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The effects of patient-controlled analgesia (maternal fever, interleukin 6 and interleukin 8) applied intravenously and epidurally in labor analgesia

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Abstract

The aim of this study was to compare maternal fever, interleukin-6 (IL-6), and interleukin-8 (IL-8) levels among women who were administered either epidural or intravenous labor analgesia. The study included 30 pregnant women who had applied to the Gynecology & Obstetrics Clinics of Antalya Training and Research Hospital to have normal delivery. Patients were randomized to receive either epidural (Group I) or intravenous (Group II) analgesia. In both groups before analgesia and after the termination of labor, 5 ml blood was taken into yellow-cap gel tubes, which were centrifuged at 4100 rpm for 10 minutes. Sera were stored in 1-ml Eppendorf tubes at -800C. Serum IL-6 and IL-8 levels were measured with Human IL-6-PicoKine ELISA kit with a control vial and Human IL-8-PicoKine ELISA. The temperature was followed throughout the labor period. No patient in either group had a temperature above 380C during the labor period. Both groups showed significant increases in post-delivery IL-6 levels compared to pre-delivery levels ($p<0.05$). Post-delivery IL-8 levels were also raised in both groups, albeit statistically significant merely in Group II ($p<0.05$). Pre-delivery IL-6 level in Group 1 was significantly higher than that of Group II ($p<0.05$). Group I and Group II did not differ in terms of post-delivery IL-6 levels ($p>0.05$). Both the pre-delivery and post-delivery IL-8 level of Group I was significantly elevated compared with those of Group II ($p<0.05$). The difference between pre-and post-delivery IL-6 and IL-8 levels of both groups was found to be similar ($p>0.05$). While more markedly in epidural analgesia group, IL-6 and IL-8, which were among the cytokines released during normal delivery, exhibited elevations in pregnant women who were administered either epidural or intravenous analgesia. It implies no alteration to occur in cellular immune response by the analgesia method used in normal delivery.

Keywords: Interleukin, labor analgesia, maternal fever

Introduction

Labor pain is one of painful conditions that might be faced by adult women. American Society of Anesthesiologists (ASA) and American Obstetrics and Gynecology Association recommends the presence of labor pain as an indication to be treated. Different options are available for labor pain, including psychological methods, medications, and regional techniques. The latter has become more diverse and more preferred in labor pain for the last quarter of 20th century [1-3].

Therapeutic aim of each option is to minimize the pain and the stress induced by the labor. Regional techniques offer both minimization of the labor pain and active participation of the mother to the labor. In addition, intravenous methods, especially for pregnant women who are not appropriate for spinal and

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epidural anesthesia (e.g. coagulation defect, anticoagulant use, patient's preference), are available. Remifentanyl is a reasonable option in labor analgesia owing to its rapid onset of action, short half-life, and non-accumulating character in fetus [4].

IL-8 is a chemotactic cytokine and activates neutrophils and T-cells. This cytokine exhibits higher concentrations in amnion fluid of both term and preterm pregnancies regardless of infection. It promotes cervical maturation [5].

Uterine contractions originate from myometrial contractility modulated by combination of cellular, molecular, and hormonal events and play an important role in initiation and maintenance of labor.Several cytokines promote contractility by increasing prostaglandin synthesis. They further involve initiation of labor by causing cervical dilation and rupture of membranes [5].

The cytokines which may be defined as hormones of the immune system are synthesized in immune and non-immune cells upon stimulus. They may act on the cells which they are produced (autocrine effect) or neighboring cells (paracrine effect), or elicit a systemic response. Among these glycoprotein mediators, those triggering the leukocyte chemotaxis are called as chemokines whereas those who have intercellular stimulating or inhibiting properties are called as interleukins (IL). They are released from many cells, including fibroblasts, epithelial cells, dendritic cells, or keratinocytes [6,7].

IL-6 is an important mediator which is released in response to infection or tissue injury. They may be secreted by fibroblasts, macrophages, endothelial cells, keratinocytes, and endometrial stromal cells. IL-6, tumor necrosis factor, and interferons in particular increase stimulation of IL-6. IL-6 is rich in amnion fluid at term [8]. Goepfert et al. reported higher cervical IL-6 levels at 24th weeks of gestation in women who had premature birth before 35th weeks of gestation compared with that of those who had term babies [9].

IL-8 is a chemotactic cytokine which activates neutrophils and T-cells. They are abundant in amnion fluid of both term and preterm pregnancies regardless of infection. While progesteron inhibits IL-8 synthesis in choriodecidual explants, antiprogestins stimulate IL-8 synthesis. IL-8 acts on cervical dilation [5,10,11].

In pregnant women who received epidural analgesia were reported to have maternal fever and increased IL-6 and IL-8 levels.

Many cytokines and stress hormones are released during labor and preterm birth cases . Among them, IL-6 is a protein that involves both pro-inflammatory and anti-inflammatory mechanisms [11]. It is produced by T cells and macrophages in tissue injury, infection, trauma, burns, and inflammation [12]. In addition, it further serves as a "myokine", which is a cytokine produced in muscles, and released after muscle contraction [13]. IL-6 acts as a hormone regulating extracellular substrates along with other elevated cytokines during exercise [14]. Moreover, it is the most important mediator of fever and acute phase reactants. IL-6 could initiate PGE2 synthesis from hypothalamus, which can alter body temperature. Adipocytes also release IL-6, which is thought to involve elevated CRP levels in obese patients

In this study, we aimed to examine the effects of intravenous (IV) remifentanyl, which is a more recent method than epidural analgesia, on cytokines released during labor. For this purpose, we planned to compare maternal fever, IL-6, and IL-8 levels during labor by using either epidural or IV patient controlled analgesia. Several studies reported maternal fever and elevated IL-6 and IL-8 levels after epidural analgesia. However, no study was detected to compare IV remifentanyl to epidural method. Therefore, this study we aim to investigate any change in these parameters in pregnant women who were given IV or epidural analgesia.

Materials and Method

After approval by ethics committee of Antalya Training and Research (study no:2015/073), 30 pregnant nulliparous and multiparous women (19-39 years of age, ASA score: 1) who applied to obstetrics and gynecology clinics between 1 March 2015 and 1 September 2015 were included to the study upon giving written and verbal consent.

Patients were randomized to receive either epidural or intravenous patient-controlled analgesia (PCA). Demographic characteristics of all subjects were recorded (age, body weight, height, level of education, occupation, and number of pregnancy).

Subjects were included when they were at term (37th to 41st weeks of gestation), having vertex presentation and no multiple gestation. Procedure was planned to start in patients with active labor, 2-3 cm cervical dilatation, 50-70% of effacement, and without a sign of fetal distress. Cephalopelvic disproportion, preterm or intrauterine retardation, opioid allergy, long-term opioid use, obese (body mass index >40 kg/m2), high-risk pregnancy (preeclampsia, asthma, diabetes, hepatorenal disease), being younger than 18 or older than 40 years old were exclusion criteria from the study.

Patients were informed about labor analgesia and its methods, particularly epidural and intravenous PCA, their side effects, and ways of administration. Use of the device and analgesia process were explained to all subjects.

All patients included to the study were infused ringer lactate with 20 gauge IV cannula at a rate of 1-3 mL/kg/h. Ten ml of blood were taken from patients prior to infusion and kept at yellow-capped gel tubes.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAB), oxygen saturation (with Protoqol propag 106 series TBO 2676 monitor) monitoring was initiated 30 minutes before the analgesic method was started. Respiration rate was followed. Fetal heart beats and uterine contractions were monitored via cardiotocography (Hewlett-Packard 5010) during labor.

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After analgesia was established, all data were recorded at 5-minute intervals for the first 30 minutes, and then hourly till the end of the labor.

For Group 1, 0.125% bupivacaine+2 µg/mL fentanyl was prepared in 100 ml 0.9% saline as epidural solution. These patients received 5 ml bolus doses at 5-minute intervals for three times to reach a total of 15 ml. PCA device (Ambulatory infusion pump model 6300 Smith Medical ASD, Inc. St Paul, MN 55112 USA 40-3920-51E) was set at parameters of a lockout interval of 15 minutes, 5 ml bolus, and 5 ml infusion, and applied to the patients.

For Group 2, 0.02% remifentanyl solution was prepared by adding 2 mg remifentanyl to 100 ml of 0.9% saline (20 µg/kg) as an infusion solution. Intravenous PCA device was set at parameters of a lockout interval of 2 minutes, 0.25 µg/kg bolus, and 0.025 µg/kg infusion, and applied to the patients.

Pain was measured with visual analog scale (VAS). Patients were asked to mark their intensity of pain on a 10-cm horizontal line starting from "0" to "10" (0=no pain, 10=worst pain imaginable). Those patients with VAS scores of ≤3 were accepted to have effective analgesia.

Any complications of nausea, hypotension, bradycardia, pruritus, chills, and respiratory depression that might occur during anesthesia administration or 24 hours after labor were recorded. A reduction of 20% in blood pressure or <90 mmHg of SBP was regarded es hypotension, and ephedrine 5 µg/mL IV was planned to be administered if needed.

The duration till the complete dilatation of the cervix (10 cm) was recorded as first phase and the duration from complete dilatation to labor as second phase.

The way of labor was recorded as normal labor, assisted labor (via forceps or vacuum), or cesarean.

One- and five-minute APGAR scoring was used to evaluate the newborn.

Patient monitoring was carried out up until 2 hours after the labor. Any postpartum hemorrhages (≥500 ml to be treated) were identified.

After delivery, 10 mL of blood was collected into the yellow-capped gel tubes, which were centrifuged at 4100 rpm for 10 minutes. Sera were stored in 1-ml Eppendorf tubes at -800C (device: nüve DF 490). Serum IL-6 and IL-8 levels of pre-procedure and after the delivery periods were measured with Human IL-6-PicoKine ELISA kit with control vial and Human IL-8-PicoKine ELISA. Maternal temperature was measured 30-minute intervals throughout the labor period.

Statistical analysis

Statistical analysis was performed through SPSS 18.00 software. Values were presented as mean±standard deviation (Mean±SD). Normality test was examined with Shapiro-Wilk. Study groups were compared with Mann-Whitney-U test. Alfa significance value was accepted as 0.05.

Results

The group who received epidural analgesia was defined as Group I, and those received intravenous analgesia as Group II.

These groups did not differ in terms of demographic and clinical characteristics (p>0.05), (Table 1). In addition, hemodynamic data were also similar between groups in any time-point of follow-up.

There was no significant difference between Group I and Group II in terms of cervical effacement at initiation of analgesia (p>0.05). Nevertheless, Group II had about 1 cm more cervical dilation compared to that of Group I, which was statistically significant (p=0.028). Duration of labor was longer in Group I compared with that in Group II (p=0.005) (Table 2).

Table 1. Demographic characteristics in groups

Group		**I**			**II**		
	Mean	**SD Min**	**SDMax**	**Mean**	**SD Min**	**SDMax**	**P value**
Age	25.06±04	18.00	38.00	24.56±4.24	19.00	34.00	.970
	Group						
	I			**II**			
	Count	**%**		**Count**	**%**	**P value**	
Parity	1	14		87.5%	13	81.2%	.499
	2	0		0.0%	1	6.2%	
	3	2		12.5%	1	6.2%	
	4	0		0.0%	1	6.2%	
Level of education	Primary	2		12.5%	2	12.5%	.620
	High school	4		25.0%	5	31.2%	
	Illiterate	0		0.0%	1	6.2%	
	Secondary school	10		62.5%	7	43.8%	
	University	0		0.0%	1	6.2%	

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Table 2. Clinical characteristics in groups

	Group I		Group II		
	Mean	SD	Mean	SD	P value
Effacement	53.13	7.93	51.88	4.03	.934
Cervical dilation	4.69	.79	5.31	.70	.028
Duration of labor	387.31	133.02	282.06	65.10	.005

Statiscally significant (p<0.05)

Maternal fever (MF) measured at certain time-points during labor did not show significant difference till 6th time-point between Group I and Group II (p>0.05). At 6th time point of labor, Group I had significantly higher MF compared with that of Group II (p<0.05) (Table 3).

Table3. Maternal fever in groups

	Group I		Group II		
	Mean	SD	Mean	SD	P value
MF1	36.56	.18	36.50	.31	.051
MF2	36.45	.48	36.51	.16	.435
MF3	36.69	.41	36.56	.31	.446
MF4	36.86	.61	36.51	.27	.107
MF5	36.85	.56	36.58	.21	.260
MF6	36.82	.47	36.35	.16	.007
MF7	36.70	.13	36.10	.	-
MF8	36.67	.06	36.20	.	-
MF9	36.57	.15	.	.	-
MF10	36.65	.07	.	.	-
MF11	36.60	.	.	.	-

Statiscally significant(p<0.05). MF:maternal fever

In Group 1, pre-delivery IL-6 level was found as significantly higher than that of Group II (p<0.05). These groups did not differ in terms of post-delivery IL-6 levels (p>0.05). Group I exhibited significantly higher levels of pre-delivery and post-delivery IL-8 compared to those of Group II (p<0.05), (Table 4).

Table 4. Comparison of IL6 and IL8 Levels in groups

	Group I		Group II		
	Mean	SD	Mean	SD	P value
IL-6 Pre-delivery	44.86	31.79	20.59	15.22	.017*
IL-8 Pre-delivery	93.04	180.03	9.46	8.26	.007*
IL-6 Post-delivery	78.69	74.25	44.18	27.30	.073
IL-8 Post-delivery	190.84	309.90	19.68	17.08	.048*

* Statiscally significant (p<0.05)

Within-group comparison of pre-and post-delivery levels

Within-group comparison of pre-delivery and post-delivery IL-6 showed significantly increased levels in both Group I and Group II (p<0.05).

Within-group comparison of pre-delivery and post-delivery IL-8 showed increased levels in both groups, albeit only significant in Group II (p<0.05), (Table 5, Figure 1).

Table 5. Comparison of pre-delivery and post-delivery IL-6&IL-8 levels in groups

Group	Interleukin	Delivery	Mean	SD	P value
Group I	IL-6	Before	44.86	31.79	.023*
		After	78.69	74.25	
	IL-8	Before	93.04	180.03	.098
		After	190.84	309.90	
Group II	IL-6	Before	20.59	15.21	.005
		After	44.18	27.30	
	IL-8	Before	9.46	8.26	.044
		After	19.68	17.08	

*Statiscally significant (p<0.05). IL: interleukin

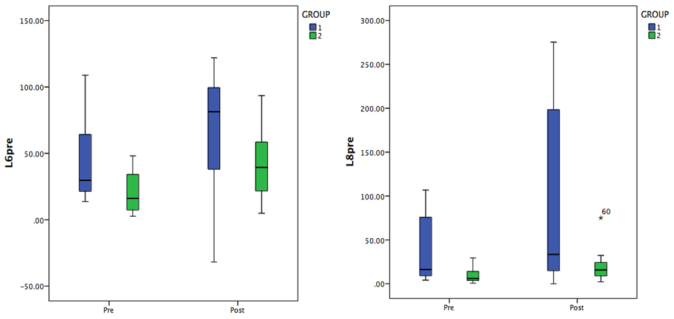

Figure 1. Pre-delivery and Post-delivery IL6&IL-8 levels in both groups

The difference between groups in terms of the difference between first and last measured levels

Group I and Group II did not differ in terms of the difference between both pre-delivery and post-delivery IL-6 and IL-8 levels (p>0.05), (Table 6).

Table 6. Postdelivery IL-6&IL-8 level differences in groups

	Group I		Group II		
	Mean	SD	Mean	SD	P value
IL-8 Difference	97.80	312.35	10.21	19.22	.250
IL-6 Difference	33.83	59.35	23.59	25.23	.895

Discussion

Labor pain is one of the most painful conditions that might be faced by adult women. A number of analgesia methods that do not compel either the mother or the baby could be used for labor pain. While patient controlled epidural analgesia has recently been the most commonly used method, IV patient controlled analgesia with short-acting opioid remifentanyl might serve as an alternative when epidural method is contraindicated or not applicable [15-17].

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During labor, a significant correlation was reported between IL-1β, IL-6, and IL-8 concentrations in lower uterine segment. IL-6 synthesis stimulates prostaglandin and leukotriene synthesis, which in turn, may lead to leukocyte extravasation by inducing cervical dilation [15,16].

In labor analgesia where epidural analgesia was administered as intermittently bolus doses or continuous infusion, maternal body temperature and IL-6 levels were reported to be similar [17]. The study by Feng which reported similar intrapartum fever by different epidural injection methods provided better understanding of the underlying mechanism. In our study, there was also no significant difference in terms of maternal body temperature (maternal fever) at first six time-points of epidural PCA and IV remifentanyl PCA. However, body temperature was higher in epidural group at sixth time-point, corresponding to 3rd hour of analgesia. This was consistent with the findings of studies regarding epidural analgesia and maternal fever. The study by Mantha et al. reported similar body temperature for the first 4 hours of continuous and intermittent epidural labor analgesia, which was altered towards continuous epidural analgesia afterwards [18,19].

Several studies investigated the association between epidural analgesia and maternal fever during labor and reported positive association between maternal fever and epidural labor analgesia [20-25].

The mechanism underlying epidural analgesia and intrapartum maternal hyperthermia is not clarified yet. While antipyretic effects of opioids and altered maternal thermoregulation may partially explain the etiology, elevated levels of maternal IL-6 involve the most probable mechanism of the fever [26,27].

On the other hand, some studies reported that corticosteroids inhibited epidural-related maternal temperature elevation and suppressed elevation of maternal/cord blood IL-6 levels [28,29]. This was interpreted as a possible relation between body temperature increase and IL-6 elevation.

Maternal serum IL-6 levels may increase as the gestational age increases [30-33]. Therefore, we considered inclusion of term pregnancies in our study.

In current study, baseline IL-6 levels of Group I were significantly higher than that of Group 2. While this difference disappeared after the delivery, both groups showed elevated levels compared to the baseline. IL-6 levels were also increased in both groups in within-group comparisons. These findings were consistent with those of published studies about epidural analgesia. Jongh et al., in the study where they compared IL-6 levels between caesarean and normal labor, reported lower IL-6 levels after caesarean which peaked at postoperative 12th hour regardless of anesthesia technique and fetomaternal characteristics. In patients with vaginal birth, IL-6 level was highest after the delivery. Among them, those patients whom epidural analgesia was applied had even higher IL-6 levels. Elevated level of IL-6 after caesarean might be explained as a typical acute phase response to the surgery. On the other hand, increased IL-6 after vaginal delivery reflects cervical dilation, labor, physiological triggers, and psychological and physical stress [34].

Group I had significantly higher baseline and post-delivery IL-8 levels compared with those of Group II. Cervical dilation occurred in earlier period of labor in Group I compared with that in Group II. The duration of labor was also longer in Group I. While higher baseline levels of IL-6 in Group I might be explained by the fact that its labor featured slower progression and longer course and required more effort, we did not consider maternal body weight in our study, which could be a limitation. In fact, some studies reported release of IL-6 by adipocytes [35,36].

Within-group comparisons showed elevated IL-8 levels after the delivery compared to baseline in both groups, albeit only significant in Group II.

Conclusion

In conclusion, IL-6 and IL-8 levels that we knew to be raised during normal labor were also found to be elevated in both analgesia groups, while more markedly in epidural analgesia group. These findings are consistent with previous studies reporting higher IL-6 and IL-8 levels in patients who received epidural analgesia. We also found a gradual increase in maternal body temperature, which was also consistent with those studies reporting similar trend in maternal body temperature. We suggested that both analgesia methods may be safely used with no effect on labor progression, and believed that higher IL-6 and IL-8 elevation in epidural analgesia group might be associated with physical stress and non-infectious inflammation, as also reported by similar studies in the literature [27,34].

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
After approval by ethics committee of Antalya Training and Research (study no:2015/073).

References

1. Cartledge A, Hind D, Bradburn M, et al. Interventions for the prevention or treatment of epidural-related maternal fever: a systematic review and meta-analysis. Br J Anaesth. 2022;129:567-80.

2. Wang H, Yang ZP, Wei SY, et al. Perinatal outcomes and risk factors for epidural analgesia-associated intrapartum maternal fever: a retrospective study. Research Square. 2022;https://doi.org/10.21203/rs.3.rs-1597834/v1.

3. S Erdine. Pain. Nobel Tıp Kitabevleri, İstanbul, 2007;142.

4. Glass PSA, Gan TJ, Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanil. Anesth Analg. 1999;89:7.

5. Beksac MS, Demir N, Koc A. Gelişen O. Erken Doğum. In: Obstetrik Maternal-Fetal Tip & Perinatoloji - Doğum Hekimliği. Medikal Network, Ankara, 2001;1149-55.

DOI: 10.5455/medscience.2023.03.041

6. Bernal AL. Overview. Preterm labour: mechanisms and management. BMC Pregnancy and Childbirth. 2007;7:S2.

7. Bilgehan H. Temel Mikrobiyoloji ve Bağışıklık Bilimi. Barış Yayınları, 1999;81-92.

8. Robertson PA, Sniderman SH, Laros RK Jr, et al. Neonatal morbidity according to gestational age and birth weight from five tertiary care centers in the United States, 1983 through 1986. Am J Obstet Gynecol. 1992;166:1629-41.

9. Goepfert AR, Goldenberg RL, Andrews WW, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The preterm prediction study: association between cervical interleukin 6 concentration and spontaneous preterm birth. Am J Obstet Gynecol. 2001;184:483-8. Erratum in: Am J Obstet Gynecol. 2008;199:e14-5.

10. Goldenberg RL, Iams JD, Mercer BM, et al. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. What we have learned about the predictors of preterm birth. Semin Perinatol. 2003;27:185-93.

11. Ferguson-Smith AC, Chen YF, Newman MS, et al.Regional localization of the interferon-beta 2/B-cell stimulatory factor 2/hepatocyte stimulating factor gene to human chromosome 7p15-p21. Genomics. 1988;2:203-8.

12. van der Poll T, Keogh CV, Guirao X, et al. Interleukin-6 gene-deficient mice show impaired defense against pneumococcal pneumonia. J Infect Dis. 1997;176:439-44.

13. Febbraio MA, Pedersen BK. Contraction-induced myokine production and release: is skeletal muscle an endocrine organ?. Exerc Sport Sci Rev. 2005;33:114-9.

14. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol (1985). 2005;98:1154-62.

15. Winkler M. Role of cytokines and other inflammatory mediators. BJOG: An International Journal of Obstetrics and Gynaecology. 2003;110:118-23.

16. Keelan JA, Blumenstein M, Helliwell RJ, et al. Cytokines, prostaglandins and parturition--a review. Placenta. 2003;24:S33-46.

17. Feng W, Xu Q, Ma L, Regular intermittent bolus provides similar incidence of maternal fever compared with continuous infusion during epidural labor analgesia. Saudi Medical Journal. 2014;35:1237-42.

18. Mantha VR, Vallejo MC, Ramesh V, et al. The incidence of maternal fever during labor is less with intermittent than with continuous epidural analgesia: a randomized controlled trial. Int J Obstet Anesth. 2008;17:123-9.

19. Mantha VR, Vallejo MC, Ramesh V, et al. Maternal and cord serum cytokine changes with continuous and intermittent labor epidural analgesia: a randomized study. The Scientific World Journal. 2012;2012:607938.

20. Sharma SK, Rogers BB, Alexander JM, et al. A randomized trial of the effects of antibiotic prophylaxis on epidural-related fever in labor. Anesth Analg. 2014;118:604-10.

21. Greenwell EA, Wyshak G, Ringer SA, et al. Intrapartum temperature elevation, epidural use, and adverse outcome in term infants. Pediatrics. 2012;129:e447-54.

22. Osborne C, Ecker JL, Gauvreau K, et al. Maternal temperature elevation and occiput posterior position at birth among low-risk women receiving epidural analgesia. J Midwifery Womens Health. 2011;56:446-51.

23. Agakidis C, Agakidou E, Philip Thomas S, et al. Labor epidural analgesia is independent risk factor for neonatal pyrexia. J Matern Fetal Neonatal Med. 2011;24:1128-32.

24. Wassen MM, Winkens B, Dorssers EM, et al. Neonatal sepsis is mediated by maternal fever in labour epidural analgesia. J Obstet Gynaecol. 2014:1-5.

25. Yue HL, Shao LJ, Li J, et al. Effect of epidural analgesia with 0.075% ropivacaine versus 0.1% ropivacaine on the maternal temperature during labor: a randomized controlled study. Chin Med J (Engl). 2013;126:4301-5.

26. Segal S. Labor epidural analgesia and maternal fever. Anesth Analg. 2010;111:1467-75.

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

28. Wang LZ, Hu XX, Liu X, et al. Influence of epidural dexamethasone on maternal temperature and serum cytokine concentration after labor epidural analgesia. Int J Gynaecol Obstet. 2011;113:40-3.

29. 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.

30. Freeman DJ, McManus F, Brown EA, et al. Short and long term changes in plasma inflammatory markers associated with preeclampsia. Hypertension 2004;43:708-14.

31. Laskowska M, Laskowska K, Gorzelak B, Oleszczuk J. Comparative analysis of the maternal and umbilical interleukin-8 levels in normal pregnancies complicated by preeclampsia with intrauterine normal growth and intrauterine growth retardation. J Matern Fetal Neonatal Med. 2007;20:527-32.

32. Casart CY, Tarrazzı K, Camejo MI. Serum levels of interleukin-6, interleukin-1ß and Human chorionic gonadotropin in pre-eclamptic and normal pregnancy. Gynecol Endocrinol. 2007;23:300-3.

33. Huang X, Huang H, Dong M, et al. Serum and placental interleukin-18 are Elevated in preeclampsia. J Reprod Immunol. 2005;65:77-87.

34. De Jongh RF, Bosmans EP, Puylaert MJ, et al. The influence of anaesthetic techniques and type of delivery on peripartum serum interleukin-6 concentrations. Acta Anaesthesiol Scand. 1997;41:853-60.

35. da Cunha Nascimento D, de Sousa NM, de Sousa Neto IV, et al. Classification of pro-inflammatory status for interleukin-6 affects relative muscle strength in obese elderly women. Aging Clin Exp Res. 2015;27:791-7.

36. Cartledge Anna, Hind Daniel, Bradburn Mike et al. Interventions for the prevention or treatment of epidural-related maternal fever: a systematic review and meta-analysis. Br J Anaesth. 2022;129:567-80.