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Association between gestational age at delivery and lymphocyte-monocyte ratio in the routine second trimester complete blood cell count

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Background: We aimed to determine whether routine second trimester complete blood cell (CBC) count parameters, including neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR), could predict obstetric outcomes.
Methods: We included singleton pregnancies for which the 50-g oral glucose tolerance test and CBC were routinely performed between 24 and 28 weeks of gestation in our outpatient clinic from January 2015 to December 2017. The subjects were divided into three groups according to their pregnancy outcomes as follows: group 1, spontaneous preterm births, including preterm labor and preterm premature rupture of membranes; group 2, indicated preterm birth due to maternal, fetal, or placental causes (hypertensive disorder, fetal growth restriction, or placental abruption); and group 3, term deliveries, regardless of the indication of delivery. We compared the CBC parameters using a bivariate correlation test.
Results: The study included 356 pregnancies. Twenty-eight subjects were in group 1, 20 in group 2, and 308 in group 3. There were no significant differences between the three groups in neutrophil, monocyte, lymphocyte, and platelet counts. Although there was no significant difference in NLR, LMR, and PLR between the three groups, LMR showed a negative correlation with gestational age at delivery ($r = -0.126$, $p = 0.016$).
Conclusion: We found that a higher LMR in the second trimester was associated with decreased gestational age at delivery. CBC parameters in the second trimester of pregnancy could be used to predict adverse obstetric outcomes.

Keywords: Blood cell count; Lymphocyte-monocyte ratio; Neutrophil-lymphocyte ratio; Preterm

Introduction

Preterm birth is a major cause of long-term morbidity and mortality in infants. Therefore, there have been many studies about the etiology and pathophysiology of preterm birth and methods for its early prediction and prevention.

Complete blood cell (CBC) count parameters including neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR) have been used for the detection of malignant diseases [1,2] or the prediction of prognosis in various diseases [3-5]. Meanwhile, in pregnant women, CBC for verifying hematocrit or hemoglobin is usually checked between 24–28 weeks during gestational diabetes mellitus (GDM) screening. Although CBC is not a good screening tool for pregnancy-associated diseases, it can provide valuable physiological information regarding pregnant women [6]. Labor is also

an inflammatory response; therefore, CBC parameters could be used to predict preterm birth [7]. Recently, several studies have reported the association between CBC parameters and adverse obstetric outcomes such as GDM, hypertensive disorder, and preterm birth [8-12]. However, they were retrospective [8], case-control studies [10], or included cases after threatened preterm labor had developed [12]. This study aimed to determine whether routine second trimester CBC parameters during GDM screening could predict obstetric outcomes in pregnancy.

Materials and methods

This prospective observational study was conducted at the Kyungpook National University Hospital, Daegu, Korea, between January 2015 and December 2017 and approved by the Institutional Review Board of the Kyungpook National University Chilgok Hospital (IRB No: 2019-12-009).

We included singleton pregnancies for which the 50-g oral glucose tolerance test (OGTT) and CBC count with differential count were routinely performed in the outpatient clinic between 24 and 28 weeks of gestation. Pregnant women were divided into three groups according to the pregnancy outcomes as follows: group 1 included preterm births due to preterm labor, preterm premature rupture of membranes (PPROM), or incompetent internal os of the cervix (IIOC). Preterm births were defined as births between $20^{0/7}$ and $37^{0/7}$ weeks of gestation. Preterm labor was defined as regular uterine contractions with a cervical change occurring at least three times every 10 minutes before $37^{0/7}$ weeks of gestation. PPROM was defined as membrane rupture occurring spontaneously without labor before $37^{0/7}$ weeks of gestation. IIOC was defined as painless cervical dilatation in the second trimester. Group 2 included preterm births due to maternal, fetal, or placental causes (hypertensive disorders including gestational hypertension and preeclampsia (PE), fetal growth restriction which was defined as the estimated fetal weight being suspected in the bottom 10 percentile at the corresponding gestational age, or placental abruption). Group 3 included term deliveries regardless of the indication of delivery. The exclusion criteria were as follows: multifetal gestation, gravidas who had diseases that could influence maternal CBC count levels, including malignant diseases, rheumatoid disorders, chronic hypertension, renal diseases, pregestational diabetes mellitus, or hematologic diseases. We compared CBC parameters between the three groups and evaluated the association of gestational age at delivery with CBC parameters using a bivariate correlation test. Statistical analyses were performed using the IBM SPSS version 19.0 (IBM Corp., Armonk, NY, USA) software. The results were considered statistically significant when the *p*-value was below 0.05.

Results

During the study period, 50-g OGTT and CBC were performed on 577 singleton pregnant women in our outpatient clinic. Among them, 221 did not deliver their babies at our institution. Consequently, we were able to include 356 singleton pregnancies. Forty-eight (13.5%) women delivered their babies before $37^{0/7}$ weeks of gestation, with 28 (7.9%) being in group 1 and 20 (5.6%) in group 2.

The maternal and neonatal outcomes are shown in Table 1. There were no significant differences in maternal characteristics except for maternal weight at delivery and the rate of cesarean section. However, neonatal characteristics, including gestational age at delivery, birth weight, and Apgar score, differed between the three groups. The comparison of CBC parameters between the three groups is shown in Table 2. No significant differences were found in neutrophil, monocyte, lymphocyte, and platelet counts. Moreover, there was no significant difference in other CBC parameters including NLR, LMR, and PLR between the three groups. However, we observed a negative correlation between LMR and gestational age at delivery ($r = -0.126$, $p = 0.016$) (Fig. 1).

Discussion

In this study, we compared the CBC parameters that were prospectively obtained from routine GDM screening between 24 and 28 weeks of gestation according to the obstetric outcomes. Although there was no significant difference in CBC parameters according to the obstetric outcomes defined as spontaneous preterm birth, indicated preterm birth, or term delivery, we found that LMR was negatively correlated with gestational age at delivery. Clinically, there seemed to be a positive correlation between NLR and gestational age at delivery ($p = 0.074$). These results suggested that an increased lymphocyte count in the second trimester could be associated with a lower gestational age at delivery.

Recently, several inflammatory markers including CBC parameters have been identified as predictive factors in various diseases [13,14]. Since labor is also an inflammatory response, the role of inflammatory markers, such as C-reactive protein or CBC parameters, has been assessed in term and preterm labor [7,12,15]. The analysis of inflammatory markers in addition to CBC parameters could be more informative; however, we aimed to obtain information about obstetric outcomes from routine CBC sampling without an additional laboratory test.

Notably, there have been studies regarding the detection of ac-

Table 1. Comparison of maternal and neonatal characteristics in three groups

Variable	Group 1 (n = 28)	Group 2 (n = 20)	Group 3 (n = 308)	*p*-value
Age (yr)	32.1 ± 4.2	34.1 ± 4.6	33.1 ± 4.8	0.328[a]
GAL (wk)	25.2 ± 1.6	25.6 ± 1.4	25.0 ± 1.4	0.200[a]
GAD (wk)	33.7 ± 2.8	34.2 ± 3.5	38.5 ± 1.1	< 0.001[a]
Nulliparity	16 (57.1)	8 (40.0)	180 (58.4)	0.271[b]
Pre-pregnancy weight (kg)	54.6 ± 2.1	58.5 ± 3.1	56.6 ± 0.6	0.498[a]
Maternal weight at delivery (kg)	63.0 ± 1.9	70.3 ± 3.0	68.9 ± 0.6	0.023[a]
Cesarean section	15 (53.6)	20 (100)	178 (57.8)	0.001[b]
Male sex	20 (71.4)	14 (70.0)	160 (51.9)	0.050[b]
Birth weight (kg)	2.23 ± 0.60	2.01 ± 0.86	3.15 ± 0.39	< 0.001[a]
AS < 4 at 1 min	2 (7.1)	5 (25.0)	4 (1.3)	< 0.001[b]
AS < 7 at 5 min	2 (7.1)	2 (10.0)	3 (1.0)	0.002[b]

Values are presented as mean ± standard deviation or number (%).
GAL, gestational age at laboratory test; GAD, gestational age at delivery; AS, Apgar score.
p-values are derived from [a]analysis of variance test and [b]Pearson chi-square test; the type 1 error was set to 0.05.

Table 2. Comparison of complete blood cell count parameters in three groups

Parameter	Group 1 (n = 28)	Group 2 (n = 20)	Group 3 (n = 308)	*p*-value[a]
WBC ($\times 10^3/mm^3$)	9.17 ± 2.10	9.47 ± 1.55	9.52 ± 2.12	0.697
PLT ($\times 10^3/mm^3$)	237.75 ± 51.48	210.50 ± 53.66	237.74 ± 58.53	0.124
Neutrophil ($\times 10^3/mm^3$)	6.85 ± 1.75	7.31 ± 1.64	7.30 ± 2.10	0.493
Lymphocyte ($\times 10^3/mm^3$)	1,71 ± 0.44	1.58 ± 0.43	1.70 ± 0.70	0.707
Monocyte ($\times 10^3/mm^3$)	0.41 ± 0.15	0.40 ± 0.13	0.44 ± 0.46	0.854
NLR	4.17 ± 1.22	5.12 ± 2.28	4.59 ± 1.66	0.150
LMR	4.45 ± 1.52	4.55 ± 2.50	4.42 ± 2.40	0.968
PLR	140 ± 38	155 ± 54	149 ± 49	0.533

Values are presented as mean ± standard deviation.
WBC, white blood cell count; PLT, platelet count; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio.
[a] *p*-value are derived from analysis of variance test; the type 1 error was set to 0.05.

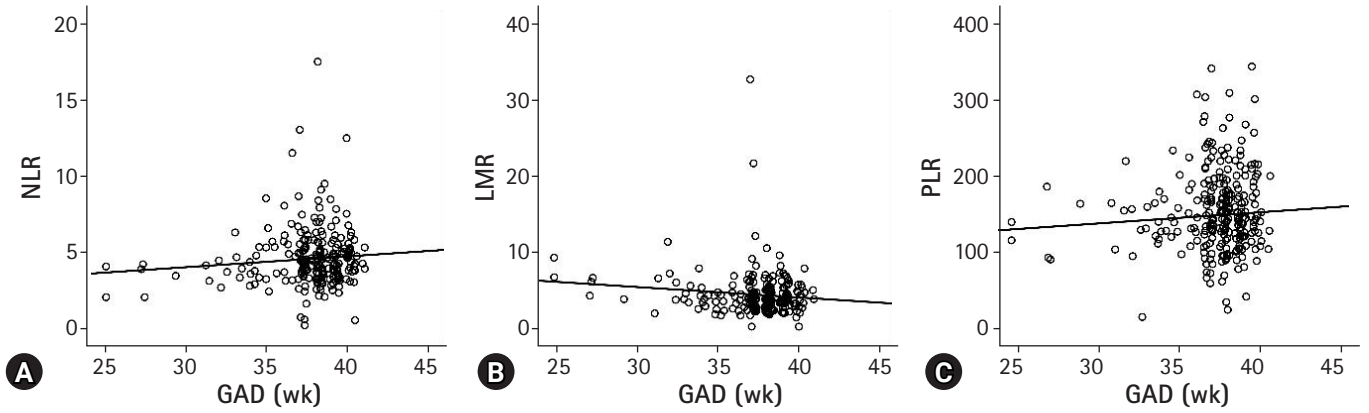

Fig. 1. Correlations of gestational age at delivery with complete blood cell count parameters. (A) Neutrophil-to-lymphocyte ratio (NLR) does not show a statistically significant correlation with GAD ($r = 0.095$, $p = 0.074$). (B) Lymphocyte-to-monocyte ratio (LMR) shows a negative correlation with GAD ($r = -0.126$, $p = 0.016$). (C) Platelet-to-lymphocyte ratio (PLR) does not show a statistically significant correlation with gestational age at delivery ($r = 0.063$, $p = 0.216$). GAD, gestational age at delivery.

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tual preterm birth in women with threatened preterm labor using CBC parameters [12,16]. Daglar et al. [12] reported that LMR was significantly increased in pregnant women with threatened preterm labor who delivered prematurely than in similar women whose pregnancies continued to term. They also showed a negative correlation between gestational age at delivery and LMR in preterm births. Additionally, Gezer et al. [16] reported that a high NLR value at the time of admission was an independent risk factor for preterm birth in women with threatened preterm labor between 34 and 37 weeks of gestation. We assumed that there had been an increase in neutrophil or lymphocyte counts in the group with true labor. However, these two studies evaluated the role of CBC parameters in women with threatened preterm labor. Unlike these two studies, we prospectively collected maternal CBC parameters during routine 50-g OGTT and enrolled our patients before they had developed threatened preterm labor.

The differential count of CBC is known to change during normal pregnancy [6,17]. Li et al. [6] established a reference interval for CBC parameters during normal pregnancy in Chinese women showing a decrease in lymphocyte count contrary to the changes in white blood cell count due to the increase in neutrophil count. They suggested the increased neutrophil count was in response to the physiologic stress of pregnancy or impaired neutrophil apoptosis [6,17]. However, they did not comment about the changes in lymphocyte count that decreased during the first and second trimesters of pregnancy and increased in the third trimester. Moreover, they recorded a definitive increase in monocytes during pregnancy [17]. The absence of lymphocyte count reduction or the monocyte count increase observed in a normal pregnancy could imply a decrease in gestational age at delivery.

LMR has been proposed as a surrogate marker for inflammation and has prognostic value too [18-20]. Further, an abnormal monocyte or lymphocyte count has been shown to have an adverse effect on the prognosis of various diseases [21,22]. In the field of obstetrics, there have been several studies regarding the association between CBC parameters and obstetric complications in addition to the ability of CBC to predict preterm birth. Sargin et al. [8] investigated whether there were differences in the NLR and PLR between glucose intolerance (e.g., GDM patients), impaired glucose tolerance, GDM-screening-positive, and control groups. They concluded that NLR or PLR could not be used for the screening of GDM. However, they also observed that the lymphocyte and neutrophil counts were higher in the glucose-intolerance group compared to those in the control group. However, Mertoglu and Gunay [9] showed differences in NLR and PLR between glucose-intolerance and normal control groups in non-pregnant adults and they suggested that these markers could be used to predict pre-diabetes and diabetes mellitus. Previous studies have suggested the efficacy of CBC parameters as a prognostic factor in women with PE [10,11]. Gogoi et al. [10] showed that NLR, PLR, red cell distribution width, and mean platelet volume were higher in women with PE in a case-control study. Oylumlu et al. [11] suggested that NLR could be used as a marker for risk stratification in PE patients. We performed subgroup analysis that included indicated preterm birth and term deliveries (group 2 vs. group 3, data not shown), but there was no significant difference between the two groups. Unlike our study, studies by Gogoi et al. [10] and Oylumlu et al. [11] were retrospective or case-control studies that included patients diagnosed as having GDM or PE. Moreover, group 3 in our study group included pregnancies complicated with PE beyond 37 weeks of gestation.

This study has several limitations that need to be taken into consideration while interpreting the results. Although we observed a negative correlation between LMR and gestational age at delivery, we could not clarify the mechanism underlying this phenomenon. Moreover, our study sample was relatively small, and we did not consider the obstetric complications in pregnancies beyond 37 complete weeks of gestation. However, we think that the most important prognostic factor is the gestational age at delivery. Additionally, we evaluated CBC parameters before the onset of obstetric complications unlike previous studies. Further studies to evaluate CBC parameters considering the changes of those parameters between the second and third trimesters would provide predictive information about perinatal morbidity related to the lower gestational age at delivery or preterm birth.

Although there was no significant difference in CBC parameters according to obstetric outcomes, we found that a higher LMR in the second trimester was associated with a decreased gestational age at delivery. CBC parameters in the second trimester of pregnancy could be used to predict adverse pregnancy outcomes.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: WJS, HHC, GOC; Data duration: JMK, HMK, MJK; Investigation: HHC, JMK, MJK, HMK, GOC; Writing-original draft: HHC; Writing-review & editing: JMK, HMK, MJK, WJS, GOC.

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