Study on perinatal related factors of maternity and newborn in parturients with intrapartum fever: a retrospective study

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Abstract

Objective To investigate the impact of intrapartum fever on maternity and fetus. Design Retrospective cohort study. Setting Women's Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China Population We studied intrapartum fever, as well as non-fever parturients, between January 1, 2018 and December 31, 2018. Methods We collected pregnancy outcomes of intrapartum fever and non-fever mother and neonatal data. Main outcomes and measures The obstetrics outcomes, complete blood cell count (CBC) and thereby converted neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR), as well as vaginal secretion were observed in women with and without intrapartum fever. Results Prepartum white blood cell (WBC), red blood cell (RBC), and hemoglobin (Hb) were all higher in febrile group, and WBC still higher but RBC and Hb lower after birth. Postpartum NLR and MLR were all higher in fever group but not preferred overtly difference before delivery. Additionally, the comparison of WBC, RBC, Hb, platelets (PLT), neutrophils, and monocytes in prepartum and postpartum all showed significant difference. Conclusions The differences of the prepartum WBC, RBC, Hb, and monocytes existed in the intrapartum fever and afebrile groups. Besides, the parturition could bring about the change of the value of CBC and intrapartum fever might aggravate or alleviate this change. Additionally, the intrapartum fever might not be caused mainly by infection and the difference between bacteria and fungus could reflect in the CBC. Keywords: Intrapartum fever, perinatal period, vaginal discharge examination

Introduction

Maternal intrapartum fever is a common obstetric complication during labor, usually defined as temperature higher than or equal to 38 [1-3], but another few defined as over 37.4 [4], occurred in 1.6% to 34% parturients[1]. A variety of causes contribute to the etiology of intrapartum fever, including infective and non-infective reasons. Infectious factors, the least common explanation, mainly associate with clinical chorioamnionitis, urinary tract infection, and upper respiratory tract infection[4-6]. Additionally, most febrile patients during childbirth are secondary to non-infectious agents, involving in epidural analgesia, environmental temperature during labor, prolonged labor time, maternal underlying diseases[4, 6-8]. Fever during labor could trigger adverse obstetric effects, including postpartum hemorrhage, dystocia, cesarean delivery[3, 9]. In addition to the obstetric outcomes, adverse neonatal sequelae contain low Apgar scores, neonatal sepsis, hypotonia, neonatal encephalopathy, epileptic seizure, respiratory distress or asphyxia, and even infants death[6, 9-11]. Thus, intrapartum fever deserves more attention because of its high incidence and severe consequences.

Traditionally, general fever is often diagnosed by complete blood cell count (CBC)[12, 13], this is because the value of CBC before and after fever alters. However, hardly publications describe the change of CBC in parturients suffered from intrapartum fever during the whole labor. Apart from this, some other new biomarkers, such as neutrophil-to-lymphocyte ratio (NLR)[14], platelet-to-lymphocyte ratio (PLR)[15], as well

as monocyte-to-lymphocyte ratio (MLR)[16], are increasingly emerged as effective markers linked to the measure of inflammation and expected to use for judging if a person has a fever. Similarly, this field also do not extend to the study of the intrapartum fever. Therefore, we focused on the pre-, intra-, and postpartum changing situation of patients with intrapartum fever during the birth process in this paper. In addition, the possibility of NLR, PLR, and MLR act as biomarkers was explored. Furthermore, the results of vaginal discharge culture in febrile mother were also observed.

Methods

Study Population

We recruited a retrospective cohort of patients who diagnosed with intrapartum fever (defined as temperature over 37.5) from January 1, 2018 to December 31, 2018 at Nanjing Maternity and Child Health Care Hospital. For the study group was the women with intrapartum fever, we randomly selected others, parturients who were afebrile, as the control group. All parturients selected in this study received epidural analgesia.

Data Collection

Data were acquired from our electronic records system retrospectively. For each woman included in this research, we collected maternal age, gestational weeks at delivery, gravidity and parity, the volume of intrapartum hemorrhage, the volume and turbidity of the amniotic fluid, newborn sex, birth weight of the newborn, degree of perineal laceration, oxytocic manner, time of the first, the second, and the third stage of labor, the volume of intrapartum hemorrhage, prenatal and postnatal data of blood routine examination. Besides, for the study group, we also recorded the intrapartum data of the complete blood count.

As for the data of the blood routine examination, we analyzed the differences between the study group and control group. In addition, we analyzed the pre- and postnatal differences between these two groups. Moreover, we calculated the NLR, PLR, and MLR defined as neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and monocyte to lymphocyte ratio, respectively.

For maternity with intrapartum fever, vaginal secretion specimens were collected in pyretic time and then diagnosed by an experienced doctor. We documented the results of secretion culture, including*Escherichia coli, Candida albicans, Staphylococcus aureus* , and so forth.

Statistical Analysis

After the normality test through the Shapiro-Wilk test, a t-test was performed for calculating the differences in the numerical variables between two normally distributed groups and Mann-Whitney U test for non-normally distributed data. And the Kruskal-Wallis test was applied among three non-normally distributed groups. For the classified variables, the chi-square test or Fisher exact test was carried out. All analyses were completed via statistical software SPSS 25.0 (SPSS Inc., Chicago, Ill., USA) and a two-tailed $P < 0.05$ was treated as statistical significance.

Results

Demographic and characteristics

Based on the original data, some data were excluded due to various kinds of reasons as follows. Firstly, we only counted clear and hierarchical color of amniotic fluid. Therefore, pink, bloody, and brown amniotic fluid was excluded. Then, for oxytocic manner, only parturients managed with one mode were recorded to shrug off the effect of interaction between disposing approaches. Besides, parturients over 2 births were excluded because of twins existing

Demographic and characteristics for all maternity and newborn

During the whole of 2018, 1797 women in labor suffered from the intrapartum fever in the hospital, and 2850 matched afebrile parturients were also enrolled in this study. And the proportion of the maximum temperature in fever group from 37.5 to 38.0 , 38.0 to 38.5 , and over 38.5 was 34.60%, 53.09%, and

12.31%, respectively (Figure S1). Table 1 displays the obstetrical characteristics of all included maternity and newborn data and the results demonstrated that the difference between intrapartum fever and afebrile groups exists in maternal age, gestational weeks at delivery, gravidity and parity, the turbidity of the amniotic fluid, birth weight of the newborn, degree of perineal laceration, oxytocic manner, time of the first and the second stage of labor. The maternity age in the study group was 28.41 ± 2.55, and up to 29.34 ± 2.82 in afebrile group ($P < 0.0001$). And the gestational weeks in intrapartum fever and afebrile group were 39.74 ± 1.59 and 39.48 ± 2.61 ($P < 0.0001$), respectively. The febrile subjects had lower gravidity and parity, especially for parity. Nearly 95% febrile parturients were nulliparous cases, but less than 69% nulliparous women in afebrile group. As for oxytocic manner during delivery, oxytocin regimens represented two thirds in fever mother-to-be women, nevertheless, more than 60% parturients without any managements in afebrile group ($P< 0.0001$). Besides, more bleeding (307.58 ± 96.25 vs. 283.25 ± 51.60, $P < 0.0001$) and cloudy amniotic fluid (31.72% vs. 18.21%, $P < 0.0001$) occurred in fever group, whereas they were less prone to bear the laceration of perineum (73.57% vs. 86.21%, $P < 0.0001$). Moreover, in intrapartum fever group, the newborn birth weight was a little higher (3384.15 ± 376.79 g vs. 3299.30 ± 442.05 g, $P < 0.0001$), and the first (632.13 ± 167.137 min vs. 417.76 ± 240.92 min, $P< 0.0001$) and the second (36.07 ± 17.47 min vs. 28.99 ±16.28 min, $P < 0.0001$) stage of labor were all longer than the afebrile group. However, the third stage of labor in these two groups had no significant difference. We additionally calculated the labor time after fever between 37.5 and 38.0 , 38.0 and 38.5 , and over 38.5 , and the corresponding results were 256 min, 242 min, and 199 min (Figure S2). Similar to the third stage of labor, the volume of amniotic fluid also showed no significant difference.

Demographic and characteristics for nulliparity and corresponding newborn

For the sake of reducing the impact of the parity, we drew the situation of nulliparity alone (Table 2). After included nulliparity only, the number of parturients in intrapartum fever and afebrile group reduced by 91 (1797 to 1706) and 892 (2850 to 1958), respectively. Afebrile maternal age was above the fever parturients before grouping, yet decreased from 29.34 +- 3.85 to 28.00 +- 2.82 and below the febrile group ($P = 0.005$). In fever and afebrile group, the total, the first, and the second stage of labor time were all extended and the difference ($P < 0.0001$) still remained, especially for total labor time (from 455.92 +- 248.43 min to 530.27 +- 239.14 min,$P < 0.0001$) and the first stage of labor in afebrile maternity (from 417.76 +- 240.92 min to 487.22 +- 233.33 min, $P< 0.0001$). Moreover, the gravidity in afebrile group was more frequent ($P < 0.0001$) but had no significant difference between the two groups in nulliparity ($P = 0.411$).

For neonatal data, the weight difference of newborns became larger due to the birth weight in fever group unchanged nearly (from 3384.15 +- 376.79 g to 3382.86 +- 371.97 g), nonetheless, declined to 3264.99 +- 427.58 g from 3299.30 +- 442.05 g in afebrile group.

Other variables, including gestational weeks, oxytocic manner, the volume of intrapartum hemorrhage, amniotic fluid turbidity, and the degree of perineal laceration, all of the above altered not notably in both groups after grouping. Besides, the volume of amniotic fluid ($P = 0.924$) and the third stage of labor ($P = 0.539$) still showed no striking difference in two types of population.

The intrapartum fever and afebrile complete blood cell counts

In order to reveal the impact of intrapartum fever to maternity, we compared the complete blood cell counts and converted NLR (neutrophil to lymphocyte ratio), MLR (monocyte to lymphocyte ratio), and PLR (platelet to lymphocyte ratio) between intrapartum fever and afebrile groups. The results (Table 3) demonstrate the difference remains in prepartum WBC, RBC, Hb, and monocytes and postpartum WBC, RBC, Hb, neutrophils, monocytes, NLR, and MLR between fever and afebrile parturients. Prepartum mean value of WBC (9.53 x 10^9/L vs. 9.42 x10^9/L, $P = 0.010$), RBC (4.02 x10^{12}/L vs. 3.98 x 10^{12}/L, $P< 0.001$), and Hb (119.75 g/L vs. 118.23 g/L, $P< 0.0001$) were all a little higher in febrile group than afebrile group, and postpartum WBC in afebrile group still higher (12.48 x 10^9/L vs. 11.71 x 10^9/L, $P< 0.0001$). However, postpartum RBC (3.70 x 10^{12}/L vs. 3.81 x 10^{12}/L, $P< 0.001$) and Hb (110.53 g/L vs. 113.55 g/L, $P< 0.0001$) in fever parturients were inferior to non-fever women. And for neutrophils, prenatal data did not

uncover the significant difference, but postnatal neutrophils in the intrapartum fever group (10.11 x 10^9/L) were higher than afebrile group (9.19 x 10^9/L, $P < 0.0001$). Monocytes between the two groups implied the difference in both prepartum and postpartum. Additionally, postpartum NLR and MLR were all higher in fever group (P <0.001) while not preferred overtly difference before the delivery. However, PLR in two groups not presented obviously difference whether it was in prepartum ($P = 0.711$) or postpartum ($P = 0.938$). Correspondingly, PLT also showed no discrepancy between intrapartum fever and afebrile group.

Prepartum and postpartum complete blood cell counts and its difference

The results of pre- and postpartum complete blood cell count of parturients are shown in Table 4. Almost all displayed data illustrated the significant difference between prepartum and postpartum maternity apart from the lymphocytes in intrapartum fever expectant mother ($P = 0.307$). The elevated value of complete blood cell counts after labor included WBC, PLT, neutrophils, monocytes, and lymphocytes in both fever and non-fever parturients. On the contrary, postnatal RBC and Hb fallen remarkably. The mean of postpartum RBC fallen from 4.02 x 10^{12}/L to 3.70 x 10^{12}/L (P< 0.0001) in fever parturients and fallen from 3.98 x 10^{12}/L to 3.81 x 10^{12}/L (P< 0.0001) in afebrile maternity. For Hb, the value fallen from 119.75 g/L to 110.53 g/L ($P < 0.0001$) in fever group and fallen from 118.23 g/L to 113.55 g/L ($P < 0.0001$) in non-fever group.

In order to explore whether intrapartum fever would aggravate or alleviate the change of complete blood cell counts before and after delivery, we therefore used postpartum data of maternity complete blood cell count minus the corresponding prepartum data (Table 4). Table 4 illustrated that elevated WBC, PLT, and neutrophils, as well as reduced RBC and Hb, remained appreciably difference. The difference value of WBC (2.95 x 10^9/L vs. 2.28 x 10^9/L, P< 0.0001) and neutrophils (2.95 x 10^9/L vs. 2.28 x 10^9/L, $P < 0.0001$) preferred higher in intrapartum fever group, yet lower for PLT (10.60 x 10^9/L vs. 11.91 x 10^9/L, $P = 0.023$) in intrapartum fever subjects. Besides, RBC (-0.32 x 10^{12}/L vs. -0.17 x 10^{12}/L, P< 0.0001) and Hb (-9.21 g/L vs. -4.68 g/L, P< 0.0001) descended more obviously in fever maternity. However, monocytes ($P = 0.185$) and lymphocytes ($P = 0.459$) recommend pronounced discrepancy in intrapartum fever and afebrile group.

Results of positive vaginal secretion culture

For all 1797 parturients who undergone the fever during childbirth, vaginal secretion culture was performed. Out of 1797 intrapartum fever women in labor, 276 cases (15.36%) were tested with positive vaginal secretion culture (The detailed results of the vaginal secretion culture were presented in Figure S3). We then further subdivided positive section into gram-positive bacteria (G+), gram-negative bacteria (G-), and fungus, as for each group, the number of positive women was 122, 69, and 85, respectively. Table 5 describes the pre-, intra-, and postpartum complete blood cell count in three subgroups. From Table 5, we could find the value of the positive test results difference mainly existed in RBC, Hb, and PLT, including prepartum RBC, Hb, and PLT, intrapartum RBC and Hb, as well as postpartum PLT. The value of prepartum RBC was 4.12 x 10^{12}/L, 4.10 x 10^{12}/L, and 3.93 x 10^{12}/L for subgroup G+, G-, and fungus, respectively ($P = 0.009$). And for intrapartum RBC, the matching value was 4.13 x 10^{12}/L, 4.20 x 10^{12}/L, and 3.97 x 10^{12}/L ($P = 0.011$). But this difference did not exist in postpartum ($P = 0.984$). The changing trend of Hb was consistent with RBC (P =0.025, 0.010, and 0.071 for pre-, intra-, and postpartum RBC, respectively). However, the value of PLT showed different tendency. Prepartum and postpartum PLT manifested difference but not in intrapartum (P =0.022, 0.080, and 0.014 for pre-, intra-, and postpartum RBC, respectively). In addition, post hoc test (results not shown) suggested that the difference appeared in fungus with G+ or G- but not G+ with G-. In other words, the difference principally occurred in fungus with bacteria rather than different bacteria. Nonetheless, the value of WBC, neutrophils, monocytes, and lymphocytes in three groups presented no significant difference.

Discussion

Maternal intrapartum fever, a usual abnormal status during labor, result in most kinds of adverse outcomes affecting the health of mothers and newborns strongly[4-8]. However, in most cases, fever comes during birth

time silently. In other words, intrapartum fever often occurs without obvious pathogens or symptoms. All these problems put clinicians in a dilemma and worth being noticed.

In present study, we focus on the influence of intrapartum fever to the whole labor. Before the delivery, the value of white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), and monocytes in mother with intrapartum fever were all higher than non-fever parturients. Though the difference reflected not obvious in value between two groups, the results demonstrated that women with intrapartum fever may have a manifestation in partial complete blood cell count (CBC) in the prenatal. On one hand, these phenomena could make clinicians stay alert. On the other hand, several of these cells play a key role in the development of fever. For example, WBC, one of the vital defense cells to protect the human body, could resist exogenous bacteria, fungal, and virus[17, 18]. Before suffering from the fever, heat-sensitive activators, including pathogens and elevated generation of IL-17, IL-1β, and IL-1α in intestinal tissue, increase the release of neutrophils from bone marrow and followed infiltration[19]. Besides, fever related soluble IL-6Rα for signal transduction may be supplied by monocytes[20]. As is well-known, monocytes and neutrophils were contained in WBC in the test of CBC. Hence, may be due to the pre-activation of the febrile stress response, monocytes and neutrophils, as well as other types of leukocyte, increased slightly and finally reflected in the change of the value of WBC. Moreover, another latest article demonstrated that the function of RBC not only limited in the oxygen transportation, but also contained the pathogen capture and presentation[21](21). And this may attribute to its change in the blood. Additionally, literature reported that maternal Hb no more than 110 g/L was considered to be associated with maternal fever[8]. However, in our exploration, mean Hb of intrapartum fever parturients reached 119.75 g/L and even a little bit higher than afebrile subjects. This imparity needs to be deeply investigated by more large clinical trial.

Subsequently, we compared the relative parameter of prepartum and postpartum value for further investigation. Whether in intrapartum fever or afebrile group, almost all parameter demonstrated difference between prepartum and postpartum status except for lymphocytes in fever group. These results illustrated that delivery as a stress reaction changed the value of CBC through a set of immune responses. Pioneering studies suggested that delivery is an inflammatory process[22-24] and our outcomes ulteriorly proved this view. Then, the results of the comparison of the CBC difference manifested that the fever further aggravated the change value of the WBC, RBC, Hb, and neutrophils and alleviated the change value of the PLT caused by parturition. In other words, the blood was concentrated after delivery, and more concentrated in intrapartum fever parturients. As for reduction in the value of RBC and Hb, it might be resulted from intra- or postpartum hemorrhage. All these consequences remind us that we need to pay close attention to the maternal situations after birth process.

In recent years, accumulating researches revealed that neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) could be employed as biomarkers, including prognostic markers for tumor therapy[25, 26], diagnostic markers of cardiovascular disease[27, 28](27, 28), predictor of certain disease mortality[29], as well as in fever[30]. Previous study demonstrated that NLR and MLR could be applied as the diagnostic marker of bacterial infection[30]. Inspired by this practice, we planned to predict whether the maternity got a fever during the labor using NLR, PLR, and MLR. Regretfully, our data showed that these three ratios could not predict maternal intrapartum fever appropriately. This result may be due to that we considered fever and non-fever only, but not other relevant disease which might lead to the change of the ratio. This is also a question deserves further detailed research.

Vaginal secretion was cultured in fever subjects and 15.36% positive test rate in this paper. There was an article reported the positive blood and/or placental cultures were occurred in 13.9% women[1]. Though the site of the examination differs, both results declared that intrapartum fever during the labor might not primarily caused by infection. Combined with the characteristic data, we speculated that nulliparity may be a risk factor for intrapartum fever because of its longer labor time. And the longer labor time resulted in the maternal long-term touching of the external environment and this distracted the puerperae. Along with the fact that the childbirth was likely an inherently stress reaction, women were in a hypoimmunity state after long time labor and then fever came. In addition, more intrapartum hemorrhage, more oxytocin usage rate,

and more cloudy amniotic fluid were found in intrapartum fever group. These findings also implied the fever parturients during labor in a poor state. After vaginal discharge examination, corresponding comparison of the CBC was implemented. And several differences were found among three groups. Then, post hoc analysis indicated the difference mainly existed in bacteria and fungus but not between gram positive and negative bacteria. These phenomena gave us a hint that we may develop a new marker to identify whether it is bacteria or fungus and thereby do more fundamental research to exploit the potential mechanism creating this result.

Generally speaking, intrapartum fever was defined as temperature greater than 38 during labor[3, 31]. But there were also studies set the temperature as over 37.4 or 37.5 [4, 32]. And in our study, we defined the intrapartum fever as more than 37.5 because fever during labor were associated with neonatal morbidity, sepsis, and even to death and a series of other obstetric complications[4, 32]. Besides, for the most part, fetal heart rate would faster in pregnant women with temperature over 37.5 . Given this, we were looking for better care for parturients and set the temperature of the intrapartum fever as 37.5 .

Several shortages existed in this study. Firstly, all included parturients received epidural analgesia because of childbirth analgesia rate reached to 90% in our hospital. We had no control group without epidural analgesia, so we could not clarify whether the hematological indicators and converted NLR, PLR, and MLR increased during the delivery in those patients without epidural analgesia or not. Therefore, this research was difficult to reflect the situation of all populations combined with almost all of the included parturients were Chinese. And a large multi-center study deserved to be carried out for both maternal and fetal health. Besides, receiving epidural analgesia was a risk factor for intrapartum fever[7, 33, 34] and its influence on the followed examination still unknown. Secondly, due to the limitation of conditions, we only designed this retrospective analysis but not randomized controlled study. And further large prospective clinical trials need to be carried out for the purpose of mother and child health. Thirdly, we measured the axillary temperature of maternity, which affected the accuracy of body temperature because of non-core temperature. Lastly, some data were not collected such as times of vaginal exams, internal fetal monitoring, duration of ruptured membranes, instrumental delivery, cesarean section, maternal and fetal umbilical vein serum IL-6 levels, which potentially affected the development of intrapartum fever.

Conclusion

In conclusion, we found differences existed between intrapartum fever and afebrile parturients in prepartum WBC, RBC, Hb, and monocytes. Meanwhile, the delivery could result in the change of maternity and reflected in the value of CBC and intrapartum fever might aggravate or alleviate this change. In addition, the results of the positive vaginal discharge demonstrated that the intrapartum fever might not principally caused by infection and the difference between bacteria and fungus could reflect in the CBC and might be other hematological examination. And more prospective studies were urgently to be done in order to reduce the danger of the maternity and child.

Disclosure of interests

The other authors have nothing to disclose regarding potential conflicts of interest. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

PL, SF, and XZ conceived and designed the study, and also offered funding support. YF, CF, CR, XW, and WH collected the data. PM, TL, and ZD completed the statistical analyses. YF, CF, and PM wrote the manuscript.

Details of ethics approval

This study was approved by the Ethics Committee of Nanjing Maternity and Child Health Care Hospital (NO. KY-035; data: 27 August 2020).

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Supporting information

Figure S1. The proportion of the maximum temperature in fever group for different temperature range.

Figure S2. The labor time after fever between 37.5 and 38.0 , 38.0 and 38.5 , and over 38.5 .

Figure S3. Detailed results of the vaginal secretion culture.

References

1. Ashwal E, Salman L, Tzur Y, et al. Intrapartum fever and the risk for perinatal complications - the effect of fever duration and positive cultures. *J Matern Fetal Neonatal Med*2018;31:1418-1425.

2. Lange EMS, Segal S, Pancaro C, et al. Association between Intrapartum Magnesium Administration and the Incidence of Maternal Fever: A Retrospective Cross-sectional Study. *Anesthesiology*2017;127:942-952.

3. Sultan P, David AL, Fernando R, Ackland GL. Inflammation and Epidural-Related Maternal Fever: Proposed Mechanisms. *Anesth Analg*2016;122:1546-1553.

4. Apantaku O, Mulik V. Maternal intra-partum fever. *J Obstet Gynaecol* 2007;27:12-15.

5. Maayan-Metzger A, Mazkereth R, Shani A, Kuint J. Risk factors for maternal intrapartum fever and short-term neonatal outcome.*Fetal Pediatr Pathol* 2006;25:169-177.

6. Curtin WM, Katzman PJ, Florescue H, Metlay LA, Ural SH. Intrapartum fever, epidural analgesia and histologic chorioamnionitis. *J Perinatol* 2015;35:396-400.

7. Sharpe EE, Arendt KW. Epidural Labor Analgesia and Maternal Fever. *Clin Obstet Gynecol*2017;60:365-374.

8. Burgess APH, Katz JE, Moretti M, Lakhi N. Risk Factors for Intrapartum Fever in Term Gestations and Associated Maternal and Neonatal Sequelae. *Gynecol Obstet Invest* 2017;82:508-516.

9. Dior UP, Kogan L, Eventov-Friedman S, et al. Very High Intrapartum Fever in Term Pregnancies and Adverse Obstetric and Neonatal Outcomes. *Neonatology* 2016;109:62-68.

10. Lieberman E, Lang J, Richardson DK, Frigoletto FD, Heffner LJ, Cohen A. Intrapartum maternal fever and neonatal outcome. *Pediatrics*2000;105:8-13.

11. 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:e447-454.

12. Cruz AT, Mahajan P, Bonsu BK, et al. Accuracy of Complete Blood Cell Counts to Identify Febrile Infants 60 Days or Younger With Invasive Bacterial Infections. *JAMA pediatr*2017;171:e172927.

13. Rubio E, Alejo-Cancho I, Aylagas C, et al. Diagnostic Value of Platelet and Leukocyte Counts in the Differential Diagnosis of Fever in the Returning Traveler. *Am J Trop Med Hyg* 2019;100:470-475.

14. Chandrashekara S, Mukhtar Ahmad M, Renuka P, Anupama KR, Renuka K. Characterization of neutrophil-to-lymphocyte ratio as a measure of inflammation in rheumatoid arthritis. *Int J Rheum Dis* 2017;20:1457-1467.

15. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The Platelet-to-Lymphocyte Ratio as an Inflammatory Marker in Rheumatic Diseases. *Ann Lab Med* 2019;39:345-357.

16. Cananzi FCM, Minerva EM, Samà L, et al. Preoperative monocyte-to-lymphocyte ratio predicts recurrence in gastrointestinal stromal tumors. *J Surg Oncol* 2019;119:12-20.

17. Wang X, Lin G, Cui G, Zhou X, Liu GL. White blood cell counting on smartphone paper electrochemical sensor.*Biosens Bioelectron* 2017;90:549-557.

18. Daniel C, Leppkes M, Muñoz LE, Schley G, Schett G, Herrmann M. Extracellular DNA traps in inflammation, injury and healing. *Nat Rev Nephrol* 2019;15:559-575.

19. Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat Rev Immunol*2015;15:335-349.

20. Chen Q, Wang WC, Bruce R, et al. Central role of IL-6 receptor signal-transducing chain gp130 in activation of L-selectin adhesion by fever-range thermal stress. *Immunity*2004;20:59-70.

21. Ukidve A, Zhao Z, Fehnel A, et al. Erythrocyte-driven immunization via biomimicry of their natural antigen-presenting function. *Proc Natl Acad Sci U S A* 2020.

22. Norman JE, Bollapragada S, Yuan M, Nelson SM. Inflammatory pathways in the mechanism of parturition. *BMC Pregnancy Childbirth* 2007;7 Suppl 1:S7.

23. Goldfarb IT, Adeli S, Berk T, Phillippe M. Fetal and Placental DNA Stimulation of TLR9: A Mechanism Possibly Contributing to the Pro-inflammatory Events During Parturition. *Reprod Sci*2018;25:788-796.

24. Gomez-Lopez N, Romero R, Xu Y, et al. A Role for the Inflammasome in Spontaneous Preterm Labor With Acute Histologic Chorioamnionitis.*Reprod Sci* 2017;24:1382-1401.

25. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer* 2017;111:176-181.

26. Capone M, Giannarelli D, Mallardo D, et al. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. *J Immunother Cancer* 2018;6:74.

27. Angkananard T, Anothaisintawee T, McEvoy M, Attia J, Thakkinstian A. Neutrophil Lymphocyte Ratio and Cardiovascular Disease Risk: A Systematic Review and Meta-Analysis. *Biomed Res Int*2018;2018:2703518.

28. Chen T, Yang M. Platelet-to-lymphocyte ratio is associated with cardiovascular disease in continuous ambulatory peritoneal dialysis patients. *Int Immunopharmacol* 2020;78:106063.

29. Xiang F, Chen R, Cao X, et al. Monocyte/lymphocyte ratio as a better predictor of cardiovascular and all-cause mortality in hemodialysis patients: A prospective cohort study. *Hemodial Int* 2018;22:82-92.

30. Naess A, Nilssen SS, Mo R, Eide GE, Sjursen H. Role of neutrophil to lymphocyte and monocyte to lymphocyte ratios in the diagnosis of bacterial infection in patients with fever. *Infection*2017;45:299-307.

31. Remaschi G, Ricci S, Cortimiglia M, et al. TREC and KREC in very preterm infants: reference values and effects of maternal and neonatal factors. *J Matern Fetal Neonatal Med*2019:1-6.

32. Impey L, Greenwood C, MacQuillan K, Reynolds M, Sheil O. Fever in labour and neonatal encephalopathy: a prospective cohort study.*BJOG* 2001;108:594-597.

33. Lieberman E, Lang JM, Frigoletto F, Jr., Richardson DK, Ringer SA, Cohen A. Epidural analgesia, intrapartum fever, and neonatal sepsis evaluation. *Pediatrics* 1997;99:415-419.

34. Yin H, Hu R. A cohort study of the impact of epidural analgesia on maternal and neonatal outcomes. *J Obstet Gynaecol Res* . 2019;45:1435-1441.

Table 1. Characteristics between intrapartum fever and afebrile groups

Variable	Intrapartum fever (n=1797)	Afebrile (n=2850)	P
Maternal age	28.41 ± 2.91	29.34 ± 3.85	<0.0001
Gestational age (weeks)	39.68 ± 1.29	39.41 ± 1.62	<0.0001
Gravidity			<0.0001
1	1259 (70.06)	1486 (52.14)	
2-4	527 (29.33)	1312 (46.04)	
[?]5	11 (0.61)	52 (1.82)	
Parity			<0.0001
1	1706 (94.94)	1957 (68.67)	
2	90 (5.01)	874 (30.67)	
Oxytocic manner			<0.0001
No	531 (29.55)	1819 (63.82)	
Propess	13 (0.72)	67 (2.35)	
Oxytocin	1210 (67.33)	914 (32.07)	
Water balloon	0 (0)	3 (0.11)	
Volume of intrapartum hemorrhage (ml)	307.58 ± 96.25	283.25 ± 51.60	<0.0001
Amniotic fluid			
Volume (ml)	381.98 ± 53.10	387.74 ± 60.92	0.186
Turbidity			<0.0001
Clear	1227 (68.28)	2331 (81.79)	
I	143 (8.12)	204 (7.16)	
II	167 (9.29)	181 (6.35)	
III	250 (13.91)	126 (4.42)	
Degree of perineal laceration			<0.0001
No	475 (26.43)	393 (13.79)	
I	966 (53.76)	2042 (71.65)	
II	356 (19.81)	415 (14.56)	
Labor time (min)			
The first stage of labor	632.13 ± 167.137	417.76 ± 240.92	<0.0001
The second stage of labor	36.07 ± 17.47	28.99 ±16.28	<0.0001
The third stage of labor	9.17 ± 3.37	9.16 ± 4.13	0.222
Total	677.37 ± 173.16	455.92 ± 248.43	<0.0001
Birth weight (g)	3384.15 ± 376.79	3299.30 ± 442.05	<0.0001

Table 2. Characteristics of nulliparity between intrapartum fever and afebrile groups

Variable	Intrapartum fever (n=1706)	Afebrile (n=1958)	P
Maternal age	28.21 ± 2.55	28.00 ± 2.82	0.005
Gestational age (weeks)	39.74 ± 1.59	39.48 ± 2.61	<0.001
Gravidity			0.411
1	1258 (73.74)	1479 (75.54)	
2-4	444 (26.03)	476 (24.31)	
[?]5	4 (0.23)	3 (0.15)	
Oxytocic manner			<0.0001

Variable	Intrapartum fever (n=1706)	Afebrile (n=1958)	P
No	480 (28.14)	1085 (55.41)	
Propess	13 (0.76)	62 (3.17)	
Oxytocin	1171 (68.64)	771 (39.38)	
Volume of intrapartum hemorrhage (ml)	308.64 ± 99.73	286.54 ± 54.12	<0.0001
Amniotic fluid			
Volume (ml)	381.13 ± 52.32	384.10 ± 55.40	0.924
Turbidity			<0.0001
Clear	1157 (67.82)	1569 (80.13)	
I	137 (8.03)	139 (7.10)	
II	161 (9.44)	135 (6.89)	
III	242 (14.19)	108 (5.52)	
Degree of perineal laceration			<0.0001
No	456 (26.73)	281 (14.35)	
I	899 (52.70)	1313 (67.06)	
II	351 (20.57)	364 (18.59)	
Labor time (min)			
The first stage of labor	641.18 ± 163.55	487.22 ± 233.33	<0.0001
The second stage of labor	36.99 ± 17.59	33.93 ±16.55	<0.0001
The third stage of labor	9.14 ± 3.32	9.12 ± 3.50	0.539
Total	687.30 ± 169.42	530.27 ± 239.14	<0.0001
Birth weight (g)	3382.86 ± 371.97	3264.99 ± 427.58	<0.0001

Table 3. Complete blood cell counts of intrapartum fever and afebrile groups

Variable	Intrapartum fever (n = 1786)	Afebrile (n = 1882)	P
Prepartum			
WBC (10^9/L)	9.53 (7.72-10.89)	9.42 (7.58-10.71)	0.010
RBC (10^{12}/L)	4.02 (3.77-4.23)	3.98 (3.73-4.22)	<0.001
Hb (g/L)	119.75 (112-127)	118.23 (110-126)	<0.0001
PLT (10^9/L)	192.49 (155-223)	190.41 (153-221)	0.179
Neutrophils (10^9/L)	7.08 (5.33-8.25)	7.05 (5.20-8.17)	0.103
Monocytes (10^9/L)	0.59 (0.47-0.69)	0.59 (0.45-0.69)	0.038
Lymphocytes (10^9/L)	1.73 (1.38-2.06)	1.71 (1.37-2.01)	0.210
NLR	4.60 (2.91-5.36)	4.71 (2.90-5.30)	0.994
MLR	0.37 (0.27-0.43)	0.40 (0.27-0.42)	0.322
PLR	120.20 (89.12-142.58)	122.84 (86.79-143.02)	0.711
Postpartum			
WBC (10^9/L)	12.48 (10.58-14.02)	11.71 (9.75-13.35)	<0.0001
RBC (10^{12}/L)	3.70 (3.41-3.99)	3.81 (3.52-4.10)	<0.0001
Hb (g/L)	110.53 (101-121)	113.55 (104-123)	<0.0001
PLT (10^9/L)	203.09 (166-236)	202.32 (166-234)	0.691
Neutrophils (10^9/L)	10.11 (8.26-11.56)	9.19 (7.47-10.66)	<0.0001
Monocytes (10^9/L)	0.64 (0.47-0.76)	0.61 (0.46-0.73)	<0.001

Variable	Intrapartum fever (n = 1786)	Afebrile (n = 1882)	P
Lymphocytes (10^9/L)	1.75 (1.43-2.01)	1.75 (1.41-2.03)	0.938
NLR	6.26 (4.64-7.05)	5.70 (4.20-6.52)	<0.0001
MLR	0.41 (0.27-0.45)	0.38 (0.26-0.43)	<0.001
PLR	124.35 (94.95-143.97)	123.41 (94.12-144.87)	0.938

Table 4. Prepartum and postpartum complete blood cell count and its difference of intrapartum fever and afebrile groups

P' for the comparison of prepartum and postpartum complete blood cell count, and P" for the comparison of complete blood cell count difference (postpartum data minus the corresponding prepartum data) in intrapartum fever and afebrile groups. Superscript a-g means two compared variables for P".

Variable	Prepartum	Postpartum	P'	Difference	P"
Intrapartum fever (n=1786)					
WBC (10^9/L)	9.53 (7.72-10.89)	12.48 (10.58-14.02)	<0.0001	2.95 (1.02˜4.89) [a]	<0.0001
RBC (10^{12}/L)	4.02 (3.77-4.23)	3.70 (3.41-3.99)	<0.0001	-0.33 (-0.58˜-0.02) [b]	<0.0001
Hb (g/L)	119.75 (112-127)	110.53 (101-121)	<0.0001	-9.21 (-17˜0) [c]	<0.0001
PLT (10^9/L)	192.49 (155-223)	203.09 (166-236)	<0.0001	10.60 (-8˜30) [d]	0.023
Neutrophils (10^9/L)	7.08 (5.33-8.25)	10.11 (8.26-11.56)	<0.0001	3.03 (1.17˜4.95) [e]	<0.0001
Monocytes (10^9/L)	0.59 (0.47-0.69)	0.64 (0.47-0.76)	<0.0001	0.04 (-0.10˜0.17) [f]	0.185
Lymphocytes (10^9/L)	1.73 (1.38-2.06)	1.75 (1.43-2.01)	0.307	0.02 (-0.30˜0.33) [g]	0.459
Afebrile (n=1882)					
WBC (10^9/L)	9.42 (7.58-10.71)	11.71 (9.75-13.35)	<0.0001	2.28 (0.57˜4.23) [a]	
RBC (10^{12}/L)	3.98 (3.73-4.22)	3.81 (3.52-4.10)	<0.0001	-0.17 (-0.40˜0.11) [b]	
Hb (g/L)	118.23 (110-126)	113.55 (104-123)	<0.0001	-4.68 (-12˜3) [c]	
PLT (10^9/L)	190.41 (153-221)	202.32 (166-234)	<0.0001	11.91 (-5˜30) [d]	
Neutrophils (10^9/L)	7.05 (5.20-8.17)	9.19 (7.47-10.66)	<0.0001	2.15 (0.52˜4.02) [e]	
Monocytes (10^9/L)	0.59 (0.45-0.69)	0.61 (0.46-0.73)	<0.0001	0.02 (-0.11˜0.15) [f]	
Lymphocytes (10^9/L)	1.71 (1.37-2.01)	1.75 (1.41-2.03)	0.030	0.03 (-0.29˜0.36) [g]	

Table 5. Complete blood cell counts of intrapartum fever parturients with positive vaginal secretion culture[a] $P < 0.05$,[b] $P < 0.05$, and[c] $P < 0.05$ expressed the post hoc analysis between G+ and G-, G+ and fungus, G- and fungus, respectively.

Variable	G+ (n = 122)	G- (n = 69)	Fungus (n = 85)	P
Prepartum				
WBC (10^9/L)	9.43 (7.58-10.74)	9.81 (7.73-11.41)	9.60 (7.89-11.37)	0.465
RBC (10^{12}/L)	4.12 (3.81-4.31) [b]	4.10 (3.90-4.33) [c]	3.93 (3.70-4.17) [b,c]	0.009
Hb (g/L)	121.42 (113-128.75) [b]	122.00 (113-130)	116.04 (108-124) [b]	0.025
PLT (10^9/L)	184.79 (140.25-215.50) [b]	189.18 (149.50-219.75)	201.86 (169-234) [b]	0.022
Neutrophils (10^9/L)	6.99 (5.20-8.11)	7.36 (5.53-8.61)	7.10 (5.19-8.85)	0.365
Monocytes (10^9/L)	0.61 (0.46-0.71)	0.64 (0.49-0.69)	0.61 (0.49-0.71)	0.665
Lymphocytes (10^9/L)	1.72 (1.43-1.99)	1.64 (1.40-2.00)	1.83 (1.42-2.16)	0.251
Intrapartum				
WBC (10^9/L)	14.89 (12.74-16.16)	15.21 (12.70-17.50)	14.75 (12.54-16.72)	0.592
RBC (10^{12}/L)	4.13 (3.91-4.36)	4.20 (3.94-4.36) [c]	3.97 (3.69-4.26) [c]	0.011

Variable	G+ (n = 122)	G- (n = 69)	Fungus (n = 85)	P
Hb (g/L)	123.07 (116-130.75)	125.17 (117-131) [c]	117.17 (108-128) [c]	0.010
PLT (10^9/L)	176.03 (137-204.75)	184.82 (144.50-216.75)	190.41 (150-232)	0.080
Neutrophils (10^9/L)	13.01 (10.89-14.32)	13.28 (10.96-15-41)	12.81 (10.89-14.59)	0.659
Monocytes (10^9/L)	0.73 (0.53-0.91)	0.72 (0.54-0.92)	0.75 (0.58-0.85)	0.959
Lymphocytes (10^9/L)	1.12 (0.90-1.37)	1.16 (0.89-1.40)	1.17 (0.90-1.36)	0.904
Postpartum				
WBC (10^9/L)	12.57 (10.73-14.46)	12.75 (10.31-14.10)	12.63 (10.61-14.14)	0.949
RBC (10^{12}/L)	3.70 (3.40-4.02)	3.70 (3.35-4.05)	3.67 (3.43-3.99)	0.984
Hb (g/L)	111.22 (100.50-123)	110.00 (100-121.75)	108.42 (99-111)	0.071
PLT (10^9/L)	192.82 (157.25-217) [a]	205.98 (170-232.75) [a]	208.86 (172-245)	0.014
Neutrophils (10^9/L)	10.27 (8.37-11.84)	10.32 (8.14-11.64)	10.21 (8.22-11.76)	0.995
Monocytes (10^9/L)	0.61 (0.46-0.74)	0.63 (0.47-0.72)	0.71 (0.50-0.85)	0.222
Lymphocytes (10^9/L)	1.70 (1.36-1.98)	1.78 (1.45-2.05)	1.80 (1.40-2.14)	0.388