Original Article

Evaluate the correlations of maternal systemic ınflammatory markers such as neutrophil to lymphocyte ratio and platelet to lymphocyte ratio with gestation age

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ABSTRACT

Objective: In this study, we aim to study the correlation between the maternal systemic inflammatory markers such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) including complete blood count (CBC) variables with gestation age, at the labor of our patients.

Materials and Methods: This retrospective study was performed with 1127 patients and their infants. We used the maternal CBC variables analyzed within the last day before active labor. We analyzed the statistical differences between the NLR, PLR, and other CBC variables in terms of gestational age.

Results: There was no statistically significant difference between the gestational age with NLR and PLR values, ($P = 0.414$ and $P = 0.341$, respectively). When we compare the NLR and PLR values in normal spontaneous vaginal delivery (NSVD) group, no statistically significant difference was found ($P = 0.250$; $P = 0.995$, respectively). In correlation analyses, no statistically significant correlation was detected between NLR and PLR with a birth weight of the infant and gestational age ($P = 0.132$ and $P = 0.344$, respectively). A linear, negative, weak correlation, and statistically significant correlation was detected between white blood cell count (WBC) with the infant's birth weight and gestational week ($P < 0.01$ and $P = 0.024$, respectively).

Conclusions: Inflammation plays an important role especially at the beginning of the labor. In our study, we showed no correlation of the NLR and PLR with a gestational week or infant's birth weight at labor. Also, in our research, the NLR and PLR values did not differ statistically among the four groups in terms of the gestational age of delivery with the highest values in the preterm birth (<37 weeks) groups ($P = 0.414$, $P = 0.341$, retrospectively).

Key words: Gestation week; inflammation; neutrophil to lymphocyte ratio; platelet to lymphocyte ratio.

Introduction

The signals and mechanisms that synchronize the timing of human parturition remain a mystery, and a better understanding of these processes is essential to avert adverse pregnancy outcomes.[1] The length of human gestation is related to many signals and mechanisms, such as fetal organs and systems maturation, production of hormones, and other soluble mediators (including alarmins) that promote inflammation and immune cascades, which trigger the parturition. So, it is considered that inflammation also plays a role in the timing of human parturition.[2-4]

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It appears that the presence of activated platelets in circulation rapidly and transiently induces systemic leukocyte rolling, giving the animal a head start on inflammation.[5] Platelets and leukocytes are the main cellular elements for inflammation pathophysiology. The total white blood cell count (WBC) is a composite variable and a relatively crude marker of inflammation. The ratio of subtypes of blood cells like neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), which can be easily measured, are suggested as strong predictors of inflammation.[6,7]

Inflammatory markers have been suggested previously to be potential predictors of birth weight[8] and in another study predictors of preterm deliveries.[9] Therefore, in this study, we aim to study the correlation between the maternal systemic inflammatory markers such as NLR, PLR, and complete blood count (CBC) variables with the gestational age at the labor of our patients.

Materials and Methods

It is a retrospective study that has been conducted with 1430 patients who delivered in a hospital, between August 2016 and December 2018. The Ethics Committee approved this study. The study included healthy mothers between ages 18 and 43 years bearing a single fetus, taking no medications except iron and multivitamin preparations, and without any systemic comorbidities. Patients smoking a cigarette, having a fever of unknown origin, or any signs and symptoms of active infection (urinary infection, chorioamnionitis) or severe anemia, were not included in the study. We also excluded twin pregnancies, hypertension, diabetes, hypothyroidism, hyperthyroidism, and patients with any chronic inflammatory diseases like ulcerative colitis, Crohn's disease, rheumatoid arthritis. Because of this exclusion criteria, in total, we excluded 303 patients, and the study continued with 1127 patients. The gestational week was determined based on the first day of the last menstrual period or the first-trimester ultrasonographic measurement of the crown-rump length. The clinical data including the age, gravida, parity, gestation week at delivery, the gender of the baby, type of delivery, and the laboratory data such as CBC were recorded for each participant. Keçirören Education and Research Hospital Ethics, Committee number: 2012-KAEK-15/1735, Approval date:12.09.2018.

The study group was further divided into four groups according to the gestational age. The first group was preterm delivery defined as birth between 20+0 and 37+0 weeks of gestation, the second group was the early term, which was defined as 37+0 and 38+6 weeks of gestation, the third group was the full term, which is defined as 39+0 to 40+6 weeks of gestation, and the fourth group was the late term, which was 41+0 to 41+6 weeks of gestation. Postterm was ≥42+0 weeks of gestation (≥294 days from the first day of the last menstrual period and ≥14 days from the estimated day of delivery).[10-12] There was no patient at that interval. The clinical and laboratory data were compared between groups.

We used the maternal CBC variables analyzed within the last day before active labor. CBC variables including hemoglobin (HBG), white blood cell (WBC), lymphocyte, neutrophil, platelet (PLT), platelet distribution width (PDW), red cell distribution width (RDW), and mean platelet volume (MPV) were measured by an automatic hematology analyzer at the central laboratory of the hospital. The NLR and PLR calculated quickly from the CBC was an assessable index, which had already been used as a prognostic tool in several clinical conditions.[13] NLR and PLR values were calculated by dividing the absolute neutrophil, and platelet counts, respectively, by the total lymphocyte counts.

Statistical analyses were conducted with Statistical Package for the Social Sciences (SPSS) Statistics (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk NY) and MS-Excel 2007 software. The variables such as age, parity, gestational week of delivery, type of delivery, the sex of the baby, and birth weight were expressed in number and percentage. Shapiro-Wilk test was used to analyze normally distributed data including values of each variable. Comprehensive data related to these variables were represented in the mean, standard deviation, and median. The one-way analysis of variance (ANOVA) was applied to determine the differences between the means of independent groups for homogeneous groups with the normal distribution. All non-normally distributed data were compared using the Kruskal–Wallis test. The Tukey honestly significant difference (HSD) test was used when homogeneous distribution and Tamhane's T2 test were used when non-homogeneous distribution at post-hoc analysis. The box-plot graphs were drawn for the NLR and PLR variables. Correlation analyses were made to determine the relationship between the gestational and the weight of the baby with the variables of the CBC. The Spearman rho coefficients were also calculated. A P value <0.05 was considered statistically significant.

Results

In this study, a total of 1127 mothers and their babies were enrolled. The patients were divided into four groups based on their gestational week at delivery. First group was preterm delivery (<37 weeks), second group was early term (37+0 to

38+6 weeks), third group was full term (39+0 to 40+6 weeks), and fourth group was late term (41 + 0 to 41 + 6 weeks), which were consisted of 3.72% (n = 42), 56.61% (n = 638), 38.33% (n = 432), and 1.33% (n = 15) patients, respectively. Of the study participants, 66.01% (n = 744) underwent cesarean section (CS), whereas 33.98% (n = 383) had normal spontaneous vaginal delivery (NSVD). In addition, the gender of the infants were 52.4% (n = 591) males and 47.6% (n = 536) females.

The mean age of the participants was 29 ± 4.34 years, whereas the mean weight of the infants was 3294 ± 428 g. The demographic data of the groups such as age, parity, and birth weight were comparable between groups in Table 1. Also, the results related to the comparisons of CBC variables between the groups were summarized in Table 1. As seen in the table, admission levels of HGB, WBC, PLT, lymphocyte, neutrophil, platelets distribution width (PDW), red blood cell distribution width (RDW), mean platelet volume (MPV), NLR, and PLR values were compared among the groups. In terms of WBC values, there was a significant difference between the preterm group, with the early term and term group, respectively ($P = 0.015$; $P = 0.042$), no difference was observed among the other groups.

Lymphocyte and neutrophil percentages values were statistically different between groups in the Kruskal–Wallis test, but in the posthoc analysis, between groups, there was no statistical significance in the binary comparison.

The mean values of the NLR in study groups were assessed as follows: 3.79 ± 2.24 in the group of preterm delivery, 3.09 ± 1.99 in the group of early term, 3.27 ± 1.94 in the group of term, 3.67 ± 1.49 in the group of late term [Table 1, Figure 1]. Also, the mean values of the PLR in study groups were assessed as follows: 116 ± 44 in the group of preterm delivery, 113 ± 45 in the group of early term, 112 ± 56 in the group of term, 107 ± 30 in the group of late term [Table 2, Figure 2]. Furthermore, there was no statistically significant difference between the birth of gestation week with NLR and PLR values, ($P = 0.414$ and $P = 0.341$, respectively).

The mean maternal hemoglobin (HGB) values included in the early term and term pregnancy groups were found to be 11.8 ± 1.5 and 12.2 ± 1.5, respectively, showing a significant difference between the delivery groups in the posthoc analysis (p = 0.001), there was no statistically significant difference between the other groups. In PLT, PDW, and RDW values, there was no statistically significant difference between groups. Furthermore, there was no statistically significant difference in binary comparison between groups for MPV values. When we compared the NLR and PLR values

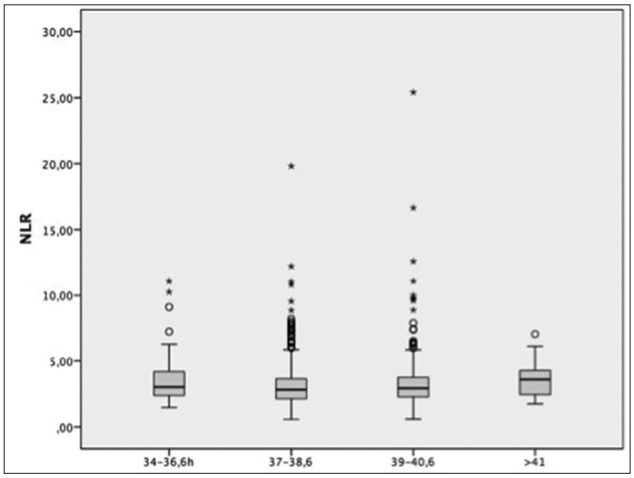

Figure 1: Boxplot of NLR values according to gestational week

Table 1: Comparisons of the variables in term of gestational age

Parameters	Preterm (<37 w) (*n*=42)	Early term (37-38.6 w) (*n*=638)	Term (39-40.6 w) (*n*=432)	Late term (41-41.6 w) (*n*=15)	*P*
Maternal age (mean) yrs	28.5±4.7	30.2±4.47	28.7±3.9	30.0±3.79	**<0.005****
Parity (median), range	2 (1-3)	3 (1-4)	3 (1-4)	2 (1-3)	**<0.001****
Birth weigh	2744 gr±408	3263 gr±427	3393 gr±388	3308 gr±234	**<0.05****
Hemoglobin (g/dL)	12.2±1.6	11.8±1.5	12.2±1.5	12.6±1.2	**<0.001***
WBC ($mm^3 \times 10^3$)	11740±3311	9944±2540	10137±2624	10452±2433	**<0.005***
Lymphocyte (%)	22.3±7.2	24.7±7.9	23.8±7,2	21.3±5,8	**0.033***
Neutrophil (%)	69.5±8.7	66.3±9.2	67,1±9.5	70.4±8.4	**0.022***
Platelet ($mm^3 x 10^3/L$)	265±77	249±74	241±73	229±75	**0.123***
PDW (%)	14.6±2.8	15.1±3.0	14.9±3.16	15.8±3.49	0.545*
RDW (%)	12.5±1.5	13.0±1.9	12.9±1.7	12.4±1.4	0.273*
MPV (%)	8.80±0.85	9.01±0.90	9.09±1.05	9.65±1.33	0.072*
NLR	3.79±2.24	3.09±1.99	3.27±1.94	3.67±1.49	0.414*
PLR	116±44	113±45	112±56	107±30	0.341*

*Kruskal-Wallis test **ANOVA test. $P<0.05$ were considered statistically significant. HBG: hemoglobin ; WBC: white blood cell; PLT: platelet; PDW: platelet distribution width, RDW: red cell distribution width; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet to lymphocyte ratio; ANOVA: analysis of variance

Table 2: Correlation analyses in CBC variables between the birth weight and the gestational age

Parameters	Birth weight		Gestational age
	Spearman rho correlation	*P*	Spearman rho correlation
NLR	-0.045	0.132	0.28
PLR	-0.003	0.909	-0.50
HGB	-0.050	0.092	0.120
RDW	0.128	**<0.01**	0.028
PDW	0.065	**0.030**	0.017
MPV	0.026	0.385	0.096
WBC	-0.100	**<0.01**	-0.415
Lymphocyte (%)	0.029	0.327	-0.033
Neutrophils (%)	-0.065	**0.029**	0.032
PLT	-0.070	**0.018**	-0.100

P<0.05 were considered statistically significant. HBG: hemoglobin; WBC: white blood cell; PLT: platelet; PDW: platelet distribution width, RDW: red cell distribution width; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet to lymphocyte ratio

in the NSVD group, no statistically significant difference was found (p: 0.250 and p: 0.995, respectively). Also in the NSVD group regarding the WBC, lymphocyte (%), neutrophil (%), HGB, RDW, MPV, and PLT values there was no significant difference. Only PDW values were significantly different between early term and term groups (p = 0.044).

In correlation analyses, no statistically significant correlation was detected between NLR and PLR with the birth weight of the infant and gestational week ($P = 0.132$ and $P = 0.344$, respectively). A linear, negative, weak correlation, and statistically significant correlation was detected between WBC with the infant's birth weight and gestational week ($P < 0.01$ and $P = 0.024$, respectively). A linear, negative, weak correlation, and statistically significant correlation was detected between PLT with the infant's birth weight and gestational week ($P = 0.018$ and $P < 0.01$, respectively). A linear, positive, weak correlation, and statistically significant correlation was detected between HGB with the gestational week (p = <0.01) [Table 2].

Discussion

In our study, the main finding is no correlation of the NLR and PLR with a gestational week or infant's birth weight at labor.

Several studies have shown that maternal and maternal-fetal inflammation may trigger premature labor.[14,15] Inflammation plays an important role especially at the beginning of the labor. Because of this, many studies have been designed to establish which mechanisms initiate labor. In our study, the main hypothesis is also this idea.

In the literature, although Akgun *et al*.,[8] showed a negative correlation between the NLR and PLR with gestational week

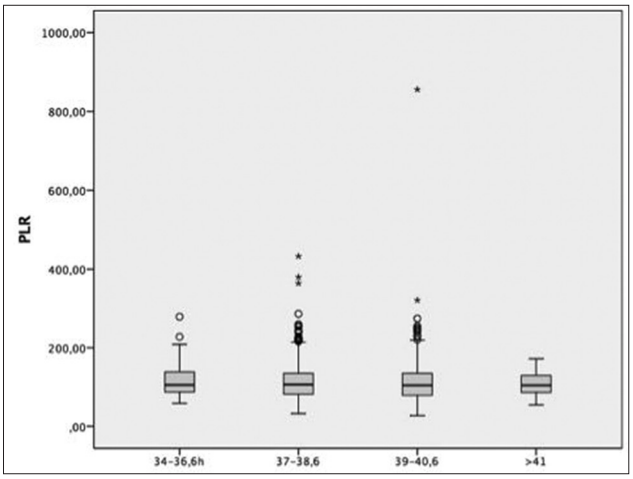

Figure 2: Boxplot of PLR values according to gestational week

and the infant's birth weight, in our study we showed no association of the NLR and PLR with a gestational week or infant's birth weight at labor [Table 2]. Also, in our study the NLR and PLR values did not differ statistically among the four groups in terms of the gestational week of delivery with the highest values in the preterm birth (<37 weeks) groups ($P = 0.414$ and $P = 0.341$, retrospectively) [Table 1].

In the literature, anemia was associated with preterm delivery (Relative Risk [RR]:1.63, 95% CI: 1.33, 2.01).[16] But this study did not confirm this condition. Probably this is because of the low number of patients in the preterm and late-term group. Also, it has been affected by the patients with high socio-economic levels which are followed up at a private hospital.

The RDW blood test measures the amount of red blood cell variation in volume and size. High RDW values may mean you have a nutrient deficiency, anemia or other underlying condition. RDW seems to be a predictor for a wide range of conditions due to systemic factors such as inflammation and oxidative stress that alter erythrocyte hemostasis.[17] In RDW values there were no statistically significant differences between groups in this study. In the course of a healthy pregnancy, RDW values increase, as the gestational week progresses.[18] This knowledge did not support our research (Spearman rho correlation 0.028, $P = 0.352$).

In the literature, PDW which is the measurement of platelet anisocytosis calculated from the distribution of individual platelet volumes and it is an assessment of circulating platelet mass, and it is defined as a marker of coagulation.[19] In the PLT and PDW values, there were no statistically significant differences between groups. MPV is a measure of platelet size that shows platelet function and activation and can be measured by full blood count analyzers as part of a routine

CBC test cycle, with no additional cost.[20] Based on data showing that PDW and MPV values are associated with inflammation, we investigated if any alterations PDW and MPV, during the gestational age. We found no significant difference. Furthermore, there was no statistically significant difference in binary comparison between groups for MPV values.

The first major limitation of our study is, it is a retrospective design. Nonetheless, the second limitation of our study is the unequal distribution of the number of cases among the groups. Although the total number of cases was sufficient for analysis, it was challenging to reveal the statistical differences due to the unequal distribution among the groups. This is one private center study. Only low-risk patients with mid and high socioeconomic levels were involved in this study. We can say this homogenous distribution of the patients is the powerful side of our research.

In conclusion, this retrospective study is one of the few studies in the literature which investigates the correlation of NLR and PLR with the gestational week of labor. Also, to the best of our knowledge, this is the first study using term pregnancy classification.[11-13] Our study suggested that the maternal NLR and PLR are not correlated with the gestation week of birth and weight of the infant.

Disclosure statement

The authors report no declarations of interest.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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