

# Effect of Intrapartum Fever Associated With Epidural Analgesia on Short-Term Maternal and Neonatal Outcomes in Nulliparous Women: A Case Control Study

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## Research article

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# Abstract

## Background

The effects of intrapartum fever associated with epidural analgesia in nulliparous women on the short-term maternal and neonatal outcomes are not well understood.

## Methods

We included 2076 nulliparous women who received regular obstetric examination and gave birth at Guangzhou Women and Children's Medical Center from January 1, 2020 to June 30, 2020. All cases were singleton full-term pregnancies, and all foetuses were in cephalic presentation. We allocated 817 women with temperature  $>38^{\circ}\text{C}$  during labour into the fever group and 1259 women with temperature  $\leq 38^{\circ}\text{C}$  during labour to the non-fever group. The short-term maternal and neonatal outcomes in the two groups were compared.

## Results

in the fever group, 8.3% of pregnant women converted to caesarean delivery. The conversion rate in the non-fever group was 5.2% ( $p = 0.004$ ). The rates of mild neonatal asphyxia, severe neonatal asphyxia, and neonatal hospitalisation in the fever group were higher than those in the non-fever group ( $\chi^2 = 12.070, 6.325, \text{ and } 6.821$ , respectively, all  $P < 0.05$ ). The 1194 pregnant women in the fever group who had vaginal deliveries spent  $756.46 \pm 256.43$  minutes in the first stage of labour and  $65.74 \pm 47.63$  minutes in the second stage, significantly longer than the 749 women who had vaginal deliveries in the non-fever group ( $P < 0.001$ ,  $P = 0.001$ ). The assisted delivery rate for vaginal delivery in the fever group was 49.0%, significantly higher than that in the non-fever group ( $\chi^2 = 49.738$ ,  $P < 0.001$ ). The rates of mild neonatal asphyxia, severe neonatal asphyxia, neonatal acidosis, and neonatal hospitalisation with vaginal delivery in the fever group were higher than those in the non-fever group ( $\chi^2 = 15.375, 6.597, 22.265, \text{ and } 7.322$ , respectively, and  $p < 0.001, 0.010, < 0.001, \text{ and } 0.007$ , respectively).

## Conclusions

Epidural analgesia-associated intrapartum fever in nulliparous women increased the rates of short-term adverse maternal and neonatal outcomes, indicating that efforts are needed to prevent incidence of intrapartum fever due to administration of epidural analgesia.

## Introduction

Epidural analgesia (EA) is administered to women in labour because it effectively reduces labour pain. It is also recognised as the gold standard for labour analgesia because it causes few complications in mothers and neonates<sup>[1]</sup>. It has been more than thirty years since the first report on the association between EA and intrapartum fever<sup>[2]</sup>. Various studies have confirmed this correlation<sup>[3-5]</sup>. Nevertheless,

reports of maternal and neonatal outcomes of EA-related intrapartum fever in different studies are conflicting<sup>[6-8]</sup>. In particular, there remains a great deal of controversy regarding the impact of EA-related intrapartum fever on maternal and neonatal outcomes in nulliparous women. Therefore, in the present study, we explored the effect of EA-related intrapartum fever on short-term maternal and neonatal outcomes in nulliparous women using a case-control study.

## Materials And Methods

### Study population

We included 2076 nulliparous mothers who received regular obstetric examinations, had singleton full-term pregnancy, and requested EA after entering labour with the foetuses in cephalic presentation from January 1, 2020 to June 30, 2020. Data was collected from medical records retrospectively. The 817 mothers with body temperature  $>38$  °C during labour were included in the fever group, and 1259 mothers with body temperature  $\leq 38$  °C during labour were included in the non-fever group. The body temperature of both groups before epidural analgesia was within the normal range. The study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center.

### Methods

When mothers requested analgesia, the anaesthesiologist in the delivery room evaluated them and excluded contraindications to intraspinal anaesthesia, established intravenous access, inserted a needle at the level of L2-3, and then introduced the catheter from L2-3 upward; 0.1% ropivacaine, 5 mcg sufentanil and physiological saline with a total volume of 10 ml were given through epidural injection. The loading dose of the analgesic pump was set at 6 ml, the maintenance dose was set at 6 ml/h, and the patient-controlled dose was set at 8 ml/15 min. The total maintenance dose was 0.0625% ropivacaine and 0.41 mcg/ml sufentanil with a total volume of 240 ml. Epidural analgesia was continued during the second stage of labour, and maintained for 1 day after delivery. Similar analgesia protocol was used in another research by our team which the paper had published this year<sup>[9]</sup>.

We recorded age at delivery, gestational age at delivery, body mass index, pregnancy complications, usage of oxytocin, rates of category II or III foetal heart rate tracing, and birth weights of the new-borns in both groups. We compared delivery modes, neonatal asphyxia rates, and neonatal hospitalisation rates. For mothers with vaginal delivery in both groups, the delivery duration, delivery mode, and neonatal outcomes were also compared.

### Statistical methods

SPSS 20.0 (IBM Corp., Armonk, N.Y., USA) was used for data analysis. Measurement data were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm S$ ), and the independent samples t-test was used to compare the two groups. Enumeration data was expressed as percentage (%), and the  $\chi^2$  test was used for data analysis. The level of significance was set at  $p < 0.05$ ; high significance was set at  $p < 0.01$ .

# Results

## Baseline data comparison between the women in the fever and non-fever groups

There were 2076 nulliparous women requiring epidural analgesia in this study. Among them, 817 (39.4%) presented with  $T > 38^{\circ}\text{C}$  during labour. There were significant between-group differences in terms of maternal age at delivery, gestational age at delivery, and body mass index. No significant between-group differences were found for pregnancy complications. Mothers in the fever group used more oxytocin than those in the non-fever group. The rates of category II or III foetal heart rate tracings were substantially higher in the fever group than in the non-fever group (Table 1).

## Comparisons of maternal and neonatal short-term outcomes between the fever and non-fever groups

In the fever group, the rate of conversion to caesarean delivery was 8.3%, which was higher than that in the non-fever group (5.2%). The amount of blood loss in 24 hours after caesarean delivery was higher in the fever group than in the non-fever group. The neonatal asphyxia and hospitalisation rates were higher in the fever group (Table 2).

## Comparison of maternal and neonatal outcomes of nulliparous women with vaginal delivery between the fever and non-fever groups

A total of 1943 (93.6%) mothers gave birth through vaginal delivery. The average duration of the first and second stages of labour in the fever group were 150 and 7 minutes longer than those in the non-fever group, respectively. The mothers in the fever group lost more blood in 2 hours after natural delivery than those in the non-fever group. The rates of forceps delivery were 49.0% and 34.1% in the fever and non-fever groups, respectively, a significant between-group difference. There were higher rates of neonatal asphyxia, acidosis, and hospitalisation in the fever group than in the non-fever group (Table 3).

# Discussion

It has been confirmed in various studies and is widely accepted that epidural analgesia increases the rate of intrapartum fever. Nevertheless, there remains a considerable controversy regarding whether EA-related intrapartum fever causes adverse maternal and neonatal outcomes. A study showed that the rate of EA-related intrapartum fever could be as high as 46%<sup>[10]</sup>; and 25.2% and 22.5% of the women with intrapartum fever required caesarean delivery and assisted delivery, respectively, all of which were higher than those in women without intrapartum fever<sup>[11]</sup>. We found that 8.3% of the mothers were converted to caesarean delivery, a rate that was significantly lower than those of other reports. However, the rate of forceps delivery in our study was 49.0%. We believe that the reasons for the discrepancies include: (1) a high EA-related intrapartum fever rate (39.4%) and long durations of first and second stages of labour; it was impossible to differentiate EA-related intrapartum fever from intrauterine infection-related fever; therefore, forceps delivery was used in those deliveries with intrapartum fever eligible for assisted vaginal delivery, so as to prevent adverse neonatal outcomes (such as cerebral palsy) because of intrauterine

infection; (2) a high incidence of category II and III foetal heart rate tracing (69.6% in the fever group); to reduce the incidence of neonatal asphyxia, obstetricians were more inclined to use assisted delivery to shorten the duration of the second stage; (3) a high rate of amniotic fluid contamination (36.7%); intrapartum amniotic fluid contamination increases the incidence of foetal distress and therefore leads to adverse neonatal outcomes; for these reasons, steps should be taken promptly to accelerate the delivery for the nulliparous women presenting with amniotic fluid contamination; (4) a low conversion rate to caesarean delivery resulting in a high assisted delivery rate. EA-related intrapartum fever significantly increases the rate of assisted delivery; nevertheless, it will not increase the rate of caesarean delivery.

There have been various views regarding the impact of EA-related intrapartum fever on neonatal outcomes. Some studies suggested that it is associated with neonatal asphyxia, requiring more assisted ventilation, oxygen usage, and resuscitation procedures, as well as increased incidence of neonatal sepsis and usage of antibiotics. It is also possibly related to early neonatal seizures<sup>[6,12]</sup>. However, there are also studies suggesting that EA-related intrapartum fever is only a rise of body temperature of a benign nature, and there is no causal relationship between intrapartum fever and neonatal nervous system outcomes<sup>[13]</sup>. We showed that, despite the fact that the neonatal asphyxia rates in both groups were not high, the rates of neonatal asphyxia, hospitalisation, and acidosis in the fever group were higher than those of the non-fever group, suggesting that EA-related intrapartum fever increases the rate of adverse short-term neonatal outcomes. At present, the short-term impact of EA-related intrapartum fever on neonates requires more research.

The mechanism of EA-related intrapartum fever remains unclear, and there is no effective method for controlling EA-related intrapartum fever. Nevertheless, minimising the incidence of EA-related intrapartum fever and shortening the duration of fever may be the effective ways to reduce maternal and neonatal adverse outcomes. We believe that two aspects deserve attention. Firstly, we must optimise the dosing regimens of epidural analgesia (e.g., various types, concentrations, and administration routes of local anaesthetics). Some studies confirmed that different ways of drug administration affect the rates of EA-related intrapartum fever. Delivering intermittent low-dose ropivacaine can reduce the rates of intrapartum fever and assisted delivery<sup>[14]</sup>. The American Association of Anaesthesiologists recommends the use of low-dose local anaesthetics and patient-controlled epidural analgesia to reduce maternal and neonatal side effects<sup>[15]</sup>. In this study, patient-controlled epidural analgesia of low-concentration ropivacaine was used for all nulliparous women; however, 39.4% of the patients still had intrapartum fever. For these reasons, optimising the dosing regimens of epidural analgesia should be a direction of further studies. Secondly, shortening the duration of labour and reducing the incidence and duration of intrapartum fever are effective strategies to reduce the adverse maternal and neonatal outcomes. Prolonged labour is an independent risk factor for intrapartum fever; therefore, avoiding prolonged labour can effectively control intrapartum fever. The reason why multiparous women are less likely to have intrapartum fever is that they have rapid labour. Measures for shortening the labour duration include: (1) reasonable and timely switching of the delivery mode; when abnormal foetal heart rate tracing results or protracted labour occur, reasonable conversion to caesarean delivery in the first stage of labour and timely use of assisted

delivery in the second stage can effectively reduce the duration of labour; in our study, all seven cases of severe neonatal asphyxia and 67% of mild neonatal asphyxia events occurred during vaginal births, suggesting that timely conversion to caesarean delivery in cases of intrapartum fever may reduce the neonatal asphyxia rate; (2) using a higher dose of oxytocin as early as possible in the first stage of labour<sup>[16]</sup>, and maintaining the usage in the second stage; even low concentrations of local anaesthetics can inhibit tocolysis, affecting coordinated contractions between the abdominal muscles and the pelvic floor muscle group, as well as weakening the mothers' feelings of passive exertion; for these reasons, large doses of oxytocin need to be continuously used to provide effective contractions; (3) other measures such as minimising the usage of manual rupture of membranes, reducing the number of vaginal examinations, and use of temperature-lowering methods as soon as possible when body temperature rises.

## **Strengths and limitations**

Our study was a single-centre study with a large sample size. The study focused on the population of nulliparous women who received low-dose local anaesthetics and patient-controlled epidural analgesia as recommended by the current guidelines. This population of nulliparous women may have prolonged labour stage associated with epidural analgesia that made them more susceptible to developing fever<sup>[17]</sup>. Management of the delivery process and analgesia protocol are followed according to the uniform standards in our medical centre, which limits the influence of the outcomes by other different delivery management techniques. There are several limitations in this study. Firstly, it was a single-centre study, and therefore may be subject to selection bias. Secondly, it was a retrospective case control study, which would make confounding inevitable in the study. For these reasons, we instituted strict inclusion and exclusion criteria. Further research through multi-centre prospective studies are needed to validate our findings.

## **Conclusion**

Our findings suggest that EA-related intrapartum fever in nulliparous women leads to a slight increase in the risk of conversion to caesarean delivery, a substantial increase in assisted delivery, and increases in the rates of neonatal asphyxia, hospitalisation, and acidosis. It is necessary to reduce the incidence of EA-related intrapartum fever in nulliparous women; therefore, it is necessary to conduct multidisciplinary randomised controlled trials to determine the mechanisms and to determine how to prevent intrapartum fever. In Year 2019, the American College of Obstetricians and Gynecologists advocated for reducing human interventions in obstetrics<sup>[18]</sup>. For this reason, taking limited but effective obstetric measures without increasing the impact of intrapartum fever on the mothers and new-borns is a great challenge as well as a possible future research direction for obstetricians.

## **Abbreviations**

EA: Epidural analgesia

BMI: Body mass index

EFM: Electronic foetal monitoring tracing

MSAF: Meconium-stained amniotic fluid

## **Declarations**

### **Ethical approval and consent to participate**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research ethics committee of Guangzhou Women and Children's Medical Centre and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data was collected from the medical records retrospectively and informed consent was not applicable.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no conflicts of interest in this work.

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### **Author contribution**

Huiqian Zeng was involved in data analysis and manuscript writing; Baohua Lin and Huizhu Zhang were involved in data collection; Kaimin Guo is involved in manuscript editing; Ping He contributed to project development; Yumin Lai contributed to protocol development and data management.

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## Tables

<b>Table 1. Baseline characteristics of the nulliparous women who received epidural analgesia with and without fever during delivery</b>				
	EA without fever (N=1259)	EA with fever (N=817)	<i>t/χ<sup>2</sup></i>	<i>P</i>
Age (years)	29.25±3.52	29.63±3.22	-2.527	0.012
Gestational weeks	39.52±1.00	39.66±0.92	-3.323	0.001
BMI	25.51±2.96	26.15±2.85	-4.855	<0.001
Complications	378 (30.0%)	259 (31.7%)	0.656	0.418
Oxytocin administration	769 (61.1%)	655 (80.2%)	83.826	<0.001
Category I and/or Category II EFM	673(53.5%)	569(69.6%)	54.035	<0.001
EA: Epidural analgesia. BMI: Body mass index. EFM: Electronic foetal monitoring tracing.				

**Table 2. Maternal and foetal outcomes of the nulliparous women who received epidural analgesia with and without fever during delivery**

	EA without fever (N=1259)	EA with fever (N=817)	<i>t</i> / $\chi^2$	<i>P</i>
Delivery pattern				
Vaginal	1194(94.8%)	749(91.7%)	8.253	0.004
Caesarean	65(5.2%)	68(8.3%)		
Neonatal weight (g)	3183.61±354.48	3272.31±354.66	-5.569	<0.001
Mild asphyxia	17(1.4%)	30(3.7%)	12.070	0.001
Severe asphyxia	1(0.1%)	6(0.7%)	6.325	0.012
Neonatal admission	72(5.7%)	71(8.7%)	6.821	0.009
MSAF	399(31.7%)	300(36.7%)	5.608	0.018
EA: Epidural analgesia. Mild asphyxia: Apgar score of 1 minute after birth <8 and >3. Severe asphyxia: Apgar score of 1 minute after birth ≤3. MSAF: Meconium-stained amniotic fluid.				

**Table 3. Maternal and foetal outcomes of the primipara who delivered vaginally and received epidural analgesia with and without fever**

	EA without fever (N=1259)	EA with fever (N=817)	<i>t/χ<sup>2</sup></i>	<i>P</i>
First stage of labour (min)	607.70±250.42	756.46±256.43	-12.628	<0.001
Second stage of labour (min)	58.08±49.65	65.74±47.63	-3.364	0.001
Haemorrhage at 2 hours postpartum (ml)	304.50±158.85	346.70±167.28	-5.518	<0.001
Delivery pattern				
No episiotomy	271(22.7%)	101(13.5%)	49.738	<0.001
Episiotomy	516(43.2%)	281(37.5%)		
Forceps	407(34.1%)	367(49.0%)		
Mild asphyxia	15(1.3%)	30(4.0%)	15.375	<0.001
Severe asphyxia	1(0.1%)	6(0.8%)	6.597	0.010
Umbilical arterial pH < 7.2	567(47.5%)	438(58.5%)	22.265	<0.001
Neonatal admission	62(5.2%)	62(8.3%)	7.322	0.007
EA: Epidural analgesia. Mild asphyxia: Apgar score of 1 minute after birth <8 and >3. Severe asphyxia: Apgar score of 1 minute after birth ≤3.				