Labor Induction And The Incidence of Intrapartum Maternal Fever In Epidural Labor Analgesia: A Retrospective Case-Control Study

Min Wang
Xuzhou Medical University
Yiting Li
Southern Medical University
Zhongya Gu
Nanjing Jinling Hospital: East Region Military Command General Hospital
Duan Manlin (duanml1200@163.com)
Xuzhou Medical University https://orcid.org/0000-0002-4154-7198

Research article

Keywords: Labor induction, Intrapartum fever, Epidural analgesia, Labor

Posted Date: November 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-102668/v1

Abstract

Background: To assess the influence of labor induction on the intrapartum maternal fever in epidural labor analgesia and to determine its association with intrapartum fever.

Methods: A retrospective case-control study was performed during 2016–2018 in a first-class tertiary hospital. All patients who received epidural labor analgesia were allocated into either case (parturients who received labor induction and had intrapartum fever) or control (parturients who did not receive labor induction but had intrapartum fever) groups. Maternal demographic and intrapartum data, epidural infusions records, and neonatal short-term outcome were studied.

Results: A total of 710 epidural labor analgesia occurred during the study period and 119 (16.76%) women had intrapartum fever. Intrapartum fever occurred in 66 (25.68%) women who received labor induction and in 53 (11.70%) who did not. After correction for confounding factors, labor induction (OR 2.818, 95% CI, 1.778–4.467, P<0.001), number of vaginal examinations (OR 1.242, 95% CI, 1.048–1.471, P=0.012), baseline maternal temperature (OR 6.702, 95% CI, 2.065–21.755, P=0.002), admission white blood cell count (OR 1.171, 95% CI, 1.052–1.303, P=0.004), and neonatal birth weight (OR 3.015, 95% CI, 1.739–5.227, P<0.001) were risk factors for intrapartum maternal fever during epidural labor analgesia.

Conclusion: Labor induction was significantly associated with an increased risk of intrapartum maternal fever during epidural labor analgesia.

Background

Epidural analgesia has been widely used as a safe and effective method of administering satisfactory pain relief to parturients [1, 2]. However, in recent years, a majority of randomized controlled trials have indicated that labor epidural analgesia is associated with intrapartum maternal fever (defined as maternal temperature ≥ 38.0 °C during labor) [3–6]. More importantly, it has also been postulated that intrapartum fever may be associated with poor maternal and neonatal outcomes. For example, the elevated maternal temperature is associated with an increase in oxygen consumption and catecholamine generation [2], neonatal hypotonia, low Apgar score, and early-onset neonatal seizures [7].

Although the relationship between intrapartum maternal fever and epidural analgesia has been fully recognized, the mechanism of this relationship remains controversial [8]. It may refer to the role of infection, thermoregulatory factors, effects of opioids, or inflammation [8, 9]. Endogenous heat production generated by the contracting uterus may be also an important noninfectious factor [10]. Since oxytocin induces uterine contractions that cause related endogenous heat production, we retrospectively analyzed women who underwent induction of labor. This study was designed to assess the changes in maternal temperature before and after labor analgesia, and to determine possible effects of several intrapartum factors including labor induction, on maternal temperature. A better understanding of the causes of intrapartum maternal fever may help develop interventions to reduce its incidence.

This study was performed to determine whether labor induction increases the rate of intrapartum maternal fever during epidural labor analgesia. And our secondary research aim was to find variables associated with fever and to study the natural history of fever in epidural labor analgesia.

Methods

The study was approved by the local Clinical Research Ethics Committees in Jinling hospital of the Medical School of Nanjing University (NO. 2019NZKY-031-03). The Jinling Hospital is a tertiary referral center with approximately 1,500 deliveries per year. The anesthetic department provides a twenty-four-hour epidural service. The overall epidural rate in recent years was about 20%. All the patients in whom epidural labor analgesia was applied from January 2016, until December 2018, were identified from the electronic hospital Obstetric Database. This time interval was selected because, after this period, our standard epidural infusion protocol for labor analgesia was changed.

Study patients were allocated into two groups: the labor induction (LI) group (cases) comprised parturients who received labor induction had intrapartum fever, and the control group (controls) consisted of parturients who did not receive labor induction but had intrapartum fever. Obstetrical indications for labor inductions in our institution included the following aspects: postterm for women with gestational age over 40 weeks, multiparity and gestational age of at least 39 weeks, and fetal conditions such as suspected fetal growth retardation [10]. Parturients with clinical chorioamnionitis or other infections (i.e. respiratory or urinary tract infections) were excluded from the final analysis [11]. Women whose prenatal temperature over 38.0 °C, who concomitantly received any other kind of regional or general anesthesia, or had no epidural infusions records were also ineligible.

Epidural catheters were inserted at the L2-3 or L3-4 interspace when patients had cervical dilation of ≥ 2 cm. A 3-ml test dose of 2% lidocaine with 1:200,000 adrenaline was given to all patients. Our standard epidural infusion protocol for labor analgesia consisted of patient-controlled epidural analgesia (PCEA) of 100 ml 0.1% ropivacaine and 2 μg/ml fentanyl repeating during labor on demand. The epidural bolus dose was set at 5 ml every 15 minutes by patient demand, with a 20 ml/h maximum. To the end of the third stage of labor, the pump was stopped and the epidural catheter was removed by an anesthesiologist.

The primary outcome measure was the incidence of intrapartum maternal fever during epidural labor analgesia. In our institution, the maternal oral temperature was measured every 2 hours after the initiation of epidural analgesia until delivery by the nurse, with an electronic thermometer positioned under the tongue. The mean value of two measurements was recorded. Intrapartum maternal fever was defined as an oral temperature ≥ 38.0 °C at least once during labor. The temperature in labor and delivery suites was maintained between 20 °C and 22 °C.

Demographic and intrapartum data collected for each subject were abstracted from the electronic hospital databases (Heren, Health, China). Demographic data included the following: maternal age,

height, weight, gravidity, parity, estimated gestational age, admission white blood cell count ($\times 10^9$/L), and hemoglobin count (g/dL), baseline cervical dilatation and maternal temperature, premature rupture of membrane. Intrapartum data included the highest body temperature, labor duration, other medications during labor (included antibiotic usage and oxytocin augmentation), mode of delivery (spontaneous vaginal delivery, forceps delivery, cesarean section), vaginal examination, blood loss, meconium-stained amniotic fluid (MSAF), hospital stay after delivery, and occurrence of maternal complications (included lower limb motor block). Lower limb motor block (defined as Bromage score < 5) was evaluated according to the modified Bromage scale by a midwife every hour until delivery. The numeric rating scale (NRS), an 11-point scale from 0 to 10, where 0 = no pain and 10 = the worst pain imaginable, was used for measurement of uterine contraction pain before analgesia and 30 min after analgesia. Neonatal data included sex, birth weight, Apgar scores at 1 and 5 min after birth, admission to the neonatal ward, and fetal distress. The records of the epidural infusions including the epidural analgesia duration, infusion volume, PCEA attempts, and PCEA given were collected from the wireless electronic analgesia pump system (EZIS, Medtech, China). The drug calculation excluded the local anesthetic specifically used for forceps delivery analgesia.

Before data analyses, the main study aims and analytic plan were reviewed by all study investigators in March 2020. Data was collected in an EXCEL (Microsoft, Redwood, MS). The primary outcome variable was binary and summarized using frequencies and percentages. Chi-square or Fisher's exact tests were used to detect differences between groups. Independent samples t test was used to analyze continuous variables with normal distribution and Mann-Whitney U test was used to analyze continuous variables with nonnormal distribution.

Univariate logistic regression analyses were performed to screen variables that might be associated with intrapartum maternal fever in epidural labor analgesia. Independent variables with P less than 0.10 were included in a multivariate logistic regression model to determine the risk-adjusted association between the labor induction and intrapartum maternal fever in epidural labor analgesia with a backward stepwise procedure (likelihood ratio). Missing data were not replaced. The variance inflation factors were used to evaluate the collinearity of all variables entered into the final model. Two-tailed P values less than 0.05 were considered to be of statistical significance. Statistical analysis was performed with IBM SPSS Statistics software (Version. 22.0; IBM Corp., Armonk, New York, USA).

Results

A total of 710 parturients received epidural labor analgesia in our maternal unit during the study period and 119 (16.76%) women had intrapartum fever. Labor induction was given to 257 (36.2%) parturients whereas 453 (63.8%) was not. Intrapartum fever occurred in 66 (25.68%) women who received labor induction and in 53 (11.70%) who did not. Three entries were not studied due to prenatal temperature over 38.0 °C and lack of epidural infusions records (Fig. 1).

When compared with parturients who did not receive labor induction, those who received labor induction had lower BMI ($P = 0.028$), older gestational age ($P < 0.001$), fewer percentage of multiparas ($P = 0.038$), lower admission white blood cell count ($P < 0.001$), larger baseline cervical dilatation ($P < 0.001$), lower baseline maternal temperature ($P < 0.001$), longer first-stage labor duration ($P = 0.026$), lower rate of antibiotic used ($P = 0.028$), higher number of vaginal examinations ($P < 0.001$), more estimated blood loss ($P = 0.035$), and higher birth height ($P = 0.025$) (Tables 1 and 2). Variables regarding characteristics of patient-controlled epidural analgesia of the two groups were comparable (Table 3).

Table 1
Demographic and baseline data

	LI group (Cases) (n = 64)	Control group (Controls) (n = 52)	*P* value
Maternal age (year)	27(26–28)	28(26–31)	0.054
Height (cm)	163.56 ± 3.81	162.71 ± 4.17	0.254
Weight (kg)	70.39 ± 10.70	73.83 ± 9.65	0.075
Body mass index (kg m^{-2})	26.32 ± 3.96	27.84 ± 3.20	0.028
Gestational age (week)	41.12 ± 0.41	39.76 ± 0.88	< 0.001
Gravidity	1(1–2)	1(1–2)	0.712
Parity n(%)			0.038
Primiparous	64(100.00)	48(92.31)	
Multiparous	0(0.00)	4(7.69)	
Admission white blood cell count (× 10^9/L)	8.22 ± 1.89	9.02 ± 2.02	< 0.001
Admission hemoglobin count (g/dL)	117.28 ± 12.21	117.12 ± 13.24	0.066
Baseline cervical dilatation (cm)	4(3–4)	2(2–3)	< 0.001
Baseline maternal temperature (°C)	36.51 ± 0.24	36.65 ± 0.18	< 0.001
Spontaneous rupture of membranes at epidural analgesia initiation n(%)	14(21.88)	13(25.00)	0.826

Data are presented as mean±SD (standard deviation), number (%) or median (interquartile range). LI: labor induction.

Table 2
Labor events and neonatal outcomes

	LI group (Cases) (n = 64)	Control group (Controls) (n = 52)	*P* value
Total duration of labor (min)	603(526–780)	635(495–740)	0.279
Duration of the first stage[▯](min)	580(480–720)	480(420–645)	0.026
Duration of the second stage[▯] (min)	60(36–90)	66(57–86)	0.133
Duration of the third stage[▯] (min)	8(6–9)	8(7–9)	0.433
NRS[▯] pain score			
Before analgesia	9(9–9)	9(8–9)	0.072
30 min after analgesia	3(2–3)	3(2–3)	0.292
Antibiotic usage n(%)	8(12.50)	15(28.85)	0.028
Oxytocin augmentation n(%)	36(56.25)	23(44.23)	0.198
Number of vaginal examinations n(%)	4(3–4)	2(2–3)	< 0.001
Mode of delivery n(%)			0.523
Vaginal delivery n(%)	62(96.88)	49(94.23)	
Forceps delivery n(%)	0(0.00)	1(1.92)	
Cesarean delivery n(%)	2(3.13)	2(3.85)	
MSAF[§] n(%)	8(12.50)	15(28.85)	0.028
Hospital stay (day)	3(3–4)	3(3–4)	0.794
Estimated blood loss (ml)	155(130–200)	148(120–175)	0.035
Birth height (cm)	50.75 ± 1.55	50.15 ± 1.27	0.025
Birth weight (kg)	3.59 ± 0.44	3.45 ± 0.32	0.065
Apgar score after birth (score)			
1-min	9(9–9)	10(10–10)	0.200
5-min	9(9–9)	10(10–10)	0.090

Data are presented as mean ± SD (standard deviation), number (%) or median (interquartile range). LI: labor induction. [▯]Excluded those who underwent cesarean delivery. [▯]Numeric rating scale, an 11-point scale from 0 to 10, where 0 = no pain and 10 = the worst pain. [§]Meconium-stained amniotic fluid, including any meconium: fresh, old, thick (dark green in color and of pea soup consistency with particulate matter), or thin (lightly stained yellow or greenish color).

	LI group (Cases) (n = 64)	Control group (Controls) (n = 52)	*P* value
Admission to neonatal ward n(%)	1(1.56)	1(1.92)	1.000
Fetal distress n(%)	1(1.56)	0(0.00)	1.000

Data are presented as mean ± SD (standard deviation), number (%) or median (interquartile range). LI: labor induction. [‖]Excluded those who underwent cesarean delivery. [‖]Numeric rating scale, an 11-point scale from 0 to 10, where 0 = no pain and 10 = the worst pain. [§]Meconium-stained amniotic fluid, including any meconium: fresh, old, thick (dark green in color and of pea soup consistency with particulate matter), or thin (lightly stained yellow or greenish color).

Table 3
Characteristics of patient-controlled epidural analgesia

	LI group (Cases) (n = 64)	Control group (Controls) (n = 52)	*P* value
Duration of epidural analgesia(min)	480(420–580)	455(380–544)	0.132
Consumption of ropivacaine (mg)	44.25 ± 22.63	42.15 ± 16.08	0.575
Consumption of fentanyl dose (μg)	88.50± 45.26	84.30 ± 32.17	0.575
Patient-controlled epidural analgesia given	7(4–8)	6(5–10)	0.779
Patient-controlled epidural analgesia attempts	9(7–11)	8(6–14)	0.902
Patient-controlled epidural analgesia attempts/given	1.29(1.20–1.40)	1.20(1.09–1.60)	0.129
Lower limb motor block n(%)	2(3.13)	2(3.85)	0.832

Data are presented as mean ± SD (standard deviation), number (%) or median (interquartile range). LI: labor induction.

Apart from labor induction, the univariate analysis identified 10 other variables with *P* values less than 0.10, including parity, gestational age, number of vaginal examinations, baseline maternal temperature, admission white blood cell count, birth weight, birth height, oxytocin augmentation, spontaneous rupture of membranes at epidural analgesia initiation, and meconium-stained amniotic fluid (MSAF). Of these,

gestational age was excluded because of significant correlation with labor induction. The other 10 variables were included in a multivariate regression model.

After adjusting for confounding factors, the use of labor induction was significantly associated with an increased risk of intrapartum fever (odds ratio [OR] 2.818, 95% confidence interval [CI], 1.778–4.467, $P < 0.001$). Among other factors, the number of vaginal examinations (OR 1.242, 95% CI, 1.048–1.471, $P = 0.012$), baseline maternal temperature (OR 6.702, 95% CI, 2.065–21.755, $P = 0.002$), admission white

blood cell count (OR 1.171, 95% CI, 1.052–1.303, *P* = 0.004), and birth weight (OR 3.015, 95% CI, 1.739–5.227, *P* < 0.001) were associated with an increased risk of intrapartum maternal fever, whereas parity (OR 0.322, 95% CI, 0.113–0.922, *P* = 0.035) was associated with a decreased risk of intrapartum maternal fever (Table 4).

Table 4
Factors associated with the intrapartum maternal fever in epidural labor analgesia

Factors	Univariate analysis[¶]		Multivariate analysis[¶]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Parity	0.262(0.095–0.724)	0.010	0.322(0.113–0.922)	0.035
Gestational age (week)	1.473(1.202–1.804)	< 0.001	–	–
Number of vaginal examinations	1.387(1.194–1.612)	< 0.001	1.242(1.048–1.471)	0.012
Baseline maternal temperature (°C)	3.159(1.136–8.779)	0.027	6.702(2.065–21.755)	0.002
Admission white blood cell count ($\times 10^9$/L)	1.109(1.007–1.220)	0.035	1.171(1.052–1.303)	0.004
Induced labor	2.578(1.720–3.863)	< 0.001	2.818(1.778–4.467)	< 0.001
Birth weight (kg)	2.926(1.750–4.890)	< 0.001	3.015(1.739–5.227)	< 0.001
Birth height (cm)	1.246(1.086–1.430)	0.002	–	–
Oxytocin augmentation	1.684(1.129–2.512)	0.011	–	–
Spontaneous rupture of membranes at epidural analgesia initiation	1.790(1.127–2.843)	0.014	–	–
MSAF[§]	1.755(1.045–2.946)	0.033	–	–

OR, odds ratio; CI, confidence interval. [¶]The presence of intrapartum maternal fever was modeled as a function of a single factor. [¶]The presence of intrapartum maternal fever was modeled as a function of all factors with P values less than 0.10 in the univariate analyses. Multivariate logistic regression analysis was performed by using a backward stepwise procedure (likelihood ratio). Hosmer–Lemeshow test of goodness of fit of the model:χ^2=13.050, df = 8, P = 0.110. [§]Meconium-stained amniotic fluid, including any meconium: fresh, old, thick (dark green and of pea soup consistency with particulate matter), or thin (lightly stained yellow or greenish color).

Discussion

Our results showed that, in parturients who received epidural labor analgesia, 16.76% suffered from intrapartum fever. After correction for confounding factors, the use of labor induction was significantly associated with an increased risk of intrapartum maternal fever during epidural labor analgesia. These associations indicate that if a woman receives labor induction, she is at more than twice increased risk of developing a fever during epidural labor analgesia.

There is currently no method that can accurately reflect maternal core temperature, we measured maternal oral temperature sublingually. Considering the latter limitation, oral temperature is the most accurate reflection of core body temperature compared to skin, tympanic, or axillary temperature [10, 12]. A majority of research about intrapartum fever used 38 °C as the critical value for defining fever and provided an incidence of epidural-related maternal fever [13]. Therefore, we used this definition in our research to make meaningful comparisons with data reported by others. Besides, at our institution, the obstetrics department uses 38 °C as a trigger for suspecting chorioamnionitis.

Our data is compatible with those of previous studies that reported the absolute risk of intrapartum fever in nulliparas with epidural analgesia ranging from 14.5–33% [14, 15]. A prospective cohort study [10] including 81 women who scheduled for induction of labor observed an overall significant linear trend of temperature over time with an estimated temperature slope of + 0.017 °C/h (P = 0.0093). They also found that temperature increase was associated with higher body mass index values and longer time from rupture of membranes to delivery.

In recent years, considerable attention has been attached to the increased risk of intrapartum fever in women receiving epidural analgesia. Up to now, the mechanisms of fever associated with the epidural labor analgesia are still emphasized. Several prospective randomized controlled trials have described the association between maternal temperature increases and epidural analgesia in the context of placental inflammation [16–18] and neonatal sepsis [19]. Moreover, Goetzl et al. [20] found that epidural fever was associated with increased maternal and fetal serum interleukin-6 levels, which were a kind of markers of inflammation. And another research [21] led by the same group found that prophylaxis with high-dose corticosteroids could significantly lower the interleukin-6 levels and reduce the incidence of fever. These emerging evidence suggests the role of inflammation in the etiology of epidural analgesia-associated fever. Our result showed that admission white blood cell count and baseline maternal temperature were associated with intrapartum maternal fever, which implied that infectious inflammation may be a contributing factor to fever in this study. These patients with high baseline temperatures may have an underlying systemic proinflammatory status.

In our institution, intravenous oxytocin infusion is widely utilized clinically for labor induction. Oxytocin, as a powerful uterotonic agent [22], induces uterine contractions that may cause related endogenous heat production. To exert its uterotonic effects, oxytocin must bind its receptor mRNA. Interestingly, activation of the oxytocin receptor stimulates the activity of the decidual prostaglandin synthetase and increases prostaglandin synthesis [23]. Prostaglandins increase body temperature by increasing heat production

and decreasing heat loss [24]. Also, our research results showed that the first stage of labor was longer and the number of vaginal examinations was higher in women who received induction than those who did not (Table 2). Burgess et al. [25] proved that the duration of the first stage of labor and the number of vaginal examinations were significantly associated with increased risk of maternal fever. This association was probably caused by an increased risk of chorioamnionitis, and a long duration of the first stage of labor may sustain an inflammatory process that may result in the temperature elevation in those patients.

It could not be ignored that 10% of our study population was induced by vaginal dinoprostone suppository—a commercial prostaglandin E_2 (PGE_2) formulation. As an important lipid mediator, PGE_2 which are cyclopentane derivatives of arachidonic acid plays a key role in triggering fever [26]. Additionally, previous studies have confirmed that prostaglandins can induce a maternal body temperature raise [27, 28]. Among other variables, neonatal birth weight was also found to be associated with fever. We speculate that the painful and inefficient contractions caused by higher fetus weight may be related to it.

The results of this study must be interpreted within the context of its limitations. First, maternal body temperature was not measured continuously and transient increases in body temperature may not be completely recorded. Second, parturients with inadequate analgesic effects are more likely to open their mouths to breathe than those with adequate analgesia [12]. Open-mouth breathing may cool the oral mucosa, causing erroneous body temperature records and leading to possible bias. Further, another possible bias in this study stems from the selection of induced labor. Women were not randomized to labor induction or no labor induction group. If parturients with conditions associated with the development of fever were more likely to receive induction treatment than those without these conditions, and these conditions were not taken into account in the analysis, selection bias would have occurred.

In summary, under the conditions of our study, we found that labor induction, number of vaginal examinations, baseline maternal temperature, admission white blood cell count, and neonatal birth weight are risk factors or risk markers for maternal fever. This suggests that before choosing epidural analgesia in a parturient who have received labor induction, its effects on the maternal temperature changes should be considered. Well-designed prospective studies in the future are needed to investigate the incidence of chorioamnionitis in parturients with fever during epidural labor analgesia and explore the mechanisms by which labor induction affects maternal temperature during epidural labor analgesia.

Abbreviations

MSAF: Meconium-stained amniotic fluid; NRS: Numeric rating scale; PCEA: patient-controlled epidural analgesia

Declarations

Ethics approval and consent to participate

The study was performed following the ethical standards of the 1964 Declaration of Helsinki. The requirement for written informed consent was waived because women

were not subject to intervention. Approval was obtained from the local Clinical Research Ethics Committees in Affiliated Jinling hospital of the Medical School of Nanjing University (NO. 2019NZKY-031-03).

Consent for publication

Not applicable.

Availability of data and materials

All data and related metadata underlying the findings reported in our study are

provided as part of the submitted article. Additional data is available on reasonable

request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

No external funding was received for study design, data acquisition, data interpretation, manuscript preparation or revision. The study received no specific financial support. This work was supported by the Department of Anaesthesiology of

Jinling Hospital, Jiangsu, China.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Min Wang, Yiting Li, and Manlin Duan.

The first draft of the manuscript was written by Min Wang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank the staff of the Department of Obstetrics and Gynecology in Jinling hospital. Without their persistent help, this study would not have been possible.

References

[1] Sharma SK, Rogers BB, Alexander JM, McIntire DD, Leveno KJ. A randomized trial of the effects of antibiotic prophylaxis on epidural-related fever in labor. Anesth Analg. 2014;11:604-10.

[2] Leighton BL, Halpern SH. The effects of epidural analgesia on labor, maternal, and neonatal outcomes: a systematic review. Am J Obstet Gynecol. 2002;186:S69-77.

[3] Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham FG. Cesarean delivery: a randomized trial of epidural versus patient-controlled meperidine analgesia during labor. Anesthesiology. 1997;87:487-94.

[4] Sharma SK, Alexander JM, Messick G, et al. Cesarean delivery: a randomized trial of epidural analgesia versus intravenous meperidine analgesia during labor in nulliparous women. Anesthesiology. 2002;96:546-51.

[5] Lucas MJ, Sharma SK, McIntire DD, et al. A randomized trial of labor analgesia in women with pregnancy-induced hypertension. Am J Obstet Gynecol. 2001;185:970-5.

[6] Ramin SM, Gambling DR, Lucas MJ, Sharma SK, Sidawi JE, Leveno K. Randomized trial of epidural versus intravenous analgesia during labor. Obstet Gynecol. 1995;86:783-9.

[7] Greenwell EA, Wyshak G, Ringer SA, Johnson LC, Rivkin MJ, Lieberman E. Intrapartum temperature elevation, epidural use, and adverse outcome in term infants. Pediatrics. 2012;129:e447-54.

[8] Sharpe EE. Epidural labor analgesia and maternal fever. Clin Obstet Gynecol. 2017;60:365-74.

[9] Alexander JM. Epidural analgesia for labor pain and its relationship to fever. Clin Perinatol. 2005;32:777-87.

[10] Frölich MA, Esame A, Zhang K, Wu J, Owen J. What factors affect intrapartum maternal temperature? A prospective cohort study: maternal intrapartum temperature. Anesthesiology. 2012;117:302-8.

[11] Agakidis C, Agakidou E, Philip Thomas S, Murthy P, John Lloyd D. Labor epidural analgesia is independent risk factor for neonatal pyrexia. J Matern Fetal Neonatal Med. 2011;24:1128-32.

[12] Herbst A, Wølner-Hanssen P, Ingemarsson I, et al. Risk factors for fever in labor. Obstet Gynecol. 1995;86:790-4.

[13] Jansen S, Lopriore E, Naaktgeboren C, et al. Epidural-Related Fever and Maternal and Neonatal Morbidity: A Systematic Review and Meta-Analysis. Neonatology. 2020:1-12.

[14] Riley LE, Celi AC, Onderdonk AB, et al. Association of epidural-related fever and noninfectious in flammation in term labor. Obstet Gynecol. 2011;117:588-95.

[15] Goetzl L, Rivers J, Zighelboim I, Wali A, Badell M, Suresh MS. Intrapartum epidural analgesia and maternal temperature regulation. Obstet Gynecol. 2007;109:687-90.

[16] Dashe JS, Rogers BB, McIntire DD, Leveno KJ. Epidural analgesia and intrapartum fever: Placental findings. Obstet Gynecol. 1999;93:341-4.

[17] Smulian JC, Bhandari V, Vintzileos AM, et al. Intrapartum fever at term: Serum and histologic markers of inflammation. Am J Obstet Gynecol. 2003;188:269-74.

[18] Saper CB, Breder CD. The neurologic basis of fever. N Engl J Med. 1994;330:1880-6.

[19] Kaul B, Vallejo M, Ramanathan S, Mandell G: Epidural labor analgesia and neonatal sepsis evaluation rate: A quality improvement study. Anesth Analg. 2001; 93:986-90.

[20] Goetzl L, Evans T, Rivers J, Suresh MS, Lieberman E. Elevated maternal and fetal serum interleukin-6 levels are associated with epidural fever. Am J Obstet Gynecol. 2002;187:834-9.

[21] Goetzl L, Zighelboim I, Badell M, et al. Maternal corticosteroids to prevent intrauterine exposure to hyperthermia and inflammation: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol. 2006;195:1031-7.

[22] Ramsey PS, Ramin KD, Ramin SM. Labor induction. Curr Opin Obstet Gynecol. 2000;12:463-73.

[23] Smith JG, Merrill DC. Oxytocin for induction of labor. Clin Obstet Gynecol. 2006;49:594-608.

[24] Milton AS. Prostaglandins and fever. Prog Brain Res. 1998;115:129-39.

[25] Burgess APH, Katz JE, Moretti M, Lakhi N. Risk Factors for Intrapartum Fever in Term Gestations and Associated Maternal and Neonatal Sequelae. Gynecol Obstet Inves. 2017;82:508-16.

[26] Garami A, Steiner AA, Romanovsky AA. Fever and hypothermia in systemic inflammation. Handb Clin Neurol. 2018;157:565-97.

[27] Ononge S, Campbell OM, Kaharuza F, Lewis JJ, Fielding K, Mirembe F.

Effectiveness and safety of misoprostol distributed to antenatal women to prevent

postpartum haemorrhage after child-births: a stepped-wedge cluster-randomized

trial. BMC Pregnancy Childbirth. 2015;15:315.

- Garrigue A, Pierre F. Misoprostol : utilisation hors AMM dans la prise en charge de l'hémorragie du post-partum [Misoprostol: off-label use in the treatment of post-partum hemorrhage]. J Gynecol Obstet Biol Reprod (Paris). 2014;43:179-89.

Figures

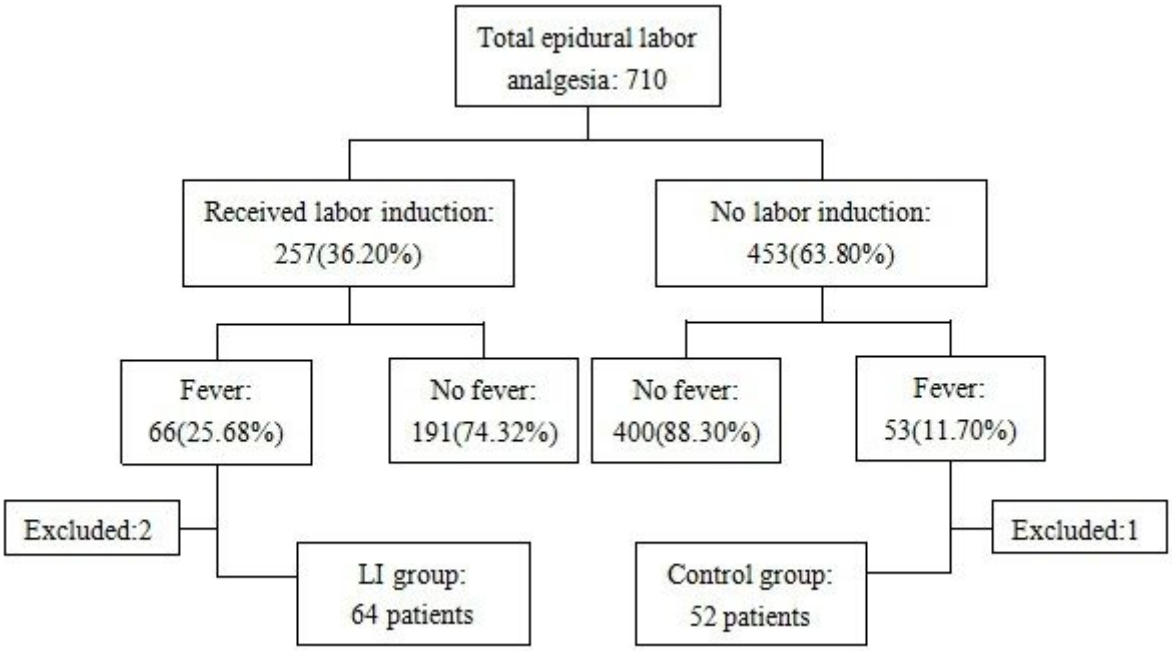

Figure 1

Flow diagram of participants.

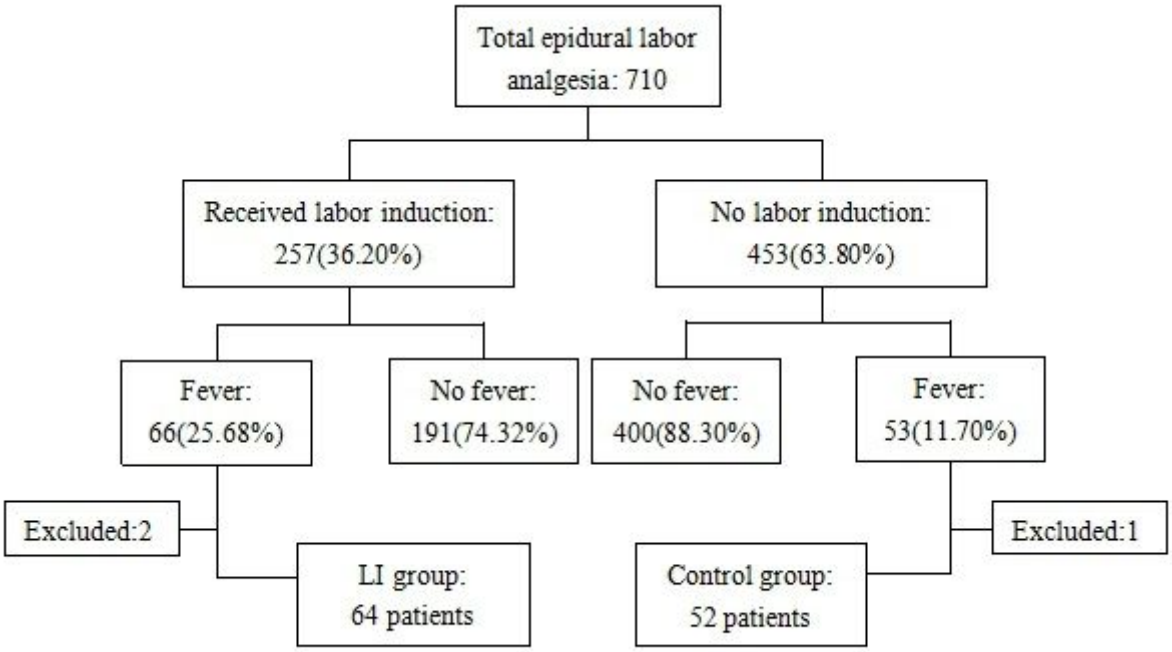

Figure 1

Flow diagram of participants.