*P* value or OR or AOR or ARR
Evron et al[30]	2007	RCT	Israel	≥38°C tympanic	Nulliparous	Conventional Epidural. 2 mL lidocaine test dose. 0.2% ropivacaine 4 mL increments to achieve T9, followed by CEI 5 mL/h+PCEA 5 mL, lockout 20 min	IV meperidine	N, but all placentas examined for inflammation. No clinical features of intraamniotic infection amongst those with epidural and fever	24(7/29)	0(0/27)	.02
Evron et al[31]	2008	RCT	Israel	≥38°C oral	Mixed[b]	Conventional Epidural. Test dose 3 mL 2% lidocaine alone. 0.2% ropivacaine 5–10 mL increments, followed by 0.2% ropivacaine 5 mL/h and PCEA 5 mL, lockout 20 min	IV Remifentanil. Basal infusion 0.025 μg/kg/min, PCA 20 μg 3 min lockout	N, but patients presenting with fever, signs of infection and ruptured membranes>24 h excluded. No placental histology	14 (7/50)	2 (1/44)	.175
Douma et al[32]	2015	RCT	The Netherlands	≥38°C site not stated	Mixed[c]	Conventional Epidural. 0.2% ropivacaine 12.5 mL loading dose, followed by CEI 0.1% ropivacaine and sufentanil 5 μg/mL at 10 mL/h, 10 mL bolus if needed	IV Remifentanil. PCA 40 μg 2 min lockout, max 1200 μg/h	N, but patients presenting with fever, signs of infection and ruptured membranes>24 h excluded. No placental histology	37 (18/49)	10 (5/49)	<.001

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						Epidural	Nonepidural		Epidural % (n/N)	Nonepidural % (n/N)	*P* value or OR or AOR or ARR
de Orange et al[33]	2011	RCT	Brazil	≥38°C axillary	Mixed[d]	CSE. 2.5 mg 0.5% hyperbaric bupivacaine and 5 μg sufentanil intrathecally, followed by 5 mL 0.05% bupivacaine and sufentanil 0.2 μg/mL every 30 min until delivery	None (non-pharmacological)	N, but patients presenting with fever, signs of infection or requiring antibiotics were excluded. No placental histology	14 (5/35)	0 (0/35)	.027
Freeman et al[34]	2015	RCT	The Netherlands	≥38°C site not stated	Mixed[a]	Conventional Epidural. Ropivacaine/ sufentanil, levobupivacaine/ sufentanil, bupivacaine/ fentanyl	IV Remifentanil. PCA 30 μg 3 min lockout, titrated to effect	N	18 (55/347)	9 (35/447)	<.001
Logtenberg et al[35]	2017	RCT	The Netherlands	≥38°C site not stated	Mixed[d]	Conventional Epidural. 0.2% ropivacaine 12.5 mL loading, followed by CEI 0.1% ropivacine with 0.5 μg/mL sufentanil of variable rate	IV Remifentanil. PCA 30 μg 3 min lockout, titrated to effect	N	7.9% (6/76)	9.6% (9/94)	.7
Lucas et al[36]	2001	RCT	United States	≥38°C site not stated	Mixed[h]	Women with PIH (DBP>90 mm Hg). Conventional Epidural. 0.25% bupivacaine to achieve T10, followed by 0.125% bupivacaine with 2 μg/mL fentanyl at variable rate	IV Meperidine 50 mg with IV promethazine 25 mg, followed by IV meperidine PCA 15 mg bolus, lockout 10 min	N	20.4 (76/372)	7.1 (26/366)	<.001

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Nafisi[37]	2006	RCT	Iran	≥38°C site not stated	Nulliparous	Conventional Epidural. Test dose 3 mL lidocaine and epinephrine. 1.0% lidocaine 10 mL bolus with 1 mL increments to achieve T10, followed 1% lidocaine 2 mL bolus as needed	IV meperidine 25–50 mg	N	21.8% (43/197)	6.6% (13/198)	<.001
Philip et al[38]	1999	RCT	United States	≥38°C tympanic	Mixed[i]	Conventional Epidural. 0.25% bupivacaine volume not stated, followed by CEI 0.125% bupivacaine with 2 μg/mL fentanyl rate not stated	IV Meperidine 50 mg with IV promethazine 25 mg, followed by IV meperidine PCA 15 mg bolus, lockout 10 min	N	15.1 (54/358)	4.0 (14/357)	<.001
Ramin et al[39]	1995	RCT	United States	≥38°C site not stated	Mixed[d]	Conventional Epidural. Test dose 0.25% bupivacaine alone 3 mL. 0.25% bupivacaine 3 mL increments to achieve T10, followed by CEI 0.125% bupivacaine with 2 μg/mL fentanyl at 8–10 mL/h	IV Meperidine 50 mg with IV promethazine 25 mg, followed by IV meperidine 50 mg bolus, maximum 200 mg/4 h	N	22.7 (98/432)	4.8 (21/437)	<.001
Sharma et al[40]	1997	RCT	United States	≥38°C site not stated	Mixed[d]	Conventional Epidural. Test dose 0.25% bupivacaine alone 3 mL. 0.25% bupivacaine 3 mL increments to achieve T10, followed by CEI 0.125% bupivacaine with 2 μg/mL fentanyl at 8–10 mL/h	IV Meperidine 50 mg with IV promethazine 25 mg, followed by IV meperidine PCA 10 mg bolus, lockout 10 min for 1 h, followed by 15 mg bolus lockout 10 min	N	23.8 (58/243)	6.1 (16/259)	<.0001

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(continued)

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Summary of studies that investigated the association between epidural analgesia and maternal fever *(continued)*

Randomized controlled trials

Study	Year	Study design	Country	Definition of maternal fever	Parity	Drugs and doses		Were patients with possible intraamniotic infection excluded from study?	Incidence of fever		
						Epidural	Nonepidural		Epidural % (n/N)	Nonepidural % (n/N)	*P* value or OR or AOR or ARR
Sharma et al[41]	2002	RCT	United States	≥38°C site not stated	Nulliparous	Conventional Epidural. Test dose 3 mL lidocaine and epinephrine. 0.25% bupivacaine 3 mL increments to achieve T10, followed by CEI 0.0625% bupivacaine with 2 μg/mL fentanyl at 6 mL/h with PCEA 5 mL bolus lockout 15 min	IV Meperidine 50 mg with IV promethazine 25 mg, followed by IV meperidine PCA 15 mg bolus, lockout 10 min. Additional 25 mg prn to max 100 mg/2 h	N	33 (75/226)	7 (16/233)	<.001

AOR, adjusted odds ratio; *ARR*, adjusted relative risk; *CEI*, continuous epidural infusion; *CSE*, combined spinal epidural; *CSI*, continuous spinal infusion; *DBP*, diastolic blood pressure; *DPE*, dural puncture epidural; *ERMF*, epidural-related maternal fever; *IM*, intramuscular; *IV*, intravenous; *N20/02 mixture*, nitrous oxide/ oxygen mixture; *PCEA*, patient-controlled epidural analgesia; *PIH*, pregnancy induced hypertension; *OR*, odds ratio.

[a] No subgroup analysis for nulliparous/multiparous patients; [b] No difference between primiparous and multiparous groups; [c] No subgroup analysis for nulliparous/multiparous patients, but nulliparity independently associated with epidural use and intrapartum fever; [d] No subgroup analysis for nulliparous/multiparous patients, but no difference in parity between epidural and non-epidural groups; [e] No subgroup analysis for nulliparous/multiparous patients, but each case/control matched for parity; [f] No subgroup analysis for nulliparous/multiparous patients, but parity was not associated with fever or duration of epidural analgesia; [g] No subgroup analysis for nulliparous/multiparous patients, but nulliparity independently associated with epidural use; [h] No subgroup analysis for nulliparous/multiparous patients, but nulliparity was higher in non-epidural group; [i] Increased risk of intrapartum fever in nulliparous women vs multiparous women with epidural analgesia.

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et al[33] evaluated the impact of the CSE technique on ERMF and showed that it was associated with increased maternal temperature (incidence 14.3%) despite a significantly shorter duration of labor.

Intrathecal catheters

Although intrathecal (or spinal) catheters are usually inserted in the event of an unintentional dural puncture, obstetrical anesthesiologists may electively place intrathecal catheters in laboring patients with a high body mass index and concerning airway features. Earlier work evaluating intrathecal catheters for labor analgesia reported the occurrence of maternal fever in 14% of laboring patients.[56] More recently, Selier et al[23] conducted a large, retrospective study comparing continuous spinal analgesia with epidural analgesia (CSE, DPE, and conventional epidural) and reported no difference in the incidence of maternal fever between the 2 techniques (9.9% and 11.1%, respectively).[23]

Local anesthetic administration techniques

Once an epidural catheter has been placed, delivery of local anesthetic mixtures through the catheter can be achieved via continuous epidural infusion (CEI), patient-controlled epidural analgesia (PCEA), or programmed intermittent epidural bolus (PIEB) administration techniques. Two studies have shown that utilizing an intermittent bolus technique (manual or programmed) for epidural maintenance is associated with a lower incidence of maternal fever when compared with CEI.[52,57] Furthermore, Li et al[58] investigated the effect of different PIEB regimens on maternal fever. This group found that using a PIEB regimen of 10 mL bolus with a lockout of 60 minutes was associated with a significantly lower incidence of maternal fever when compared with a PIEB regimen of 5 mL bolus with a 30 minutes lockout (18% vs 7%, respectively). Collectively, these preliminary studies indicate that maintenance regimens may have a role in minimizing ERMF, but further work needs to be conducted before definitive conclusions can be made.

Neuraxial opioids

Opioids are routinely used as an adjunct for epidural mixtures because they have the potential to augment the effects of local anesthetics. Opioids have pharmacologic actions that can suppress fever,[4,59,60] and it was postulated that they may have a role in preventing ERMF. However, an early RCT that investigated the effect of epidural opioids on ERMF demonstrated no difference in the incidence and clinical course of ERMF when 0.25% bupivacaine CEI was compared with 0.25% bupivacaine with 2 μg/mL fentanyl.[50] Fever suppression by systemic opioids as a mechanism of ERMF has therefore not been supported by evidence;[14] in addition, ERMF can occur with or without epidural opioids.[50]

Local anesthetic type, concentration, and dosing strategy

ERMF has been reported using different local anesthetics with varying concentrations (Table 1). There is very limited clinical data available to investigate the effect of different local anesthetics on ERMF. Lee et al[61] conducted a retrospective study in which they compared the administration of 0.08% ropivacaine with that of 0.06% levobupivacaine (both with 2 μg/mL fentanyl) for labor analgesia among nulliparous patients.[61] Levobupivacaine was associated with a higher incidence of maternal fever than ropivacaine (25% vs 15%; P=.02) despite administration of significantly lower doses in labor. The studies evaluating the effect of different concentrations of local anesthetics used for labor epidural analgesia on the incidence of ERMF have reported conflicting results. Some studies have shown that using lower concentrations can reduce ERMF rates,[62,63] whereas other authors found no difference in the incidence of maternal fever when comparing different local anesthetic concentrations.[64]

Summary

It seems that all commonly used neuraxial techniques, local anesthetics with or without opioids, and maintenance regimens are associated with ERMF. Although the impact of each component is unknown, the results from these clinical studies provide some insight about potential etiologies of the condition.

Proposed pathophysiology of epidural-related maternal fever

The pathophysiology of ERMF is incompletely understood, which hinders our efforts to differentiate ERMF from intrapartum infection. Several hypotheses have been proposed to explain the etiology of ERMF. Less supported theories include maternal shivering (rapid muscle contractions that generate heat), minor trauma from epidural needle insertion, intrapartum oxytocin, and reduced systemic opioid intake associated with labor epidural analgesia. Minor trauma from the epidural needle and catheter insertion seems unlikely to instigate the significant systemic inflammatory response needed for ERMF to manifest. This was the conclusion from a clinical study of orthopedic patients.[65] However, given the increased vascularity of the epidural space during pregnancy,[66] it is not impossible that an exaggerated inflammatory response could occur in this setting.[67] Furthermore, similar inflammatory cytokine profiles have been demonstrated with high- (intravenous) and low-dose (epidural) plasma fentanyl interventions, making epidural opioids an unlikely etiology for ERMF.[68]

There are 2 major theories supported by evidence. One theory proposes maternal immunomodulatory effects of labor epidural analgesia. Initially thought to be a potential cause of increased maternal infection rates, a more favored view is that local anesthetics precipitate intrapartum inflammation, which leads to the development of hyperthermia, also known as the sterile inflammation hypothesis. Second, the thermoregulation hypothesis can be explained from a neurophysiology perspective in terms of sympathetic nerve blockade by labor epidural analgesia in differing heat states.[69]

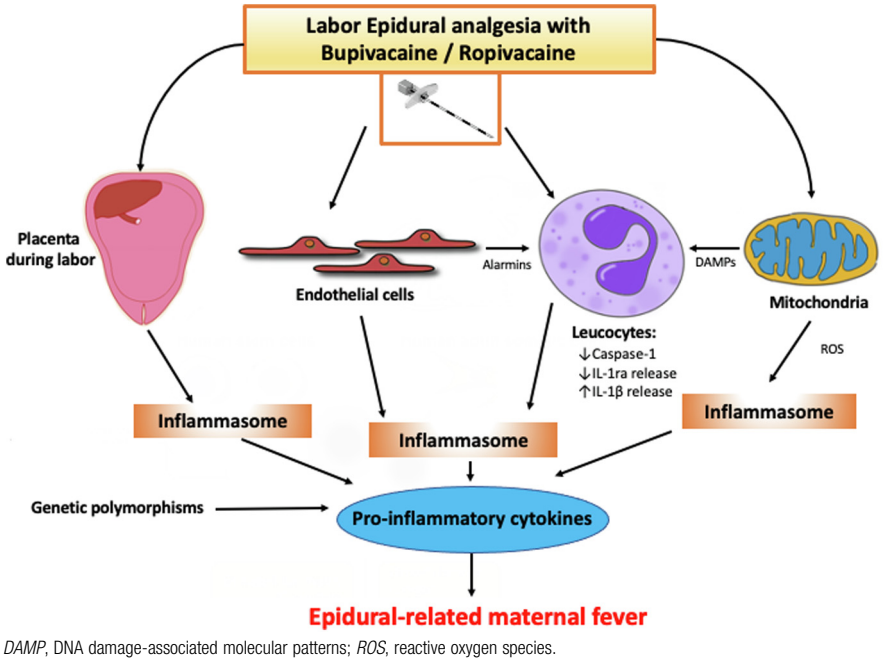
Sterile inflammation

Rates of ERMF exceed that of clinical chorioamnionitis caused by intraamniotic infection,[70] and these pathologies have been identified as

independent risk factors for the development of maternal fever.[11] An adequately powered RCT found that prophylactic broad-spectrum antibiotics failed to prevent the development of ERMF.[71] Sterile inflammation is the process of inflammation in the absence of infection[72] and is thought to play a pivotal role in parturition (Figure 1).[73] The onset of spontaneous labor has been found to be associated with an increased pro-inflammatory cytokine response.[74,75] There seems to be an inflammatory-specific feature of labor relevant to ERMF, because maternal fever does not occur in nonlaboring women who have an elective cesarean delivery under neuraxial anesthesia.[76]

Pro-inflammatory cytokines (eg, IL-1, IL-6, tumor necrosis factor-alpha [TNF-α] and interferon gamma [INF-γ]) initiate immune defense against exogenous organisms, for example, by activating neutrophils. Anti-inflammatory cytokines (eg, IL-1 receptor antagonist [IL-1ra], IL-4, and IL-10) antagonize the pro-inflammatory cytokines and thus reduce inflammation. Elevated levels of endogenous pro-inflammatory cytokines and placental inflammation have been measured in parturients following labor epidural analgesia.[7,22,77–79] Pregnant women with higher serum pro-inflammatory cytokine expression (eg, IL-6), recorded at admission to hospital, are more likely to develop ERMF.[77] This supports the narrative that epidural analgesia enhances baseline inflammation to cause ERMF, but more specifically, local anesthetic drugs infused epidurally could be promoting levels of these pro-inflammatory cytokines as a mechanism.[80,81] In addition, a randomized, double-blind, placebo-controlled trail found that prophylactic anti-inflammatory glucocorticoids reduced ERMF in a study of 200 nulliparous women. High-dose methylprednisolone (100 mg every 4 hours) reduced ERMF incidence when compared with a low-dose regimen and placebo (2%, 22%, and 34%, respectively).[82] This treatment, however, is not viable in clinical practice, with significantly increased rates of asymptomatic bacteremia reported in neonates from the study (0% vs 9.3%). A further trial involving a labor epidural infusion of dexamethasone led to a reduction in maternal temperature and IL-6 levels,[53] however, these findings were not reproduced in another study.[83] Mechanistically, these studies suggest that the release of pro-inflammatory cytokines is an important step in the process of ERMF, however, they do not elucidate how glucocorticoids reduce ERMF. Further support for the role of inflammation includes the low levels of the antipyrogenic cytokine IL-1ra associated with intrapartum inflammation and ERMF[12] and the higher levels of pro-inflammatory cytokines (eg, IL-6) reported in parturients with ERMF.[22]

FIGURE 1
Proposed mechanisms of sterile inflammation resulting in epidural-related maternal fever



DAMP, DNA damage-associated molecular patterns; *ROS*, reactive oxygen species.

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Cellular injury as an initiator of sterile inflammation

Sterile inflammation is driven by endogenous molecules called alarmins that are released following tissue and mitochondrial injury.[72] Bupivacaine absorbed from the epidural space may impair mitochondrial function,[84–87] leading to reduced adenosine triphosphate synthesis[88] and activation of the inflammasome, a multiprotein complex that produces propyrogenic cytokines (eg, IL-1β and IL-18).[89] Figure 1 summarizes potential mechanisms of sterile inflammation that may lead to ERMF.

Direct effects of local anesthetics on immune function

Local anesthetics have been found to impact immune function at plasma levels acquired during CEI.[90] Local anesthetics can lead to deleterious immune effects, including reduced neutrophil mobility,[91] phagocytosis,[92,93] chemotaxis, and superoxide generation.[94,95] Inhibition of leukocyte function could render women more vulnerable to systemic inflammation. Subcutaneous bupivacaine, for example, reduces surgical wound IL-10 levels (an anti-inflammatory cytokine) and increases substance P (a pro-inflammatory mediator) following cesarean delivery.[96]

Translational studies on the mechanisms of sterile inflammation

Recent obstetrical translational studies focused on elucidating the molecular

mechanisms of sterile inflammation secondary to local anesthetics are summarized in Table 2. Wohlrab et al[98] examined the in vitro immunologic effects of ropivacaine and lidocaine, which are commonly used local anesthetics for labor epidural analgesia. Ropivacaine exposure dose-dependently induced apoptosis and increased the release of pro-inflammatory cytokines (IL-6 and IL-8) and prostaglandin E2 (PGE2) in human cell lines and caused release of pro-inflammatory mitochondrial DNA damage-associated molecular patterns (DAMPs). Interestingly, lidocaine was found to reduce IL-6 and IL-8 release.[98] This study provides evidence that ropivacaine causes cellular injury and death via different signaling pathways and introduces the concept that different local anesthetics may be associated with ERMF in different ways.

In a clinical study involving ex vivo laboratory experiments using blood samples taken from women during established labor, bupivacaine was found to reduce leucocyte caspase-1 activity (a protease involved in apoptosis and activation of pro-inflammatory pathways)[12] and to reduce plasma IL-1ra levels. IL-1ra is an antipyrogenic factor that decreases inflammatory cytokine release, therefore, reduced IL-1ra levels lead to a pro-inflammatory and pyrogenic response. Consistent with this theory, a decreased plasma IL-1ra /IL-1β ratio was also reported in women receiving labor epidural analgesia when compared with women who did not receive labor epidural analgesia.[12] The proposed mechanism of bupivacaine-induced ERMF involving the inhibition of IL-1ra release by reducing caspase-1 activity is supported by animal data, which demonstrate the central role of IL-1 in maternal inflammatory responses.[99,100] In summary, therapeutic concentrations of bupivacaine used for labor analgesia disrupt leucocyte immune function, and pro-inflammatory cytokines may cause fever if the release of antipyrogenic IL-1ra is inhibited (Figure 1).

Genetic factors associated with epidural-related maternal fever development

There may be a genetic component that predisposes women to the development of ERMF. Carriage of the TNF-α allele 2, for example, has previously been associated with a more than 3-fold increased risk for clinical chorioamnionitis (including a temperature >38°C without histologic confirmation), even when accounting for important clinical and microbiologic risk factors.[101] Furthermore, a recent mendelian randomization analysis explored the relationship between genetic variations of IL-1ra, neuraxial analgesia, and cesarean delivery.[97] The investigation found that genetic variation associated with high circulating levels of IL-1ra was associated with lower cesarean delivery rates, but that using neuraxial analgesia disrupted this link. This was first study to investigate a genetic predisposition as a risk factor for ERMF, and although the results are promising, further work exploring this concept are needed.

Summary

There seems to be an inflammatory-specific feature of labor that, when combined with epidural local anesthetics, can impact immune cell and mitochondrial function to induce a pro-inflammatory response that can lead to ERMF. The development of bupivacaine-induced ERMF may involve impaired release of anti-pyrogenic IL-1ra from circulating leucocytes by reducing the activation of caspase-1. These laboratory data require clinical studies with larger cohorts of women with the aim of establishing detailed mechanistic processes of ERMF.

Thermoregulation

Physiological considerations for thermoregulation associated with epidural-related maternal fever

The thermoregulatory center is in the hypothalamus. Pregnancy increases evaporative (sweating), dry (skin blood flow and temperature), and behavioral heat loss from early to late pregnancy.[102] Body temperature reflects the ability of the body to balance heat production and heat loss.

Potential thermoregulatory mechanisms for epidural-related maternal fever

In normothermic, nonpregnant individuals, epidural anesthesia blocks active vasoconstriction, and as a consequence, cutaneous heat loss increases and mean body temperature decreases.[103] A similar pattern of temperature change accompanies epidural anesthesia for elective cesarean delivery.[104] However, during labor, heat production is increased.[105,106] It is possible, therefore, that labor epidural analgesia and anesthesia block active cutaneous vasodilation, leading to limited heat loss and an increase in mean body temperature. This hypothesis has been refined over the years, and proposed thermoregulatory mechanisms for ERMF (a reduction in cutaneous heat loss or skin blood flow) following neuraxial blockade include (1) limited evaporative heat loss by decreased sweating,[2] (2) thermoregulatory vasoconstriction, (3) baroreceptor-mediated reflex vasoconstriction (a physiological response to a reduction in mean blood pressure),[107] (4) nonthermoregulatory vasoconstriction (an elevated set-point during fever),[108] (5) blockade of active cutaneous vasodilation,[109] (6) decreased heat-dissipating activities such as hyperventilation[105] that are common in the absence of effective labor analgesia, which, in turn, decreases heat loss, and (7) reduced shivering thresholds.[106,110,111] These potential mechanisms are summarized in Figure 2.

Thermoregulatory changes induced by labor epidural analgesia are influenced by the body surface area in which the changes are observed (neck, arms, and face are usually spared from sympathetic blockade). Neuraxial blockade interrupts the sympathetic supply to the cutaneous vasculature, and as a consequence, the ability to regulate body temperature is decreased.[103] However, because of the unique dual sympathetic supply of the cutaneous circulation (cutaneous heat loss and skin blood flow),[109] the effect of this method on body temperature is not clear.

Studies supporting a thermoregulatory mechanism for epidural-related maternal fever

In a study involving 41 term parturients receiving labor epidural analgesia, a decrease in the minute volume (volume

TABLE 2
Summary of studies investigating proposed molecular mechanisms of sterile inflammation induced epidural-related maternal fever

Study	Human or cell-line	Number	Population	Methodology	What was measured	Main findings
Ackland et al,[97] 2022	Postpartum women with complete SNP data and 1 to 2 births, UK Biobank	Non-neuraxial (n=5611), neuraxial (n=2120)	Postpartum women	Mendelian randomization analysis	Genetic scores and delivery data	Higher IL-1ra (antipyrogenic) levels associated with reduced CD rates. Neuraxial analgesia disrupts this link, suggesting an effect on these intrapartum inflammatory pathways.
Wohlrab et al,[98] 2020	HUVECs and TBs	2 cell lines	Human	Ropivacaine (35 yM − 7 mM) or lidocaine (21 mM) with or without dexamethasone (1 yM) added to HUVECs and TBs	Apoptosis, IL-6, IL-8 and PGE2; caspase-3, nuclear factor-B and P38 mitogen-activated protein kinase pathways, extracellular signal-regulated kinase 1/2 and protein kinase B (Akt); antioxidative proteins, ICAM1, VCAM1 and PECAM1; mitochondrial function.	Ropivacaine had dose-dependent effects on apoptosis and release of pro-inflammatory cytokines and oxidative stress. Conversely, lidocaine suppressed pro-inflammatory cytokines. This study suggests that ropivacaine causes cellular injury and death via different signaling pathways. The detrimental effects induced by ropivacaine were only partially blunted by dexamethasone.
del Arroyo et al,[12] 2019	Mononuclear leucocytes (MNF) THP-1 cells	Epidural (n=38) Non-epidural (n=15)	Blood obtained from 3 groups of: (1) women in established labor (epidural or nonepidural), (2) nonpregnant women before elective surgery, (3) pregnant women not in labor	Sample incubated with control (PBS, pooled plasma) or bupivacaine for 4 h	1. Mitochondrial dysfunction (oxidative phosphorylation) 2. Apoptosis (annexin V), cell death (propidium iodide) 3. Caspase-1 activity (flow cytometry) in MNF 4. IL-1ra levels (flow cytometry) in MNF 5. IL-1ra/IL-1β ratio (enzyme-linked immunosorbent assay)	No differences in metabolic reserve or glycolysis with bupivacaine treatment. No differences in apoptosis rates in MNF cells incubated with bupivacaine. Similar apoptosis rates in lymphocytes obtained 4 h after epidural analgesia. MNF cells incubated for 4 h with bupivacaine had reduced caspase-1 activity in CD3+ lymphocytes by 14% (95% CI, 5%−16%) and CD14+ monocytes. After epidural analgesia, there was a dose-dependent reduction in caspase-1 activity. Bupivacaine reduced caspase-1 activity in CD3+ lymphocytes incubated for 4 h with serum from laboring women before epidural insertion. By contrast, caspase-1 activity was unchanged when CD3+ lymphocytes incubated with non-laboring pregnant subject serum. This also remained unchanged after bupivacaine treatment in samples from non-pregnant women. Intracellular IL-1ra protein concentrations were increased when leucocytes were incubated with bupivacaine for 4 h compared with control. Samples from women in established labor showed that plasma IL-1ra/IL-1β ratio only declined in laboring women who received epidural analgesia. Plasma IL-1β did not differ between analgesic regimes

CD, cesarean delivery; *HUVECs*, Human umbilical vein endothelial cells; *ICAM*, intercellular adhesion molecule; *IL*, Interleukin; *MNF*, mononuclear fraction; *PBS*, phosphate-buffered saline; *PECAM*, platelet endothelial cell adhesion molecule; *SNP*, single nucleotide polymorphism; *TBs*, human placental trophoblasts; *THP-1*, human monocytic leukemic cells; *VCAM*, vascular cell adhesion molecule.

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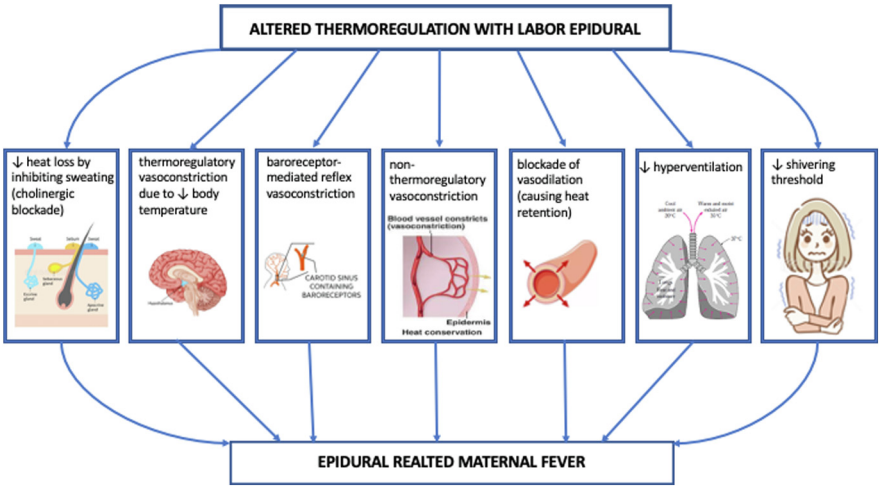
FIGURE 2
Proposed mechanisms of epidural-related maternal fever secondary to altered thermoregulation



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of gas inhaled in 1 minute) at 30 minutes and the cumulative minute volume at 2 hours was observed in women whose temperature increased by at least 0.5°C during labor.[112] Therefore, decreased heat dissipation associated with reduced ventilation caused by improved analgesia with labor epidural analgesia may contribute to development of ERMF.

Mullington et al[69] examined temperature changes in 20 women who were in established labor and recorded cutaneous heat loss and skin blood flow before and after extending epidural labor analgesia for emergency cesarean delivery by epidural top-up. Despite the fairly short time frame (median, 20; 11−25 minutes) between epidural top-up and delivery of the neonate, the mean (standard deviation) rate of increase in mean body temperature was 0.5 (0.5)°C/h. At the same time, mean cutaneous heat loss decreased by 15% from the chest and arms without significant change in skin blood flow. Given that the reduction in heat loss occurred in the chest and arms and the expected distribution of neuraxial sympathetic block,[113] blockade of active vasodilation was concluded to be the most plausible explanation for increased body temperature in this study.[69] It is possible that a similar mechanism is responsible for the hyperthermia associated with labor epidural analgesia. However, cutaneous sympathetic nerve activity was not tested directly in this study, and conclusions were reached through a process of elimination instead of quantitative examination of neuronal function.

Selier et al[23] compared rates of fever between epidural (n=162) and continuous spinal labor analgesia (n=81).[23] In their retrospective study that included matched controls receiving epidural analgesia, bupivacaine consumption was higher in the epidural group, as expected, but no difference in ERMF were demonstrable between the groups, suggesting that bupivacaine was not responsible for ERMF in a dose-dependent manner. The authors of this study did however acknowledge several important limitations, including their nonrandomized, retrospective study design, which was underpowered, and a protocol change that occurred from continuous infusion to PIEB during the study period.

Minimal evidence for a central thermoregulatory-mediated cause for epidural-related maternal fever

Goetzl et al[114] performed a double-blind, placebo-controlled trial to determine whether prophylactic acetaminophen prevented ERMF in nulliparous women. Parturients were randomized to receive either 650 mg prophylactic acetaminophen per rectum every 4 hours or a placebo immediately following labor epidural placement. This intervention did not prevent fever from occurring. However, the authors did acknowledge that the dose of acetaminophen may have been inadequate to mediate an appropriate antipyretic response.[114] Lavesson et al[115] performed a secondary case-controlled study from a cohort of parturients with continuous axillary temperature measurements available and who were given 1000 mg paracetamol orally if they developed a fever. The statistical results of maternal temperatures were conflicting. Although the analysis did not compare epidural with nonepidural labor analgesia, the authors concluded that their findings indicated that ERMF is not caused by a direct effect on the hypothalamic thermoregulatory set point.[115]

Challenges in thermoregulatory research related to epidural-related maternal fever

Direct testing of sympathetic nerve activity is not appropriate in the setting of labor and delivery, because it is time-consuming and requires intradermal bretylium tosylate and botulinum toxin administration.[116] Furthermore, although laser Doppler flowmetry used by Mullington et al[69] is the gold standard for measuring skin blood flow,[117] it is not able to determine the relative quantities of blood flow at different depths within the skin.

Summary

Neuraxial anesthesia limits cutaneous and ventilation-associated heat loss, and as a consequence, mean body temperature increases. However, it is unlikely that thermoregulatory changes alone can be responsible for ERMF because the maternal metabolic rate remains below that of gentle exercise (which is not thermogenic and does not usually induce hyperthermia), and the sympathetic block caused by labor epidural analgesia with low concentrations of local anesthetic have previously been thought to be insufficient to inhibit sweating.[110] Furthermore, hyperthermia

has been reported previously in non-obstetrical, postoperative patients who received epidural analgesia and among whom the metabolic rate was near normal.[118] Inflammation is ultimately the most plausible and evidence-based mechanism for ERMF development.[8,12,82,98,106,119] The effect of corticosteroids on reducing ERMF, in addition to the ex vivo and in vitro studies demonstrating that local anesthetics induce immune changes, further support this theory. Ultimately, the extent to which thermoregulatory and inflammatory mechanisms contribute to ERMF still remains to be determined.

Maternal- and fetal-related outcomes related to intrapartum fever

Several studies have reported maternal and neonatal outcomes associated with intrapartum fever (Supplemental Table). Our ability to distinguish between ERMF and non-ERMF currently limits our understanding of the maternal and neonatal morbidity specifically related to ERMF.

Maternal outcomes

The physiological consequences of fever are multisystemic. In the acute phase of fever (which has infectious and inflammatory origins), there is a hyperdynamic circulation with a high cardiac output state to meet the increased oxygen demand.[44] Most parturients will tolerate these changes, but they can be detrimental to those with preexisting cardiorespiratory disease. Several studies have shown that ERMF is associated with increased maternal antibiotic use, which is empirically started.[20,28,48] A meta-analysis estimated that women who receive labor epidural analgesia were more than twice as likely to receive antibiotics postpartum, although this did not reach statistical significance.[46] Antibiotic therapy can be hugely beneficial in the presence of infection, but unnecessary use is not without risk and remains a leading cause of antimicrobial resistance. Bank et al[120] performed a retrospective cohort study comparing maternal outcomes between laboring women with a nonsustained, isolated maternal fever treated with antibiotics and those who were managed expectantly. The single-gestation, term laboring parturients who received antibiotics for isolated maternal fever had a significantly longer length of hospital stay than those who did not receive intrapartum antibiotics (2.5 days vs 2.3 days; $P<.002$). Inflammation is associated with impaired uterine contractility,[121] which, in turn, is associated with increased cesarean delivery rates and postpartum hemorrhage. Therapies such as tranexamic acid and uterotonics should be considered for patients with intrapartum fever who are at risk of postpartum hemorrhage regardless of the ERMF etiology.[122,123] Intrapartum fever may also be associated with abnormal labor curves or fetal intolerance of labor, which is associated with an increased need for operative vaginal delivery.[136] Unfortunately, there are no adequately powered studies that have evaluated the risk of operative vaginal or cesarean delivery specifically related to ERMF largely because of the limitations of being unable to definitively diagnose ERMF in the setting of intrapartum fever.

Fetal outcomes

Limited data from animal and human studies suggest that uterine and umbilical cord blood flow increase significantly during maternal hyperthermia because of decreased vascular resistance.[125,126] Blood flow in the uteroplacental circulation may, however, also decrease secondary to maternal hypotension associated with sepsis. The effect of antipyretic treatment, such as acetaminophen administration, on uterine and umbilical blood flow remains unknown. Fetal temperatures in utero are normally higher than maternal temperatures by approximately 0.2°C and ERMF further increases fetal temperature during labor progression.[127,128]

Intrapartum fever (of any etiology) is associated with adverse neonatal outcomes including hypotonia, early onset seizures, reduced Apgar scores, assisted ventilation, increased neonatal sepsis evaluations, neonatal antibiotic use, and neonatal intensive care unit (NICU) admissions.[13,129–131] In a retrospective, population-based cohort study of newborns admitted to the NICU on postnatal day 0 to 1 and discharged from NICUs participating in the Pediatric Health Information System (PHIS 2006–2013), the cost of admissions for infants born at ≥35 weeks who were started on antibiotics and discharged home after no >3 days of antibiotics was $76.7 million. A recent systematic review concluded that healthcare costs ranged between approximately $1600 and $160,800 (2019 USD) per neonate with healthcare-acquired bloodstream infections, however, the cost of fever workups in newborns is not known. Probably the most worrying consequence of intrapartum fever is neonatal brain injury. Infectious causes of intrapartum fever, for example, chorioamnionitis, have a well-established association with cerebral palsy.[132,133] In addition to the direct effects of infection, it is postulated that inflammation may lead to preterm birth, which impacts neurodevelopmental outcomes.[134] A recent meta-analysis concluded that although a causal link between maternal fever and neonatal brain injury has been established (OR, 2.48; 2.28–2.70; I^2 =74%), there is currently insufficient clinical data to determine if a direct association specifically between ERMF and neonatal brain injury exists.[45] Greenwell et al[13] conducted a retrospective cohort study evaluating the impact of ERMF on neonatal outcomes and whether epidural analgesia was associated with adverse neonatal outcomes in the absence of maternal fever. Results showed that women with a labor epidural who developed a fever of >38.3°C had a 2- to 6-fold increased risk for adverse neonatal outcomes, including hypotonia, assisted ventilation, lower 1- and 5-minutes Apgar scores, and early-onset seizures than women who received a labor epidural with maximum maternal temperatures of ≤37.5°C. Furthermore, the proportion of infants experiencing adverse outcomes increased with the degree of ERMF, but most importantly, epidural use without temperature elevation was not associated with any of the adverse neonatal outcomes. These

findings suggest that if maternal fever can be reduced in parturients receiving epidural analgesia, this could improve neonatal outcomes. Several studies have failed to show an association between ERMF and an increased risk for neonatal infection,[9,17,18,131] and a meta-analysis attributed the lack of association to the low incidence of neonatal infection in studies investigating this outcome.[46] However, a recent, large propensity score-matched cohort study involving 37,786 parturients found that labor epidural analgesia with fever is associated with an increased risk for neonatal infection, including sepsis, uncharacterized infection, and pneumonia, but not necrotizing enterocolitis.[16] Most studies evaluating epidural analgesia and neonatal outcomes involve parturients of term gestation, but neonatal brain injury is more common in preterm infants. Mori et al[135] recently published preliminary results from a retrospective study investigating the impact of epidural analgesia and fever exclusively in preterm babies (23−36 weeks of gestation). Although these authors found no difference in neonatal outcomes between those who received and those who did not receive labor epidural analgesia, the study was underpowered and further prospective multicenter studies investigating ERMF specifically in preterm labor are warranted.

Diagnosis and management of intrapartum fever

The American College of Obstetricians and Gynecologists divides intraamniotic infection into the following 3 different categories: (1) isolated maternal fever, (2) suspected intraamniotic infection, and (3) confirmed intraamniotic infection.[124] Administration of intrapartum antibiotics is recommended whenever an intraamniotic infection is suspected or confirmed. Antibiotics should be considered specifically in the setting of isolated maternal fever as often occurs with ERMF (any temperature recorded between 38°C and 38.9°C with no other clinical criteria indicating intraamniotic infection and with or without persistent temperature elevation). In clinical practice, confirmed intraamniotic infection among term women in labor will most commonly be made after delivery based on histopathologic study of the placenta. Therefore, until better and less invasive intrapartum diagnostic tools become available, any practical distinction between suspected and confirmed intraamniotic infection will remain meaningful only in research settings and not for the obstetrical care provider managing a patient in labor. A diagnosis of confirmed histologic intraamniotic infection in the postpartum period does not alter postdelivery maternal treatment. Currently, given the potential benefits for the woman and newborn, antibiotics should be considered in the setting of isolated maternal fever unless a source other than intraamniotic infection is identified and documented. Whether or not a decision is made to initiate intrapartum antimicrobial therapy, the occurrence of maternal intrapartum fever should be communicated to the neonatal care team. Pediatric recommendations rely less on the clinical diagnosis of suspected intraamniotic infection and more on consideration of a variety of risk factors and newborn clinical status to determine neonatal management.

Future work

There is a paucity of research on identifying women at risk for developing ERMF, and definitive studies investigating genetic predisposition and other risk factors should be conducted. Most studies have reported on maternal and neonatal outcomes associated with intrapartum fever of any etiology, however, outcomes associated with ERMF specifically are lacking. Future work should focus on ERMF outcomes specifically, however, this will be challenging until a cost-effective, clinically feasible, and reliable diagnostic tool or biomarker with adequate sensitivity and specificity for differentiating ERMF from other causes becomes available. Laboratory studies to identify screening tools in diverse demographic, obstetrical, and medical populations are therefore urgently needed, because these could potentially prevent unnecessary maternal antibiotic treatment and obstetrical interventions. Future studies should also focus on the safest and most effective strategies for preventing ERMF, which will likely depend on its exact etiology.

Conclusion

ERMF is a clinical phenomenon affecting approximately 15% to 25% of parturients who receive a labor epidural. The etiology is not fully understood; however, it is likely to be multifactorial with sterile inflammation and alterations of thermoregulatory mechanisms as the likely potential mechanisms. Currently, there is no treatment that can safely prevent ERMF from occurring nor can it easily be distinguished clinically from other causes of intrapartum fever. Because intrapartum fever (of any etiology) is associated with adverse outcomes for both the mother and baby, it is important that all parturients who develop intrapartum fever are investigated and treated appropriately, irrespective of receiving a labor epidural. There is currently insufficient evidence to warrant a change in the recommendations regarding provision of labor epidural analgesia, and the benefits of good quality labor analgesia must be reiterated to expectant mothers. Ultimately, effective pain management during labor and delivery is associated with favorable psychological, pain, and quality of postpartum recovery related outcomes, which are of paramount importance when planning labor and delivery. Video abstract available for this article. ■

GLOSSARY

DAMPs, damage associated molecular patterns
ERMF, epidural-related maternal fever
IL-1, interleukin-1
IL-1ra, interleukin-1-receptor antagonist
INF-γ, interferon-gamma
NICU, neonatal intensive care unit
TNF-α, tumor necrosis factor-alpha

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SUPPLEMENTAL TABLE

Maternal and neonatal outcomes for randomized controlled trials powered to detect maternal fever with labor epidural analgesia

Study	Year	Duration of ROM	Use of maternal antibiotics	Oxytocin augmentation	Duration of first stage labor	Duration of second stage labor	Instrumental delivery rates	CD rate	Neonatal fever	Neonatal sepsis investigations	Use of neonatal antibiotics	Positive neonatal blood cultures	Apgar 1 min	Apgar 5 min	Apgar 10 min	Umbilical cord pH
Evron et al[30]	2007	NS		NS	NS	NS							NS	NS		↓ in nonepidural group (P=.03)
Evron et al[31]	2008	NS					NS	NS				NS	NS	NS	NS	
Douma et al[32]	2015	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS	NS	NS		NS
de Orange et al[33]	2011			NS	↓ in epidural group (P=.01)	NS	NS	NS		NS	NS			NS		NS
Philip et al[38]	1999									NS	NS	NS				

CD, cesarean delivery; *NS*, no significant differences between epidural and non-epidural groups; *ROM*, rupture of membranes.

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