Concerned topics of epidural labor analgesia: labor elongation and maternal pyrexia: a systematic review

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Abstract

Objective: Labor is a complex process and labor pain presents challenges for analgesia. Epidural analgesia (EA) has a well-known analgesic effect and is commonly used during labor. This review summarized frequently encountered and controversial problems surrounding EA during labor, including the labor process and maternal intrapartum fever, to build knowledge in this area.

Data sources: We searched for relevant articles published up to 2019 in PubMed using a range of search terms (eg, "labor pain," "epidural," "analgesia," "labor process," "maternal pyrexia," "intrapartum fever").

Study selection: The search returned 835 articles, including randomized control trials, retrospective cohort studies, observational studies, and reviews. The articles were screened by title, abstract, and then full-text, with a sample independently screened by two authors. Thirty-eight articles were included in our final analysis; 20 articles concerned the labor process and 18 reported on maternal pyrexia during EA.

Results: Four classic prospective studies including 14,326 participants compared early and delayed initiation of EA by the incidence of cesarean delivery. Early initiation following an analgesia request was preferred. However, it was controversial whether continuous use of EA in the second stage of labor induced adverse maternal and neonatal outcomes due to changes in analgesic and epidural infusion regimens. There was a high incidence of maternal pyrexia in women receiving EA and women with placental inflammation or histologic chorioamnionitis compared with those receiving systemic opioids.

Conclusions: Early EA (cervical dilation ≥1 cm) does not increase the risk for cesarean section. Continuous epidural application of low doses of analgesics and programmed intermittent epidural bolus do not prolong second-stage labor duration or impact maternal and neonatal outcomes. The association between EA and maternal pyrexia remains controversial, but pyrexia is more common with EA than without. A non-infectious inflammatory process is an accepted mechanism of epidural-related maternal fever.

Keywords: Epidural analgesia; Labor process; Maternal pyrexia; Intrapartum fever; Mechanism

Introduction

The cesarean section rate in China has been consistently high over the past few decades. With the exception of obstetric complications, a primary reason for the high cesarean rate is maternal fear of labor pain; however, labor pain is unavoidable for parturients. Various techniques are used to provide analgesia during labor, with neuraxial analgesia acknowledged as the major, safe, and effective method.[1] Although the use of epidural analgesia (EA) in our institution has been high (eg, 90%) since 2009, implementation of the "No Pain Labor & Delivery" program in China in 2008 had helped to increase EA rate by 50% in 24 hospitals as at November 2015.[2]

Neuraxial analgesia during labor provides high satisfaction for parturients because it has a superior analgesic effect and few side effects. Successful neuraxial analgesia means that expectant mothers can deliver their babies without experiencing severe labor pain. The first neuraxial analgesia used for labor was EA, which became available in the 1960s.[3] Over the next half-century, EA played a vital role in promoting natural childbirth. Recently, the programmed intermittent epidural bolus (PIEB) mode was proposed as a better choice than traditional continuous epidural infusion (CEI).[4,5] However, there are many different opinions regarding EA. For example, a previous study reported that up to 55% of obstetricians considered EA as a risk factor for increased cesarean sections,[6] with this assumed to lead to intra-operative maternal complications and neonatal morbidity[7] such as prolonged labor and maternal intrapartum pyrexia.

The appropriate timing of EA is a major point of controversy, with this timing affecting how long parturients can benefit from analgesia. A previous study found

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maternal pyrexia during labor was a significant risk factor for neonatal adverse events (eg, newborn encephalopathy), and increased rates of hypotonia and oxygen therapy.[8] A subsequent case-control study revealed the risks for newborn encephalopathy, including maternal pyrexia (odds ratio [OR] 3.82), persistent occipitoposterior position (OR 4.29), and acute intrapartum events (OR 4.44).[9]

In the present review, we located and analyzed high-quality studies focused on EA, including randomized controlled trials (RCTs), retrospective cohort studies, observational studies, and reviews. We discussed identified issues related to EA during labor.

Methods

We searched for relevant articles in PubMed using a range of keywords. To obtain articles related to both EA during labor and controversial issues, we used various terms including "labor pain" AND "epidural" AND "analgesia" OR "labor process" OR "maternal pyrexia," OR "intrapartum fever." Articles were screened by title, abstract, and then full-text, with a sample of articles independently screened by two authors according to previously reported methods.[10]

The inclusion criteria were all studies involving full-term (after 37 weeks of gestation) nulliparous parturients with singleton and cephalic presentation that described the effects of EA in the labor process (first stage, second stage, or whole of labor) or the rate of maternal intrapartum pyrexia. We excluded studies focusing on multiparae, women with severe obstetric complications, or women in premature labor (before 37 weeks of gestation).

Results

According to the inclusion criteria and exclusion criteria, initially, 835 articles were identified after title and abstract screening. Full-text articles were then retrieved for further screening. Finally, 38 articles were included in our analysis. Twenty articles related to the labor process and 18 articles clarified the point of maternal pyrexia during EA [Figure 1].

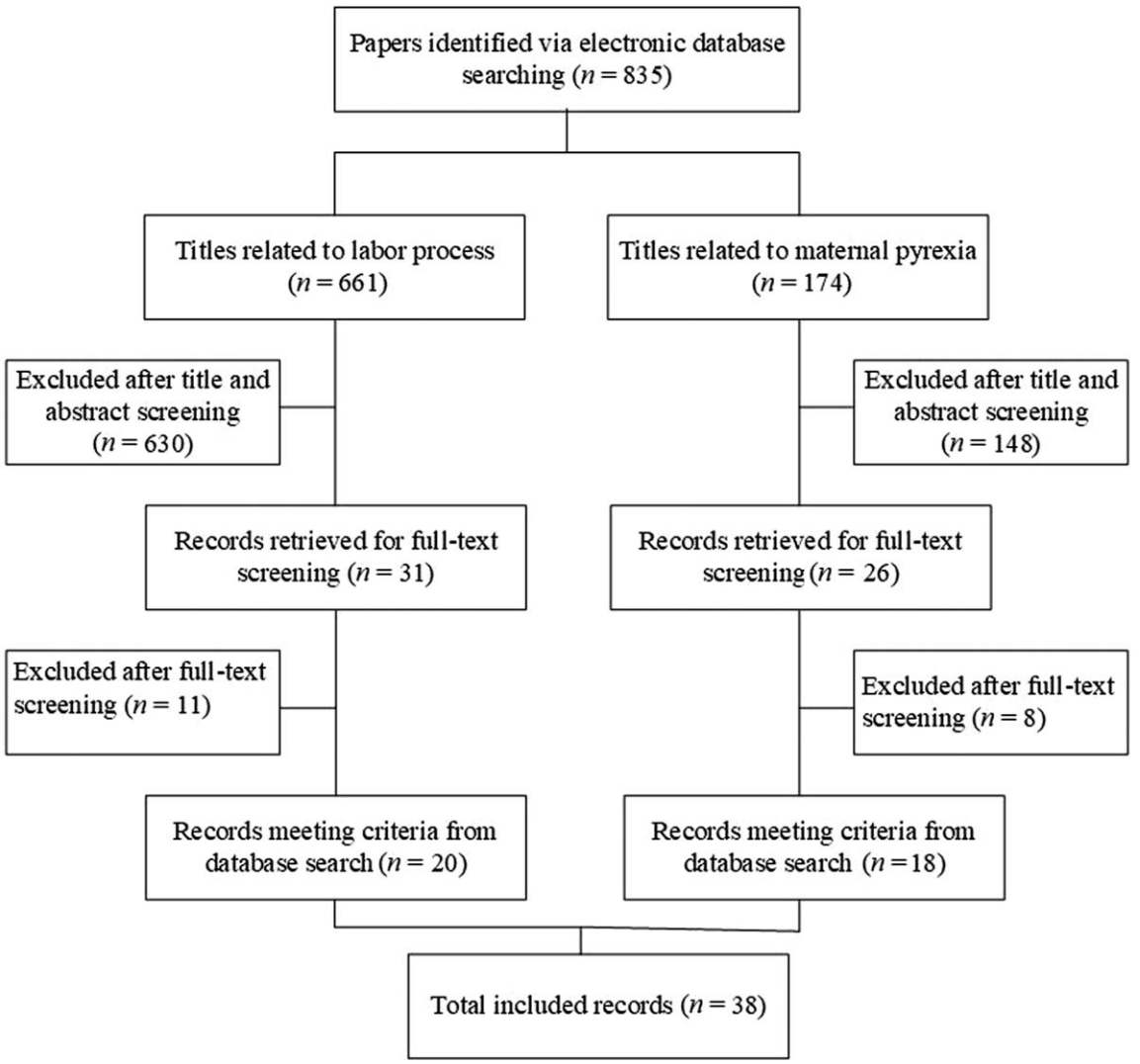

Figure 1: Flowchart outlining the screening and study selection process.

Labor Process

One study reported nulliparous parturients' attitudes regarding the major obstacles affecting patients' decision regarding use of EA during labor.[11] That study found that 67.5% of parturients rejected EA because they considered it should not be administered "too early," and 68.5% thought that it would prolong the labor process. These findings raised questions regarding the optimum time for initiating EA, and whether EA affects the outcomes of labor – specifically the duration of labor and mode of delivery. The present review focused on different perspectives of these issues for which robust evidence was available.

When to Start EA?

An early retrospective trial found that the mean number of uterine contractions was 8.0 ± 1.4 in the 30 min before EA *vs.* 8.8 ± 1.9 after administration of EA, although the difference was not statistically significant.[12] It has been suggested that timely EA conducted properly during the first stage of labor had no negative effects on the frequency of uterine contractions. However, a subsequent secondary analysis of a RCT[13] regarding the effects of patient-controlled EA versus systemic meperidine during labor on the cesarean delivery rate showed that EA led to a 1-h longer active phase of labor compared with Friedman original criteria. In addition, a lower rate of cervical dilation (1.4 *vs.* 1.6 cm/h, $P < 0.002$) and a trend of longer duration of second-stage labor (1.1 ± 1.5 *vs.* 0.9 ± 1.0 h, $P = 0.079$) were found in patients with EA compared with those without EA. The American College of Obstetricians and Gynecologists recommended cervical dilatation of 4.0 to 5.0 cm as a reasonable time for administration of EA or other forms of analgesia in nulliparous women.[14] Based on that recommendation, systemic opioid analgesia became the first option for women who request analgesia early, although this method usually provides incomplete analgesic effects.

A randomized trial by Wong *et al*[15] conducted in 2005 offered a new perspective on the effects of early and delayed neuraxial analgesia on labor outcomes. That study randomized 750 nulliparous women into two groups by timing of the request for analgesia. In the early intrathecal analgesia group, women obtained combined spinal-EA immediately at their first request for analgesia, whereas in the delayed systemic analgesia group, women only received systemic hydromorphone at their first request, and EA was initiated when the cervix was more than 4.0 cm in diameter. The results showed no differences in the rate of cesarean section and instrumental vaginal delivery between the groups; however, a significantly shorter median time of labor process from the initial analgesic intervention to complete dilatation and vaginal delivery was found in the intrathecal analgesia group. An RCT published in 2006 showed similar results, with a mean cervical dilatation of 2.4 and 4.6 cm in the early and late groups, respectively.[16]

A 5-year RCT conducted in China concerning early EA in the latent phase of labor further explored the effects of EA on maternal and neonatal outcomes.[17] In that study, 12,793 nulliparous women requesting neuraxial analgesia were randomized into an early EA group (cervical dilatation greater than 1.0 cm) or a delayed EA group (cervical dilatation greater than 4.0 cm). There was no difference in the risk for cesarean delivery between the two groups, and earlier initiation of EA in the latent phase (median diameter of cervical dilatation of at least 1.0 cm) did not prolong the duration of labor process compared with delayed analgesia at a cervical dilation of at least 4.0 cm.

A high-quality systematic review published in 2014 analyzed nine RCTs that included a total of 15,752 women.[18] The bias of the included studies was assessed using the Cochrane Handbook for Systematic Reviews of Interventions criteria and deemed to be low. All nine RCTs showed no significant differences in the risk for cesarean section or instrumental birth and duration of second-stage labor between early and late initiation of EA. However, results regarding the effects of the initiation of EA on the duration of the first stage of labor were inconsistent.

In summary, these RCTs provided strong evidence that nulliparous women can receive neuraxial analgesia early when they request analgesia, as this does not lead to adverse maternal and neonatal consequences. The initiation of early neuraxial analgesia (median diameter of cervical dilatation of ≥1.0 cm) did not increase the risk for cesarean delivery compared with systemic analgesia, which was consistent with some previous studies and the later reviews.[18-20] In addition, the reviewed studies indicated that early neuraxial analgesia may have no effect on labor duration or lead to shorter labor because of the decreased level of adrenaline [Table 1].

Is it Necessary to Terminate EA During the Second Stage?

In 1987, a randomized double-blind placebo-controlled study conducted by Chestnut *et al* focused on the effects of CEI of 0.125% bupivacaine on the duration of second-stage labor.[21] They found a longer duration of second-stage

Table 1: Influence of early *vs.* delayed epidural labor analgesia on labor process from the included RCTs.

Study	Sample, *n*	Length of first labor duration, (Median ± SD, min)		*P*	Incidence of CS, *n* (%)		*P*
		Early	Late		Early	Late	
Chestnut *et al*, 1994[19]	334	329 ± 197	359 ± 216	NS	17 (10)	13 (8.0)	NS
Wong *et al*, 2005[15]	750	398	479	<0.001	65 (17.8)	75 (20.7)	0.31
Ohel *et al*, 2006[16]	449	354 ± 174	396 ± 210	0.04	28 (13)	25 (11.0)	0.77
Wang *et al*, 2009[17]	12,793	479 ± 52	485 ± 58	0.22	1486 (23.2)	1456 (22.8)	0.51

CD: Cervical dilation; CS: Cesarean section; NS: Not significant; RCTs: Randomized control trials; SD: Standard deviation.

labor in the EA group compared with the saline placebo group (median time: 124 ± 70 *vs.* 94 ± 54 min, $P < 0.05$). Similarly, a large-scale retrospective cohort study that included 42,268 women who had successful vaginal delivery without abnormal neonatal outcomes from 1976 to 2008 indicated there was a 2-h longer duration of second-stage labor in both nulliparous and multiparous women with EA.[22] Prolonged second-stage labor duration was considered an important factor associated with adverse outcomes, such as postpartum hemorrhage, chorioamnionitis, and perineal laceration,[23,24] all of which cause concern for obstetricians and anesthesiologists. However, given the use of a modern low-concentration local epidural anesthetic solution, several prospective randomized studies presented different perspectives about the relationship between EA and the duration of the second stage of labor. For example, it was speculated that the different results may be attributable to a low incidence of motor block.

In 1990, Chestnut *et al*[25] changed the concentration of local epidural analgesics and performed a randomized double-blind placebo-controlled study in which enrolled women were randomized into two groups (EA and placebo) when the cervix was fully dilated. The EA group received 0.0625% bupivacaine-0.0002% fentanyl, which produced better analgesic effects compared with the saline placebo group. In addition, there were no significant effects on the duration of second-stage labor between the two groups (median time: 53 *vs.* 63 min). A recent prospective double-blind parallel-arm randomized trial further explored the effects of epidural bupivacaine-fentanyl on the second stage of labor compared with fentanyl only.[26] That study found no meaningful clinical differences in the length of second-stage labor, mode of delivery, or degree of motor block, indicating that the use of EA with 0.125% bupivacaine-fentanyl 2 μg/mL or only fentanyl 10 μg/mL during the second stage of labor did not result in adverse maternal or neonatal outcomes. However, the increased opioid exposure to the fetus in the fentanyl-only infusion group needs to be considered carefully given the potential impact on neurobehavior.

Awareness of the cardiotoxicity and relatively high motor block level of bupivacaine meant that ropivacaine became a commonly used EA for pain relief during labor. The relative potency of ropivacaine is approximately 0.75 times that of bupivacaine.[27] A prospective randomized placebo-controlled trial conducted in China used 0.08% ropivacaine with sufentanil 0.4 μg/mL as EA for labor pain and observed its effects on the duration of second-stage labor.[28] In total, 400 nulliparous women were randomized into an epidural ropivacaine group and an epidural saline group when the cervix was fully dilated. The results showed that replacing analgesics with saline did not affect the length of second-stage labor, rate of cesarean section, or maternal and neonatal outcomes; these results were similar to the previous study that used epidural 0.0625% bupivacaine. In summary, there is increasing evidence that the continuous use of low concentrations of local EA during second-stage labor does not increase the risk for cesarean section, prolong the duration of the second stage, or lead to adverse effects.

Furthermore, EA infusion regimens during labor, including CEI with or without patient-controlled epidural analgesia (PCEA) boluses, intermittent epidural bolus (IEB), and PIEB, have shown a significant impact on the duration of second-stage labor. A systematic review and meta-analysis that included nine RCTs, found five RCTs reported significantly shortened second-stage labor in the IEB group compared with the CEI and PIEB groups.[29] A prospective controlled before and after cohort study indicated the introduction of technology (PIEB + PCEA) significantly decreased the duration of second-stage labor compared with CEI (mean time: 79.4 *vs.* 108.2 min), although the effect was only present in primiparous women.[30] Patients with PIEB + PCEA also showed obvious benefits including fewer motor blocks and less requirement for ropivacaine compared with CEI. In summary, both low concentration of local analgesic and improved epidural infusion regimens can prevent a lengthened duration of second-stage labor probably induced by EA [Table 2].

Maternal Pyrexia or Intrapartum Fever

The Center for Disease Control and Prevention guidelines indicated the rate of intrapartum fever (≥38°C) was 3.3%, although there was a lack of sufficient evidence. However, some large retrospective studies suggested a higher rate of maternal pyrexia (around 7%).[31,32] A recent prospective cohort study supported this claim, as 412 patients developed a fever of ≥38°C among 6057 deliveries at ≥36 weeks of gestation; this suggested the incidence of intrapartum fever was approximately 6.8% (95% confidence interval [CI]: 6.2%–7.5%).[33] Maternal pyrexia during labor is a noteworthy issue because of the related adverse effects for newborns. Maternal intrapartum fever is considered to increase the risk for ischemic stroke during

Table 2: Influence of epidural analgesia on the second stage of labor.

Study	Types of research	Sample, *n*	Length of the second stage (min) (median ± SD) or median (ranges)		*P*
			Local anesthetics	Placebo	
Chestnut *et al*, 1987[21]	RCT	92	124 ± 70	94 ± 54	<0.05
Chestnut *et al*, 1990[25]	RCT	63	53 (5–283)	63 (16–181)	NS
Cheng *et al*, 2014[22]	Respective Cohort	42,268	120	47	<0.001
Shen *et al*, 2017[28]	RCT	400	52 ± 27	51 ± 25	0.52

SD: Standard deviation; RCT: Randomized control trial; NS: Not significant.

infancy, and the relationship between maternal intrapartum fever and neonatal encephalopathy was shown to be independent of other known intrapartum risk factors.[34,35]

In 1989, Gleeson *et al* reported a higher temperature in women with EA during labor than those without EA.[36] Those authors considered that this might result from vascular and thermoregulatory modifications induced by EA. Since then, a number of researchers have focused on revealing the relationship between EA and maternal pyrexia. Here, we summarize relevant literature to clarify the relationship between these factors and the proposed mechanism for epidural-related intrapartum fever.

Relationship Between EA and Maternal Pyrexia

In 1997, Lieberman *et al* retrospectively observed the effects of EA during labor on maternal temperature during labor and postpartum neonatal sepsis.[37] The incidence of maternal intrapartum fever was close to 14.5% in women with EA, but only 1% in women without EA (adjusted OR 14.5, 95% CI: 6.3–33.2). In women with EA, there was a higher rate of intrapartum fever in those with longer labor (≥18 h) than in those with shorter labor (≤6 h) (36% *vs.* 7%); however, the rate of fever in women without EA remained low regardless of the length of labor.

A control-cohort study conducted in 1999 enrolled nulliparous women with a duration of labor longer than 6 h after membrane rupture.[38] They examined maternal and neonatal markers of infection by examining the placentas in women with intrapartum fever with or without EA to assess whether EA resulted in an increased incidence of intrapartum fever. Their analysis showed that 54% of women received EA, and several indices showed relatively higher levels in women in the EA group compared with those without EA, including a temperature greater than 38°C (46% *vs.* 26%, $P = 0.01$), placenta inflammation (61% *vs.* 36%, $P = 0.002$), and length of labor (11.8 *vs.* 9.6 h, $P = 0.03$). Of note, 35% of women in the EA group had intrapartum fever combined with placental inflammation compared with 17% of those without EA. However, there was no significant difference in incidence of maternal pyrexia between the two groups without the combination of placental inflammation (11% *vs.* 9%, $P = 0.61$).

A systematic review published in 2013 included 16 studies examining this relationship (ten observational studies, five RCTs, and one before-after study).[39] Notably, nearly all studies found a higher incidence of maternal intrapartum fever in women with EA than in those without EA. A further analysis conducted to show the reliability of the results found a relatively higher rate of maternal pyrexia in women who chose EA than in those that did not. However, women who experience fever with an elevated inflammatory state may present greater labor pain and experience a more complicated labor process; these women may be more likely to choose EA. Therefore, the results may be explained by a causal correlation between intrapartum fever and EA because of selection bias. The RCTs also indicated a higher incidence of maternal pyrexia in women with EA compared with those that received systemic opioids. However, there were no randomized placebo-controlled trials that compared EA with no analgesia because that would be unethical. Therefore, it is unavoidable that some bias exists in RCTs that compare EA with systemic opioid analgesia, because several studies have shown the anti-pyretic effects of intravenous mu-opioid agonists.

A randomized double-blind trial conducted by Sharma *et al* in 2014 provided further evidence of the association between intrapartum fever and placental inflammation.[40] In that study, 400 nulliparous women who received EA were randomly assigned to either cefoxitin 2 g or placebo just before administration of EA. Intrapartum fever was confirmed when the maternal temperature was ≥38°C. That study found no significant difference in the risk for intrapartum fever between the cefoxitin and placebo groups (38% *vs.* 40%, $P = 0.68$). However, nearly 50% of women had placental inflammation, and intrapartum fever was more likely to occur in women with placental inflammation compared with those with no placental inflammation (73/158 *vs.* 33/144, $P < 0.001$). Those authors found that the preventive application of antibiotics did not decrease the risk for placental inflammation and fever. This finding suggested an association between intrapartum fever and placental inflammation but did not provide evidence for a causal relationship. Curtin *et al* conducted a logistic regression analysis to assess independent predictors of intrapartum fever; they found that EA and histologic chorioamnionitis were independent predictors of the incidence of maternal fever during labor.[41]

In summary, intrapartum fever (≥38°C) is more likely to occur in women receiving EA during labor and in those with placental inflammation or histologic chorioamnionitis. In addition, an RCT study showed a higher incidence of maternal pyrexia in patient with EA using 0.1% ropivacaine compared with those using 0.075% ropivacaine.[42] However, a possible bias may exist due to the anti-pyretic effects of intravenous opioids. Although the mechanism of epidural-related maternal fever (ERMF) is not yet clear, a preferred theory is that the release of non-infectious, inflammatory molecules is a potential mechanism in altered thermoregulation. However, it has not been confirmed whether increased maternal temperature is caused by EA or obstetric management. Further investigations are needed to clarify the relationship between maternal pyrexia and EA. Table 3 presents the literature that reports on the relationship between EA and intrapartum fever.

Proposed Mechanism of ERMF

It has been more than 25 years since ERMF was first described as an independent contributor to intrapartum maternal fever.[49] There has been speculation regarding the potentially causative role of local anesthetics in elevated temperature, with the primary hypothesis being participation of non-infectious and inflammatory molecules. Further knowledge regarding the causes of ERMF may be beneficial to reduce its incidence through

Table 3: Relationship between epidural labor analgesia and maternal intrapartum fever.

Study	Types of research	Sample, *n*	Incidence of intrapartum labor (%)		*P*
			Epidural	Systemic opioids	
Herbst *et al*, 1995[43]	Observational	3109	6.4	1.1	<0.001
Ramin *et al*, 1995[44]	RCT	1330	22.7	4.8	<0.001
Sharma *et al*, 1997[45]	RCT	715	23.9	6.2	<0.0001
Lieberman *et al*, 1997[37]	Observational	1657	14.5	1.0	<0.05
Dashe *et al*, 1999[38]	RCT	149	46	26	0.01
Lucas *et al*, 2001[46]	RCT	738	20.4	7.1	<0.001
Sharma *et al*, 2002[47]	RCT	459	33.2	6.9	<0.0001
Riley *et al*, 2011[48]	Observational	—	22.7	6.0	0.009
Sharma *et al*, 2014[40]	RCT	400	38	40	0.68

RCT: Randomized control trial.

appropriate interventions applied during EA. Therefore, we collected evidence concerning the proposed mechanism of ERMF.

Most early researchers believed that altered maternal thermoregulation induced by EA was an important cause of intrapartum fever.[50] Although vasodilatation in the lower part of the body due to EA may lead to increased heat loss, the reactive vasoconstriction in the upper part of the body and reduction of hyperventilation and sweating tend to decrease heat loss. In addition, the unbalanced blocking of warm and cold sensations leads to a false response to the thermal information reaching the body's temperature center; this causes activated stimulation of heat production, which in turn leads to maternal pyrexia. Lumbar EA during labor was found to result in temporary peripheral temperature changes, but did not significantly alter core temperature.[51] A focused review published in 2016 concluded that a non-infectious, inflammatory mechanism may be indicated in ERMF.[52] Local anesthetic agents commonly used for EA appear likely to contribute to the development of ERMF in a large proportion of women undergoing labor, which was considered as sterile inflammation. Sterile inflammation is a process that occurs without a pathogen, but is driven by endogenous molecules (called alarmins) released following tissue damage.[53,54] The release of alarmins combined with their functional receptors further activate the inflammasome that leads to the maturation of proinflammatory cytokines, including interleukin (IL)-1β and IL-18.[55]

An initiation of proinflammatory and inflammatory processes promotes the release of other fever-inducing cytokines that result in the development of fever. Several convincing clinical trials suggested that acute inflammation was the basis of the ERMF mechanism. Higher levels of proinflammatory endogenous pyrogens in a mother and her neonate have been identified in hyperthermic women after EA.[56,57] Interestingly, Riley *et al*[48] found higher levels of IL-6 and IL-8 before EA in women with ERMF, and showed elevated cytokine levels after prolonged epidural application of bupivacaine.[58] This inflammatory status was proven by administration of anti-inflammatory glucocorticoids, which successfully reduced the incidence of ERMF from 21.8% to 2.0%.[59] These previous studies provided a large body of evidence for the important role of proinflammatory-inflammatory cytokines in the development of ERMF.

ERMF occurs within 6 h after initiation of EA, which covers the time of the pharmacologic effect of local anesthetic agents. Therefore, the direct effects of local anesthetic agents on ERMF have attracted anesthesiologists' attention. As described above, some researchers speculated there was a higher risk for intrapartum fever in women with EA compared with those without EA, which was attributed to the anti-pyretic effects of systemic opioids. However, us of systemic nalbuphine in women during labor failed to decrease the incidence of ERMF, which suggested there is a different mechanism for the epidural administration of local anesthetic agents.[60] Therefore, the common hypothesis regarding the labor-specific pyrogenic effects of local anesthetic agents leading to ERMF was probably attributable to immunomodulation and cell injury. Local anesthetics routinely used for EA during labor include bupivacaine and ropivacaine, which present immunomodulatory effects when the plasma levels reach a plateau rapidly with CEI.[61] It has already been described in an obstetric population that bupivacaine may produce potential adverse immunomodulatory effects related to a reduction of the anti-inflammatory cytokine IL-10, combined with an increase of pro-inflammatory mediator substance P in surgical wounds after cesarean section.[62] Another hypothesis suggested that cell-specific pathologic changes occur because bupivacaine induces activation of the mitochondrial permeability, which is a critical event in mitochondrial-dependent programmed cell death.[63] Systemic absorption of epidural bupivacaine to an effective concentration may result in reversible mitochondrial damage through excessive reactive oxygen species caused by increased glucocorticoids that are typically in circulation during labor.[64] Therefore, inflammatory alarmins may be released from inflammatory cells and infiltrate non-lymphoid tissues in the reproductive tract and placenta.[65]

Discussion

Comfortable and safe delivery is the expectation of parturients and the goal of maternal healthcare during delivery. The emergence of EA increased the possibility of achieving these goals. However, the potential adverse

maternal and neonatal effects induced by prolonged labor process or intrapartum fever require further investigation. The relationships between EA and labor prolongation and intrapartum fever have been described in a number of studies. From this review, we considered early initiation of EA (if requested by a woman) is preferred and can safely be conducted. Furthermore, the continuous use of EA with low concentration of local anesthetics during second-stage labor does not increase the risk for c-section, prolong the duration of second-stage labor, or lead to adverse effects. The majority of studies found a higher incidence of maternal intrapartum fever (≥38°C) in women with EA, suggesting that an association exists; however, this may be attributable to selective bias, obstetric management, or the anti-pyretic effects of intravenous mu-opioid agonists. Therefore, a causative relationship cannot yet be confirmed, and the mechanism of ERMF needs more attention. The popular mechanistic hypothesis of ERMF is non-infectious inflammation through immunomodulation and cell injury that typically occurs during labor.

Our team made lots of effects to improve EA during labor, including clinical improvement and researches. The changes related to labor EA ranged from the kinds of needle and epidural catheter to the medication scheme and modes of administration. And finally, we applied the PIEB + PCEA mode with a low concentration ropivacaine (0.08%) and very small dose of sufentanil (0.4 mcg/mL) to receive satisfied analgesic effects and to reduce the motor blocking. As a result, we have helped more than 140 thousand ladies delivering their babies with EA in clinic since 2000 and the rate of labor EA has arrived greater than 90% recently in our hospital, indicating a gradually developed mature labor analgesia technology. Otherwise, we did several important researches in the area of labor analgesia, focusing on some hot topics such as the optimal initiation of EA and the effects of EA on labor duration. The primary results[17,28] have been published on-line and attracted international interests of both anesthesiologists and obstetricians. More details about the labor EA are concluded in our studies: an earlier initiation time (as early as ≥1 cm of cervical dilation) for EA can be used when the patients have a requirement of analgesia, and continuous analgesia during second stage will not affect the maternal and neonatal outcomes.

Promotion of the labor analgesia in China is a fantastic thing, which will bring great benefits for the huge population, we committed to participating in this activity. We showed our publications on the academic meeting and invited colleagues join us to see the changes of the patients' status after EA, arouse them to develop labor analgesia in their institutions. There are still several issues during labor EA, such as the prevention and treatment of maternal intrapartum fever, abnormal fetal heart rate, vaginal compress, and so on, needed to be study and resolved, which will be a long and difficult process. Proposal of comfortable medical concept lead to great challenges for the labor analgesia and there are lots of things can do. Looking for the best effective and safe method for analgesia and making ladies enjoy the process of having babies is the aim for all of us.

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Conflicts of interests

None.

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