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Complete blood count during the first trimester predicting spontaneous preterm birth

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Abstract. – OBJECTIVE: This work aimed at assessing the peripheral complete blood count during the first trimester of pregnancy in women with spontaneous preterm birth (sPTB) compared with age-matched controls who are women with healthy pregnancies.

PATIENTS AND METHODS: This was a cross-sectional case-control study, with 175 sPTB and 175 age-matched healthy controls, carried out between January 2019 and December 2019. Baseline data and the complete blood count parameters examined during the first trimester of all the participants were recorded. The receiver operator characteristic curve (ROC) was used to evaluate cut-off point and diagnostic characteristics and area under the curve predicting sPTB.

RESULTS: White blood count, platelet, lymphocyte, monocyte, and lymphocyte-monocyte ratio values were significantly higher, and platelet-lymphocyte ratio and neutrophil-lymphocyte ratio values were lower in sPTB group than healthy control group in the first trimester of pregnancy. Receiver-operator curve analysis suggested that lymphocyte, white blood count, platelet-lymphocyte ratio, neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, monocyte, and platelet in the first trimester of pregnancy had predictive value for sPTB. The greatest predictive was lymphocyte, and the areas under the receiver operator characteristic curve (AUROCs) reached 0.853.

CONCLUSIONS: Lymphocyte values during the first trimester of pregnancy were the most predictive spontaneous preterm delivery. Therefore, in the management of the higher risk of preterm delivery, lymphocyte values could be a more cost-effective method during the first trimester of pregnancy because it does not need any kit.

Key Words:
Complete blood count, Spontaneous preterm birth, First trimester, Pregnancy, Lymphocyte.

Introduction

Preterm birth, defined as delivery before 37 weeks of completed gestation, remains a leading cause of neonatal morbidity and mortality, including respiratory distress syndrome, temperature instability, feeding difficulties, and causes to adverse maternal morbidity and mortality (including endomyometritis, chorioamnionities, and postpartum hemorrhage)[1,2]. Maternal or fetal medically indications could induce the preterm birth. However, approximately 70% of them are spontaneous with or without premature rupture of membranes[3]. It is important to predict preterm birth to save time for doctors and pregnant women to perform the necessary interventions. Various strategies, including patient's history, maternal signs and symptoms[4], cervical length[5,6], fetal fibronectin[7], and other inflammatory biomarkers[8,9], have been used to predict spontaneous preterm birth (sPTB) in women who present with symptoms of preterm labor, and all of them have limited prognostic ability.

It is well-known that pregnancy and childbirth have association with inflammatory processes[10]. The etiological factor is subclinical intrauterine infection and inflammation in more than half of preterm cases[11]. A complete blood count contains important parameters indicating inflammatory events. In particular, platelet and neutrophil counts increase, and lymphocyte counts decrease[12]. The platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) are correlated with the prognosis of systemic inflammatory diseases and particularly useful in inflammatory[13-15]. The use of complete blood count parameters has been investigated in the field of preterm birth[9,16,17]. Recently, a systematic review and meta-analysis[8] confirmed that the NLR could be a useful biomarker for the prediction of sPTB. Previous studies[14,16,17] have shown the possible role of complete blood count parameters in the assessment of sPTB, yet few studies[2,8] have investigated on the first trimester of pregnancy.

Therefore, the purpose of this study was to assess peripheral complete blood count during

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the first trimester of pregnancy in women with spontaneous preterm birth compared with age-matched controls who are women with healthy pregnancies.

Patients and Methods

A total number of 350 pregnant women, 175 with sPTB, and 175 age-matched healthy controls who had been diagnosed and vaginal delivery at the Department of Obstetrics and Gynecology of Foshan Fosun Chancheng Hospital between January 2019 and December 2019 were included in this cross-sectional case-control study. The Ethics Committee of Foshan Fosun Chancheng Hospital (ID: FFCH-MEC-2020-029) approved the study protocol. As all cases were routinely and retrospectively collected and datasets were fully anonymized prior to analysis, and the data collection was registered with the audit department, informed consent, written or verbal, from all participants approval were not required. The Academic Board of the Hospital approved of our team to access the data used in our research.

Spontaneous preterm birth was defined as the presence of at least two regular uterine contractions every 10 minutes associated with cervical changes that required admission to the hospital between 28 0/7 weeks and 36 6/7 weeks. Gestational age was calculated according to the date of last menstrual period and was confirmed by an early first-trimester ultrasonography. The patients with multiple gestations, gestational diabetes mellitus, preeclampsia, systemic diseases, malignancies, acute or chronic inflammatory diseases, previous history of preterm delivery and hematopoietic system disorders, were excluded. The patients who were on any medication and with any symptoms of acute infection (pain, fever or vaginal discharge) were also excluded from the study. The healthy control group comprised women who met the entry criteria between 37 and 41 weeks, without any history of complications throughout the pregnancy.

The maternal age, gravidity, parity, birth week, birth weight, and results of complete blood count in maternal serum at first trimester between 8 0/7 weeks and 13 6/7 weeks of gestation were recorded from medical records. Samples of peripheral venous blood were drawn from the antecubital vein at the obstetric clinic and studies at the laboratory within 1-3 hours. Laboratory parameters (including complete blood count) of all the participants were recorded. Blood samples were taken into standardized tubes containing dipotassium ethylenedinitro tetraacetic acid (EDTA) for complete blood count using a Coulter LH 780 device (Beckman Coulter, Brea, CA, USA). When more than one serum sample was available, the sample closest to 10 gestation weeks was recorded for statistical analysis. The PLR was calculated as the number of platelets divided by the lymphocyte count, NLR was calculated by dividing the neutrophil count by the lymphocyte count, and lymphocyte-monocyte ratio (LMR) was calculated as the number of lymphocyte count divided by the monocyte count, all of which were obtained from the same blood samples.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM Corp., Armonk, NY, USA). Categorical data were presented as frequencies and/or percentages, while continuous data were expressed as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used to assess the normality of the distribution of continuous variables. The *t*-test and χ^2 analyses were used to analyze continuous and categorical variables, respectively. A receiver-operator curve (ROC) was used to evaluate cut-off point and diagnostic characteristics (sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio) and area under the curve. A p-value < 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of this investigation of all participants were given in Table I. There was a significant difference observed in gestational age at delivery (35.31±1.77 *vs.* 39.39±0.96, p=0.001) and birthweight (2,442.78±525.16 *vs.* 3,329.54±399.31, p=0.001) between the two groups. The maternal age, nulliparity and newborn sex were not significantly different between the two groups.

The blood parameter outcomes of the two groups were also given in Table I. White blood count (WBC) (9.74±2.18 *vs.* 7.50±1.56, p=0.001), platelet (267.28±60.90 *vs.* 252.58±48.34, p=0.022), lymphocyte (2.55±0.59 *vs.* 1.73±0.54, p=0.001), and monocyte (0.54±0.17 *vs.* 0.48±0.15, p=0.002) values were significantly higher in sPTB group

Table I. Characteristics and results of the study groups.

	Preterm delivery (n = 175)	Term delivery (n = 175)	*t*	*p*
Maternal Age (year)	29.76 ± 4.50	30.03 ± 3.06	0.659	0.511
Gestational age at delivery (week)	35.31 ± 1.77	39.39 ± 0.96	26.936	0.001
Nulliparity	91 (52.0%)	89 (50.9%)	0.046	0.915
Birthweight (gram)	2,442.78 ± 525.16	3,329.54 ± 399.31	17.762	0.001
Male sex	88 (50.3%)	91 (52.0%)	0.103	0.831
Hemoglobin (g/L)	122.56 ± 11.23	122.44 ± 9.67	0.094	0.925
WBC (*10^9/L)	9.74 ± 2.18	7.50 ± 1.56	10.199	0.001
Platelet (*10^9/L)	267.28 ± 60.90	252.58 ± 48.34	2.303	0.022
Neutrophil (*10^9/L)	6.08 ± 1.80	5.82 ± 1.74	1.254	0.211
Lymphocyte (*10^9/L)	2.55 ± 0.59	1.73 ± 0.54	0.318	0.001
Monocyte (*10^9/L)	0.54 ± 0.17	0.48 ± 0.15	3.061	0.002
PLR	109.01 ± 30.88	157.91 ± 53.10	9.709	0.001
NLR	2.47 ± 0.83	3.68 ± 1.60	8.204	0.001
LMR	5.24 ± 2.42	3.92 ± 1.93	5.204	0.001

LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; WBC, white blood cell count.

than healthy control group. PLR, NLR and LMR were also significantly different between the two groups. PLR (109.01±30.88 *vs.* 157.91±53.10, p=0.001) and NLR (2.47±0.83 *vs.* 3.68±1.60, p=0.001) were all lower, but LMR (5.24±2.42 *vs.* 3.92±1.93, p=0.001) was higher in the sPTB. No significant difference was observed for hemoglobin and neutrophil values between the groups.

We also analyzed the ROC to compare the diagnostic usefulness of parameters. ROC analysis suggested that lymphocyte had the highest area under the curve among the parameters of WBC (0.812, 95%CI 0.764-0.860), platelet (0.572, 0.507-0.637), lymphocyte (0.853, 0.810-0.895), monocyte (0.597, 0.533-0.661), PLR (0.803, 0.754-0.852), NLR (0.746, 0.690-0.802), and LMR (0.738, 0.681-0.795) in predicting sPTB. The marker of lymphocyte can accurately predict sPTB at a cutoff value of 2.10, with sensitivity and specificity of 79.2% and 75.8%, positive and negative prediction value of 76.7% and 78.5%, and positive and negative likelihood ratio value of 3.28 and 0.27, respectively (Table II, Figure 1).

Discussion

In this study, we investigated the diagnostic ability of the first trimester of pregnancy complete blood count tests to predict spontaneous preterm birth. At gestational age of 8-13 weeks, the mean values of WBC, platelet, lymphocyte, monocyte, and LMR were significantly higher, and PLR and NLR were significantly lower in sPTB group as compared with healthy controls. Another major finding is that lymphocyte, WBC, and PLR in the first trimester of pregnancy had the greatest predictive value for sPTB.

Preterm birth is an obstetric condition that complicates 5-9% of pregnancies[2]. The prevention and prediction of preterm birth remain a challenging issue. Because of serious problems, early diagnosis and appropriate management is very important to prevent poor outcomes. It is well accepted that infection and inflammation are the highly significant risk factors for preterm delivery[11,18]. Complete blood count and its derived parameters, including NLR and PLR, have been recognized as inflammatory markers for low-grade inflammatory diseases in recent years[13,15,19]. The complete blood count throughout a gestation has been theorized to be a possible predictor of preterm birth.

In a retrospective study, Isik et al[20] reported that platelet indices in the third trimester are cost-effective, widely available, and useful predictive markers for preterm labor. A study of Gezer et al[21] showed that patients delivered at preterm had significantly higher serum levels of leukocyte, neutrophil and PLR and significantly lower levels of lymphocyte count between 34 and 37 weeks of gestation. In a retrospective study of 92 patients who were diagnosed with threatened preterm labor, Tolunay and Elci[22] found that hemogram parameters, including white blood cell count, absolute lymphocyte cell count, absolute neutrophil cell count, red cell distribution width, and neutrophil to lymphocyte ratio, at 24-34 gestational weeks could predict the time of birth.

Complete blood count can be obtained from an inexpensive, simple, well-accessible, and easily

Table II. Prognostic values of optimum cut-off for first trimester parameters in predicting spontaneous preterm delivery.

	AUC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	Cutoff value
WBC	0.812 (0.764-0.860)	71.8 (63.8-78.7)	77.2 (69.5-83.5)	75.9 (69.5-83.5)	73.2 (65.5-79.8)	3.15 (2.30-4.30)	0.37 (0.28-0.47)	> 8.55*10^9/L
Platelet	0.572 (0.507-0.637)	62.4 (54.1-70.1)	53.7 (45.4-61.8)	57.4 (49.4-65.1)	58.8 (50.1-67.1)	1.35 (1.09-1.67)	0.70 (0.56-0.87)	> 248.5*10^9/L
Lymphocyte	0.853 (0.810-0.895)	79.2 (71.6-85.2)	75.8 (68.0-82.3)	76.7 (67.0-82.9)	78.5 (70.7-84.7)	3.28 (2.44-4.41)	0.27 (0.20-0.38)	> 2.10*10^9/L
Monocyte	0.597 (0.533-0.661)	26.9 (20.1-34.8)	87.2 (80.6-92.0)	67.8 (54.2-79.0)	54.4 (47.9-60.8)	2.11 (1.28-3.46)	0.84 (0.76-0.93)	> 0.65*10^9/L
PLR	0.803 (0.754-0.852)	85.2 (78.3-90.3)	62.4 (54.1-70.1)	69.4 (62.1-75.9)	80.9 (72.3-87.4)	2.27 (1.83-2.82)	0.24 (0.16-0.35)	< 132.44
NLR	0.746 (0.690-0.802)	87.3 (80.6-92.0)	56.4 (48.0-64.4)	66.7 (59.5-73.1)	81.6 (72.4-88.3)	2.00 (1.65-2.42)	0.23 (0.15-0.35)	< 3.30
LMR	0.738 (0.681-795)	81.9 (74.6-87.5)	61.1 (52.7-68.8)	67.8 (60.4-74.4)	77.1 (68.3-84.1)	2.10 (1.70-2.61)	0.30 (0.21-0.42)	> 3.82

CI, confidence interval; LMR, lymphocyte-monocyte ratio; +LR, positive likelihood ratio; -LR, negative likelihood ratio; NLR, neutrophil-lymphocyte ratio; NPV, negative predictive value; PLR, platelet-lymphocyte ratio; PPV, positive predictive value; WBC, white blood cell count.

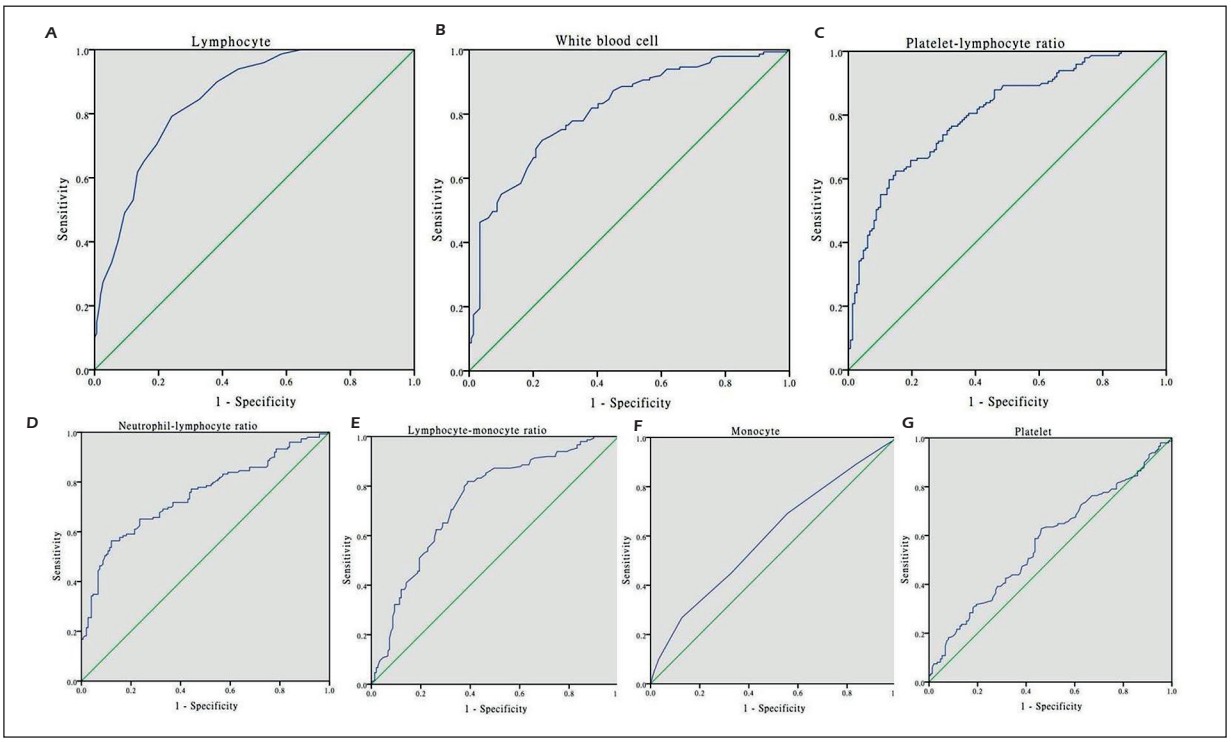

Figure 1. Receiver-operator curve analysis of **(A)** lymphocyte, **(B)** white blood cell, **(C)** platelet-lymphocyte ratio, **(D)** neutrophil-lymphocyte ratio, **(E)** lymphocyte-monocyte ratio, **(F)** monocyte, and **(G)** platelet for first trimester in the prediction of spontaneous preterm birth.

available laboratory test in many clinical settings. Previous studies have reported the predicting value of complete blood count, but most of them are focused on the second and third trimesters. In a prospective observational study[9], authors found that a higher LMR in the second trimester was associated with a decreased gestational age at delivery. Ma et al[16] also showed that, at gestational age of 20-30 weeks, the combined marker of NLR, hemoglobin, and platelet distribution width could better predict spontaneous preterm delivery. In a prospective controlled study, Daglar et al[17] demonstrated that LMR was significantly increased in pregnant women with preterm birth and threatened preterm labor more than in healthy subjects.

Few existing studies[23,24] evaluated the association between complete blood count during the first trimester and sPTB. In a single center retrospective study, Ekin et al[23] found that platelet count was significantly higher in the first trimester in women destined to develop preterm premature rupture of membranes, which is consistent with our findings. In another retrospective study, Moroz et al[24] also found NLR in the first trimester was significantly elevated in preterm birth patients when compared to term patients.

In this study, we found that WBC, platelet lymphocyte, monocyte, and LMR were higher, and PLR and NLR were lower in sPTB group in the first trimester. Moreover, we also found lymphocyte, WBC, PLR, NLR, LMR, monocyte, and platelet in the first trimester of pregnancy had predictive value for sPTB. The greatest predictive is lymphocyte, and the ROC reached 0.853. It may help early decisions and allow for the administration to identification of women at the highest risk for preterm birth, which could significantly reduce neonatal and maternal morbidity and mortality. Of course, serial peripheral complete blood count measurements throughout gestation should be evaluated in a prospective birth cohort to attempt to better capture the value as a predictor of spontaneous preterm delivery.

Limitations

Limitations of the present study include retrospective design and single-center location, making it unable to generalize to other populations of women. Moreover, we excluded many obstetric and medical situations with potential to influence the studied parameters, which affected the study conclusion.

Conclusions

In this study, we have shown that lymphocyte values during the first trimester of pregnancy were the most predictive spontaneous preterm delivery. Therefore, in the management of the higher risk of preterm delivery, lymphocyte could be used as a more cost-effective method during the first trimester of pregnancy because it does not require any kit. Further studies are needed to determine whether these parameters can be used to predict if a pregnant woman who was on any medication and with any symptoms of acute infection can be included.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

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Informed Consent

As all cases were routinely and retrospectively collected and datasets were fully anonymized prior to analysis, and the data collection was registered with the audit department, informed consent, written or verbal, from all participants approval were not required.

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