

# **Inflammation and Epidural-Related Maternal Fever: A Focused Review of Proposed Mechanisms**

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## Abstract

Intrapartum fever is associated with excess maternal interventions, as well as higher neonatal morbidity. Epidural related maternal fever (ERMF) contributes to the development of intrapartum fever. The mechanism(s) for ERMF has remained elusive. Here, we consider how inflammatory mechanisms may be modulated by local anesthetic agents and their relevance to ERMF. We also critically reappraise the clinical data with regard to emerging concepts that explain how anesthetic drug-induced metabolic dysfunction, with or without activation of the inflammasome, might trigger the release of non-pathogen, inflammatory molecules (danger associated molecular patterns; DAMPs) likely to underlie ERMF.

## Focused Review

Since the first description of epidural-related maternal fever (ERMF) more than 25 years ago,<sup>1</sup> the relationship between ERMF and a potential causative role for local anesthetic agents has been consistently demonstrated (Table 1).<sup>2-23</sup> Epidural-related fever occurs in approximately 20% of laboring women who receive epidural labor analgesia. The absence of epidural-related fever in the non-pregnant population has been attributed to the inhibition of fever by inhalational anesthetic agents<sup>24</sup> and opioids.<sup>25</sup> Thus, there may be mechanisms at play specific to the biology and/or process of labor. Despite the well-established association between labor epidural analgesia and maternal fever (temperature  $\geq 38^{\circ}\text{C}$ ),<sup>26</sup> controversy still exists surrounding its etiology. Intrapartum fever is associated with maternal interventions such as administration of intravenous antibiotics,<sup>27</sup> instrumental and cesarean delivery,<sup>28</sup> as well as higher perinatal mortality<sup>23</sup> and neonatal morbidity such as meconium aspiration, respiratory distress syndrome and encephalopathy.<sup>18,29</sup> A better understanding of the cause of ERMF may allow interventions to be developed that lead to a reduction in its incidence rate and also facilitate the differentiation from other causes of intrapartum fever. In this focused review, we review the evidence that supports the hypothesis that inflammatory mechanisms generated by anesthetic-specific interventions are responsible for the development of ERMF, and consider emerging concepts of possible mechanisms.

### **Infection versus inflammation**

Intuitively, infection would appear to be the most likely trigger for ERMF. Chorioamnionitis, the condition of acute inflammation of the membranes and chorion of the placenta, is estimated to complicate 3-5% of all births in the United States.<sup>30</sup> Although the precise frequency of chorioamnionitis varies, the highest estimates are clearly exceeded by the prevalence of ERMF (Table 1). More compellingly, a double blind, placebo-controlled

adequately powered trial in 400 laboring women found that prophylactic antibiotic therapy (broad-spectrum cephalosporin) failed to prevent ERMF.<sup>31</sup> In addition, clinically relevant models of local anesthetic administration in vivo demonstrate bactericidal activity against common pathogens.<sup>32,33</sup> The failure of antibiotic prophylaxis to reduce ERMF, combined with the consistent lack of positive microbiology in observational studies,<sup>3,34</sup> suggests that the etiology of ERMF is not primarily infectious in origin.

### **The case for systemic inflammation causing ERMF**

There are several compelling clinical clues suggesting that acute inflammation alone underlies the mechanism of ERMF. Higher levels of maternal<sup>34</sup> and fetal<sup>35</sup> pro-inflammatory endogenous pyrogens that trigger fever have been measured in pregnant patients following epidural analgesia.<sup>9,34-36</sup> However, Riley and colleagues reported that pregnant patients who subsequently developed ERMF had higher admission levels of pro-inflammatory cytokines (interleukin (IL)-6 and IL-8) prior to receiving epidural analgesia,<sup>9</sup> suggesting that prolonged epidural administration of bupivacaine may augment baseline elevated cytokine levels.<sup>37 38</sup> Conversely, anti-inflammatory glucocorticoids reduce ERMF, in part through reducing cytokine production. In 200 term laboring nulliparous women, prophylactic treatment with the high dose intravenous methylprednisolone (100 mg every 4 hours) reduced the rate of ERMF to just 2.0% compared with low dose (25 mg every 8 hours; 21.8% incidence) and placebo therapy (34.0% incidence).<sup>39</sup> However, the marked reduction in ERMF was at the expense of excess (asymptomatic) neonatal bacteremia– a finding consistent with profound immunosuppression. Dexamethasone administered via epidural infusion (mean total dose 5.8 mg (range: 3.4-14.2 mg)) was also associated with a reduction in maternal temperature rise and lower plasma IL-6 levels<sup>40</sup>, although a subsequent study has failed to replicate these findings.<sup>41</sup> Taken together, these trials of anti-inflammatory steroid therapy suggest that pro-

inflammatory pyrogen release is suppressed. However, these studies cannot rule out that glucocorticoids may modulate ERMF at the level of the hypothalamus/central nervous system.<sup>42</sup>

### **What is the source of sterile inflammation in ERMF?**

Given the lack of plausible data supporting an acute infectious etiology for ERMF, alternative triggers/sources must fuel inflammation and cytokine production. Sterile inflammation is a process through which inflammation occurs in the absence of a pathogen,<sup>43</sup> driven by endogenous molecules called alarmins that are released upon tissue damage.<sup>44</sup> Alarmins play both homeostatic and pathophysiologic roles via pattern recognition receptors, including Toll-like receptors<sup>45</sup> which are ubiquitously expressed by immune and non-immune cells. These numerous (and ever-expanding) damage-associated molecular patterns (DAMPs) – including mitochondrial DNA<sup>46</sup> – activate the inflammasome. The inflammasome is an intracellular multiprotein complex that promotes the maturation of the pro-inflammatory cytokines IL-1 $\beta$  and IL-18 and subsequent induction of other fever-inducing cytokines.<sup>47</sup>

#### *Trauma, stress and inflammation from epidural catheter insertion alone*

Both mental stress<sup>48</sup> and limited surgical trauma are associated with clinically relevant inflammation and cytokine release. However, triggering ERMF-related inflammatory changes by epidural needle/catheter insertion alone seems highly unlikely. Based on a study in orthopedic surgery patients,<sup>49</sup> the magnitude of the systemic cytokine release following catheterization of the epidural space alone is unlikely to account for the magnitude of the systemic inflammatory response associated with ERMF. However, fiberoptic imaging has confirmed that the epidural space in pregnancy differs anatomically, revealing a marked

increase in the density of the vascular network.<sup>50</sup> Local inflammation, therefore, remains a possible mechanism of ERMF, particularly given the precedent of procedures triggering a systemic inflammatory response. For example, it is notable that pulmonary artery catheterization via the internal jugular vein triggers a pro-thrombotic response, as reflected by reduced clotting time assessed using thromboelastography.<sup>51</sup>

### *Inflammation and labor*

Before and during onset of labor at term, leukocytes and inflammatory cytokines are increased in fetal membranes and decidua<sup>52</sup> – even in the absence of infection.<sup>53 54</sup>

Pregnancy in many respects mimics the immune response to sterile inflammation, with a shift to an adaptive immunity phenotype, decreased proliferation of T cells and lower cytotoxicity of natural killer cells.<sup>55</sup> Proposed sites of cytokine production in pregnancy are non-lymphoid tissues, including the placental/decidual tissues and the trophoblast.<sup>56</sup>

Spontaneous labor at term is associated with the infiltration of inflammatory cells in these tissues and increased production of pro-inflammatory cytokines<sup>57,58</sup> and multiple other immunomodulatory molecules.<sup>57</sup> Gene expression analyses have revealed that genes involved in the control of inflammation are upregulated in the chorioamniotic membranes of women with physiologic spontaneous labor at term, even in the absence of histological chorioamnionitis. This inflammatory signature is not evident in genes from whole blood analysis obtained at the same time from the same patients.<sup>59</sup> These findings emphasize that spontaneous parturition is associated with an increased pro-inflammatory cytokine response.<sup>57</sup> There appears to be an inflammatory-specific feature of labor relevant to ERMF since maternal fever does not occur in non-laboring women who have an elective cesarean delivery under neuraxial anesthesia.<sup>60</sup> In part, this may reflect that the development of ERMF



is related to the duration of exposure to neuraxial analgesia. This finding implies that the inflammatory component of the labor process is integral to the development of ERMF.

*A direct mechanistic role for local anesthetic agents.*

The majority of studies report that ERMF occurs within 6 h of the onset of epidural analgesia, with temperature increasing progressively after initiation of epidural analgesia. This timeframe is compatible with a pharmacologic effect and/or changes in RNA transcription caused by local anesthetic agents. Some have hypothesized that the observation that epidural analgesia is associated with fever compared to a control group without epidural analgesia is a result of fever suppression by systemic opioid analgesia administered to the control group. However, opioids fail to suppress ERMF (Table 1), best highlighted by the retrospective finding that the antipyretic effect of intravenous systemic nalbuphine in laboring women failed to reduce the incidence rate of ERMF observed in women who received nalbuphine prior to receiving epidural analgesia.<sup>61</sup> ERMF also occurs in the presence and absence of epidural opioid,<sup>19</sup> again suggesting a specific effect exerted by local anesthetic agents. Furthermore, albeit in male healthy volunteers, an intravenous fentanyl infusion suppressed the febrile response triggered by the pyrogen IL-2.<sup>62</sup> The development of fever was assessed following epidural analgesia using ropivacaine in the presence/ absence of fentanyl, administered either in combination with ropivacaine (2 mg.ml<sup>-1</sup>) or as an intravenous infusion (target plasma concentration of 2.5 ng.ml<sup>-1</sup>). Low plasma concentrations of fentanyl (~0.3 ng.ml<sup>-1</sup>) failed to suppress fever, in contrast to approximately 5-fold higher plasma concentrations achieved by intravenous fentanyl.<sup>62</sup> Although the raw data were not shown in this paper, the authors commented that the pattern of cytokine release was similar between treatment arms in this crossover study. We thus

consider there are two labor-specific possibilities for local anesthetics to directly trigger ERMF: immunomodulation and cell injury.

### *Immunomodulation*

Local anesthetics used routinely for epidural anesthesia in the labor ward- including bupivacaine and ropivacaine- exert profound immunomodulatory effects at plasma levels achieved rapidly with continuous epidural infusion.<sup>63,64</sup> Steady state maternal venous plasma concentrations of bupivacaine approach  $4 \times 10^{-6} \text{M}$ .<sup>65-67</sup> At far lower concentrations ( $<10^{-8} \text{M}$ ), bupivacaine modulates intracellular calcium signaling triggered by key neurotransmitters in astrocytes that have also been identified to play a role in peripheral immune cells.<sup>68</sup> While the immunomodulatory effects of local anesthetics have been found to be clinically useful under some circumstances,<sup>69</sup> the inhibitory effects of local anesthetics on neutrophil mobility,<sup>70</sup> phagocytosis,<sup>71</sup> chemotaxis,<sup>72</sup> and superoxide generation may also be deleterious.<sup>73,74</sup> Despite this spectrum of inhibitory effects, the ability of neutrophils to undergo chemotaxis appears to be preserved in laboring women with epidural analgesia, given the extent to which they contribute to placental infiltrates.<sup>75</sup> The potential reduction in capacity of leukocyte subsets to counteract ongoing reproductive tract inflammation could fuel further systemic inflammation. For example, impaired chemotaxis in neutrophils reduces survival in sepsis as a result of failure of bacterial clearance.<sup>76</sup> Potentially adverse immunomodulatory actions of bupivacaine have already been described in the obstetric population; subcutaneous bupivacaine was associated with a reduction in the anti-inflammatory cytokine IL-10 and a concomitant increase in the proinflammatory mediator substance P in surgical wounds following cesarean delivery.<sup>77</sup>

### *Cell injury*

Activated immunocytes require profound metabolic changes in order to respond to various acute environmental challenges. For example, the activation of T-lymphocytes is critically dependent upon rapid increases in both glycolysis and oxidative phosphorylation.<sup>78,79</sup>

Acute stressors alter the metabolic capacity of lymphocytes.<sup>80,81</sup> CD4+ T cells inhibit macrophage-dependent release of the pro-inflammatory cytokine IL-1 $\beta$ .<sup>82</sup> Under such circumstances, further bioenergetic compromise following the impairment of mitochondrial respiration by systemic absorption of epidural bupivacaine may promote apoptosis/necrosis and hence the release of pyrogenic DAMPs into the circulation. Several studies have described local anesthetic-induced apoptosis in various cell types, including neuronal, lymphocytic and osteoblastic cell lines.<sup>83-86</sup> Epidural lidocaine in dogs induces apoptosis and/or necrosis of peripheral blood mononuclear cells,<sup>87</sup> a finding reproduced in a lymphocyte (Jurkat) cell line.<sup>88</sup> In vitro, clinically relevant concentrations of both lidocaine and bupivacaine induce apoptosis in primary intervertebral disc cells<sup>89</sup> and human renal cells.<sup>90</sup> Studies in both isolated mitochondria and intact cells (albeit obtained chiefly from cardiac tissue), show that bupivacaine time- and dose-dependently impairs ATP synthesis in aerobic conditions<sup>91</sup> through uncoupling of oxidative phosphorylation<sup>92,93</sup> and inhibition of complexes I<sup>94</sup> and III<sup>95</sup> of the respiratory chain. Although not obligatory, generation of reactive oxygen species is associated with activation of the inflammasome.<sup>96</sup> Cell-specific pathologic changes induced by bupivacaine in highly oxidative tissues such as skeletal muscle also include activation of the mitochondrial permeability transition pore, a critical event in mitochondrial-dependent programmed cell death.<sup>97</sup>

### **The cellular source(s) of alarmins generated by local anesthetic agents**

Systemic absorption of epidurally administered bupivacaine at clinically relevant concentrations may cause mitochondrial damage through electron transport chain dysfunction,<sup>95</sup> excessive reactive oxygen species and/or apoptosis in circulating leukocytes and/or the materno-placental interface (Figure 1). Our recent work has highlighted an emerging role for acute stress hormones in modulating leukocyte metabolism. Elevations in circulating glucocorticoids—typical of the labor process—increase mitochondrial reactive oxygen species, activated caspase-1 and mature interleukin (IL)-1 $\beta$  in human lymphocytes. This is accompanied by a hypometabolic phenotype and apoptosis.<sup>81</sup> Similarly, mitochondrial electron chain dysfunction is generated by acute increases in nitric oxide<sup>98</sup>. Plasma levels of bupivacaine may be misleading, as suggested by the accumulation of bupivacaine in the myocardium resulting in reversible pathologic changes in mitochondrial structure and reduced mitochondrial oxygen consumption.<sup>99</sup> Thus, accumulation of bupivacaine in placental tissues<sup>100</sup> could induce release of alarmins from reproductive tract and placental inflammatory cell infiltrates and/or non-lymphoid tissues.<sup>56</sup>

### **Conclusion**

Epidural related maternal fever remains a phenomenon of unknown etiology, yet affects a significant proportion of laboring women with potentially important clinical consequences. Local anesthetic agents routinely utilized for epidural analgesia in labor appear to be the likeliest culprits for the development of ERMF. Plausible mechanisms involving bupivacaine have already been described in other areas of inflammation biology and relevant clinical models. Sterile inflammation and activation of the inflammasome are likely to play a key role. From a clinical perspective, more detailed epidemiologic studies comparing high-risk versus low-risk laboring women may help reveal biologic differences underlying ERMF.

Similarly, establishing whether different local anesthetic agents confer similar risk may shed further light on underlying mechanisms.

Tables

**Table 1: Summary of studies describing ERMF**

Study	Design	Fever (°C)  Measu rement  Site	Drugs and Doses		Incidence of Fever		UOR / AOR / RR  (95% CI)
			Epidural	Non-epidural	Epidural group [% (n/N)]	Non- epidural group [% (n/N)]	
<b>Lieberma n<sup>2</sup></b>	Prospect ive  Observat ional	≥38  Not stated	Drugs and doses  not stated.	Drugs and doses not stated.	14.5  (152/104 7)	1.0  (6/610)	UOR  17.10  (7.51 – 38.91)  AOR 14.5  (6.3 – 33.2)*

<b>Mayer<sup>3</sup></b>	Retrospective Observational	≥37.8 Oral	Epidural only group (n=97), IV opioid and epidural group (n=94) (drugs and doses not stated for any group)	IV opioid (drugs and doses not stated) n=96,	20.4 (39/191)	2.1 (2/96)	UOR 12.06 (2.85 – 51.11)
<b>Kaul<sup>4</sup></b>	Prospective Observational	≥38 Tympanic	3-ml test dose 1.5% lidocaine 1:200,000 epinephrine followed by bupivacaine 0.25% or ropivacaine 0.2% 5-mL increments up to 10 mL (block to T10). Followed by bupivacaine	2 mg IV butorphanol or 5–10 mg nalbuphine IV prn.	6.6 (61/922)	0 (0/255)	UOR 36.48 (2.25 – 591.90)

			0.125% (or ropivacaine 0.1%) and fentanyl 2 µg/mL at 10-12 mL/hr .				
<b>Dashe<sup>5</sup></b>	Prospective Observational	≥38  Not stated	0.125% bupivacaine 2 µg/mL fentanyl 8-10 ml/h to achieve T10 block	prn IV meperidine 50-100 mg every 2 h	46.3 (37/80)	26.1 (18/69)	UOR 2.43 (1.22 – 4.88)
<b>Vinson<sup>6</sup></b>	Observational	≥37.5 ≥38 Tympanic	Test dose of lidocaine followed by bolus of bupivacaine followed by infusion at 10-14 mg/hr and 10-20 µg/hr sufentanil (for all but 1 patient)	meperidine or nalbuphine (dose or route not stated)	26.8 (11/41) 14.6 (6/41)	8.3 (3/36) 0 (0/36)	UOR 4.03 (1.03 – 15.86)



<b>Herbst<sup>7</sup></b>	Retrospective Observational	≥38 Oral	1989 – 1992 (0.25% bupivacaine 5-8-mL doses). After 1993 (first dose 5-8 ml of 0.125% bupivacaine and sufentanil 10 µg, then 0.125% bupivacaine 8 mL for further doses)	Meperidine (dose and route not stated)	6.4 (44/683)	1.1 (28/2426)	UOR 5.90 (3.64 – 9.55) AOR 4.3 (2.4 – 7.8)*
<b>Ploeking er<sup>8</sup></b>	Retrospective Observational	≥38 Axillary	4 ml 0.25% bupivacaine 15 µg epinephrine test dose followed by 10 mL 0.25% bupivacaine. From 1989 0.025 mg/mL bupivacaine, 2.5 µg/mL fentanyl and 0.0125 µg/mL	IM tramadol 100 mg or 75 mg meperidine every 2 h prn	1.6 (17/1056)	0.2 (11/6261)	UOR 9.30 (4.43 – 19.90)

			epinephrine; rate 10-12 mL/hr				
<b>Riley<sup>9</sup></b>	Prospective Observational	>38 Oral	CSE (35/191) or epidural. Epidural and CSE regimes not stated	Drug and doses not stated	22.7 (34/150)	6 (3/50)	UOR 4.59 (1.34 – 15.68) AOR 4.9 (1.1– 22.4)*
<b>Macaulay<sup>10</sup></b>	Prospective Observational	≥37.5 Uterine	Epidural 2 ml-1% lidocaine, and 10 mL-0.5% bupivacaine.	50:50 N <sub>2</sub> O:O <sub>2</sub> (n=15), IM meperidine (n=9); (dose not stated)	45 (15/33)	8 (2/24)	UOR 9.17 (1.85 – 45.47)
<b>Halpern<sup>11</sup></b>	RCT	>38 Not stated	IV fentanyl; PCEA 0.08% bupivacaine 1.6 µg/mL fentanyl (5 mL, 10 min lockout interval)	IV 100 mcg fentanyl over 1–5 min. Additional 50 µg repeated every 5 min until adequate pain relief. PCA pump 25	15(19/12 4)	8 (10/118)	UOR 1.95 (0.87 – 4.40)

				– 50 µg fentanyl 10 min lockout. lockout and bolus dose varied at discretion of clinician			
<b>Ramin</b> <sup>12</sup>	RCT	≥38  Not stated	Low risk parturients. Epidural- 3-ml test 0.25% bupivacaine, then 3-mL increments to achieve T10 block. 0.125% bupivacaine and 2 µg/ mL fentanyl at 8-10 mL /h continuous infusion (for T8 block).	IV meperidine 50 mg and 25 mg promethazine, then IV meperidine 50 mg as required (maximum 200 mg in 4 hours)	22.7 (98/432)	4.8 (21/437)	UOR 5.81 (3.55 – 9.51)

Sharma <sup>13</sup>	RCT	≥38  Not stated	0.25%  bupivacaine 3-ml increments to achieve T10 block.  Maintenance with 0.0625% bupivacaine and 2-μg/ mL fentanyl at 6- mL /h and 5-ml bolus every 15 min (PCEA)	IV meperidine 50 mg and IV promethazine 25 mg.  Meperidine 15 mg with 10-min lockout PCA and additional boluses of IV meperidine 25 mg prn (up to 100 mg in 2 hr)	33.2  (75/226)	6.9  (16/233)	UOR 6.74  (3.78 – 12.01)
Sharma <sup>14</sup>	RCT	≥38  Not stated	0.25%  bupivacaine to achieve T10 block followed by 0.125% bupivacaine + 2 μg/ mL fentanyl 8-10 ml/hr.	PCA IV meperidine 10 mg bolus , 10-min lockout interval for first hour followed by 15-mg bolus, 10-min lockout interval	23.9  (58/243)	6.2  (16/259)	UOR 4.76  (2.65 – 8.55)

				until delivery with extra 25 mg for breakthrough ( $<100$ mg in 2 h)			
<b>Lucas<sup>15</sup></b>	RCT	$\geq 38$  Not stated	Women with pregnancy induced hypertension (diastolic blood pressure $>90$ mmHg). Epidural block to T10 with 0.25% bupivacaine followed by 0.125% bupivacaine and 2 $\mu\text{g/mL}$ fentanyl.	Initial bolus of 50 mg IV meperidine 25 mg IV promethazine followed by 15 mg IV meperidine bolus with 10- min lockout interval	20.4  (76/372)	7.1  (26/366)	UOR 3.36  (2.09 – 5.38)  AOR 2.9 (1.5-5.6)*
<b>De orange<sup>16</sup></b>	RCT	$\geq 38$  Axilla	CSE (2.5 mg bupivacaine + 5 $\mu\text{g}$ sufentanil).	No medication administered	14 (5/35)	0 (0/35)	UOR  12.80

			Epidural 5 ml 0.05% bupivacaine + sufentanil 0.2 µg/ mL every 30 min				(0.68 – 241.04)
<b>Philip<sup>17</sup></b>	RCT	≥38  Tympanic	Epidural initiated with 0.25% bupivacaine (volume not stated) and then continuous infusion 0.125% bupivacaine and 2 µg/ mL fentanyl (volume not stated).	50 mg IV meperidine and 25 mg IV promethazine at first request and 15 mg IV meperidine every 10 min via PCA	15.1  (54/358)	4.0  (14/357)	AOR 4  (2.0, 7.7)*
<b>Impey<sup>18</sup></b>	Prospective cohort study	>37.5  Oral	Drugs and doses not stated.	Drugs and doses not stated.	4915 low-risk women. Higher incidence of fever in epidural group – univariate analysis.		Not stated

					Not significant in multiple logistic regression.		
<b>Camann<sup>19</sup></b>	Prospective (patient choice)	Not stated Tympanic	Epidural – 0.25% Bupivacaine 8-12 mL followed by either 0.25% bupivacaine at 10 mL /h or 0.25% bupivacaine and fentanyl 2 µg/mL at 10 mL /h	IV nalbuphine 10-20 mg ≥ 1 occasion. Frequency not stated.	Higher temperature in epidural group after 5 hours		Not stated
<b>Yancey<sup>20</sup></b>	Retrospective Before-after study	≥37.5 ≥38 Tympanic	Epidural 3 mL 1.5% lidocaine and 1:200,000 epinephrine test dose then 8 ml 0.125% bupivacaine and 100 µg fentanyl followed by	Drugs and doses not stated	8.2(41/498) 0.6(3/498)	26.2(150/572) 11.0 (63/572)	RR 20.2 (7-86) (≥38)*

			infusion of 0.125% bupivacaine and 2-4 µg/mL fentanyl at 10 mL /h				
<b>Akerman</b> <sup>21</sup>	Audit  ?  prospective / retrospective	≥38  Not stated	Drugs and doses  not stated	Drugs and  doses not stated	Higher incidence of  fever  in epidural group.  Epidural (N = 56);  No epidural (N = 73)		Not stated
<b>Reilly</b> <sup>22</sup>	Retrospective	>38°C or 2 >37.5° C Oral	Drugs and doses  not stated.	Drugs and  doses not  stated.	1.42  (156/10,9 99)	0.09  (5/5484)	AOR 5.5  (4.0– 7.0)*  RR 16  (4.9-51)
<b>Bensal</b> <sup>23</sup>	Retrospective	≥38  Not stated	Drugs and doses  not stated	Drugs and  doses not stated	169,738 vaginal  deliveries.		UOR 1.25  (0.99 - 1.57)



					No difference in fever in epidural group	
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Reilly- fever defined as an oral maternal temperature  $>38^{\circ}\text{C}$  or 2 consecutive temperatures  $>37.5^{\circ}\text{C}$  after the onset of active labor; RCT=randomized controlled trial; UOR = unadjusted odds ratio; AOR = adjusted odds ratio; RR = risk ratio; \* signify results calculated using logistic regression analysis to adjust for potential confounding variables; PCEA=patient controlled epidural analgesia; PCA=patient controlled analgesia; CSE=combined spinal-epidural

Table 2: Cytokine levels in patients with and without labor epidural analgesia <sup>9</sup>

	Fever: no fever (n)	IL-6		IL-8	
		No fever	Fever	No fever	Fever
Epidural	102: 30	228.4	386.2	4.3	5.1
No Epidural	43: 3	107.6	333.5	2.5	4.2

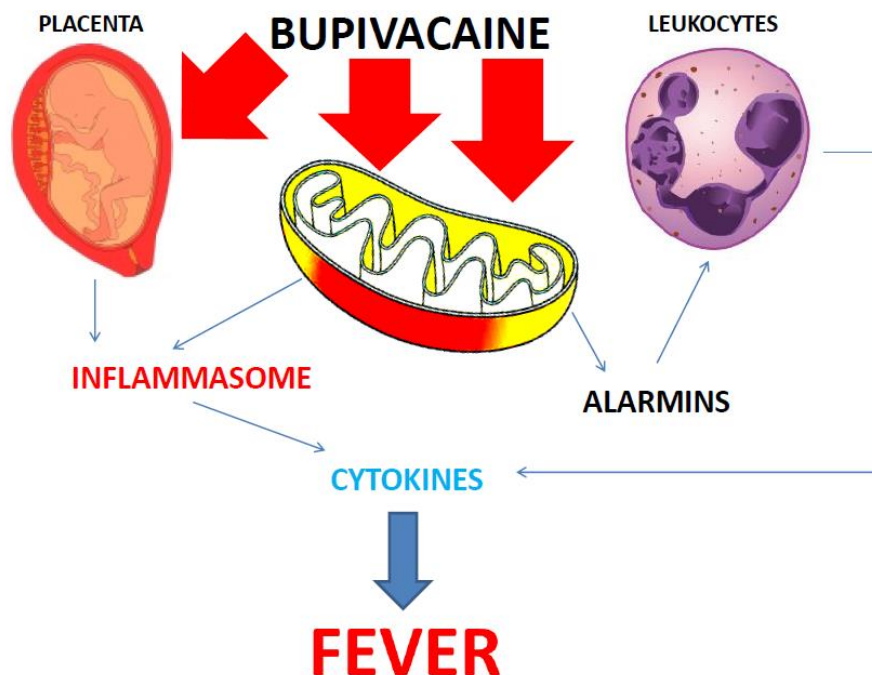
Median plasma cytokine levels (pg.mL<sup>-1</sup>; ranges were not reported in original paper) for women receiving epidural (n=132) or alternative analgesia during labor (n=46).

## Figures and Illustrations

### Figure Legends

#### **Figure 1: Proposed mechanism by which bupivacaine may cause ERMF.**

Bupivacaine causes cell injury by ‘poisoning’ mitochondria. Injured cells release danger-to-self molecules known as alarmins, which provoke immune cells to generate fever-producing cytokines (pyrogens). Arrow pointing to uterus represents bupivacaine acting on the placenta/membrane. Arrows pointing to mitochondria indicate systemic bupivacaine absorbed from the epidural space. Increased levels of reactive oxygen species from injured mitochondria can also activate the inflammasome, which promotes the maturation of the inflammatory cytokines IL-1 $\beta$ , IL-18 and the induction of other fever-inducing cytokines.



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