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Evaluation of umbilical cord blood hematological parameters in pregnant women with fetal growth restriction

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ABSTRACT

Objectives: The present study attempted to evaluate the relationship between fetal growth restriction (FGR) and the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) in singleton term pregnancy.

Methods: We carried out this prospective, case-control study at a Training and Research Hospital in Türkiye between May 2021 and January 2023. We utilized ultrasonography to assess singleton pregnancy with FGR between 37-40 weeks of gestation and considered the patients' last menstrual periods (LMD).

Results: We recruited 250 pregnant women in the study and divided them into the FGR (n = 125) and healthy control (n = 125) groups. Our findings revealed no significant difference between the groups by age, body mass index (BMI), stillbirth history, abortion, tobacco use, and regular pregnancy monitoring ($p > 0.05$). Fetal birth weights and hospitalization in the neonatal intensive care unit (NICU) were also similar between the groups. Yet, 1- and 5-minute APGAR scores were significantly lower in the FGR group than in the control group. In addition, compared to the healthy subjects, the FGR group had significantly increased white blood cell, lymphocyte, neutrophil, platelet counts and NLR and PLR values, but mean platelet volume (MPV) remained similar.

Conclusions: In a nutshell, our findings suggested that two noteworthy inflammatory markers, NLR and PLR, are likely to elevate in the presence of FGR.

Keywords: Fetal growth restriction, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), hematologic parameters, cord blood

Fetal growth restriction (FGR) persists to be among the significant causes of morbidity and mortality in both intrauterine and neonatal periods and complicates approximately 4-6% of pregnancies [1]. It is defined as the estimated fetal weight (EFW) of a healthy fetus by chromosomal or karyotyping analysis or the fetal abdominal circumference by ultrasonography below the 10th percentile [2]. Uteroplacental insufficiency, leading to insufficient blood flow along the umbilical cord, may be considered the most prominent cause of FGR, and impaired umbilical blood flow always accompanies the disorder [3, 4].

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Impaired trophoblast invasion explains the early pathophysiology of this failure [5]. Causing the fetus to be deprived of sufficient oxygen and nutrients, this situation results from the deterioration of the transformation of spiral arteries to low-resistance veins [6].

In general, the parameters of the complete blood count e.g., neutrophil and lymphocyte counts, platelet distribution width (PDW), red blood cell distribution width (RDW), and mean platelet volume (MPV) are considered the indicators of the severity and prognosis of many diseases, particularly malignant and infectious ones [7]. It was previously proposed that MPV, platelet-to-lymphocyte (PLR), and red blood cells (RBC) can be used as a simple, inexpensive method to predict early pregnancy loss in obstetric evaluation [8]. In their meta-analysis, Kang *et al*. emphasized that the neutrophil-to-lymphocyte ratio (NLR) can be a useful marker in determining the clinical prediction and severity of preeclampsia [9]. It was also determined that white blood cell counts (WBC) and NLR, PLR, and MPV values may be considered independent parameters to predict gestational diabetes mellitus (GDM) [10]. In this sense, the present study aimed to investigate the role of MPV, PDW, NLR, RDW, plateletcrit (PCT), and PLR values obtained from the cord blood of pregnant women with intrauterine growth retardation in predicting newborn outcomes.

METHODS

Research Design and Sample

After obtaining ethical approval from the Ethics Committee of Kayseri City Hospital (No.: 383 dated 04.29.2021), we carried out this prospective, case-control study at a training and research hospital in Türkiye between May 2021 and January 2023. We recruited 250 pregnant women in the study and divided them into the FGR (n = 125) and healthy control (n = 125) groups. However, we excluded patients below 37 weeks and over 40 weeks pregnant, those with multiple pregnancies, those with concomitant maternal (preeclampsia, diabetes mellitus) or fetal disease (oligohydramnios, fetal anomaly), patients with missing prenatal complete blood count, and those not administered any pregnancy-related tests (Fig. 1). We utilized ultrasonography to assess singleton pregnancy with FGR between 37-40 weeks of gestation and considered the patients' last menstrual periods (LMD). Besides, we adopted the Delphi consensus criteria for the diagnosis of FGR [11, 12].

Measurements

We initially noted down the maternal characteristics of the patients [Age, obstetric history (gestational age, gravida, parity, live births), gestational week ac-

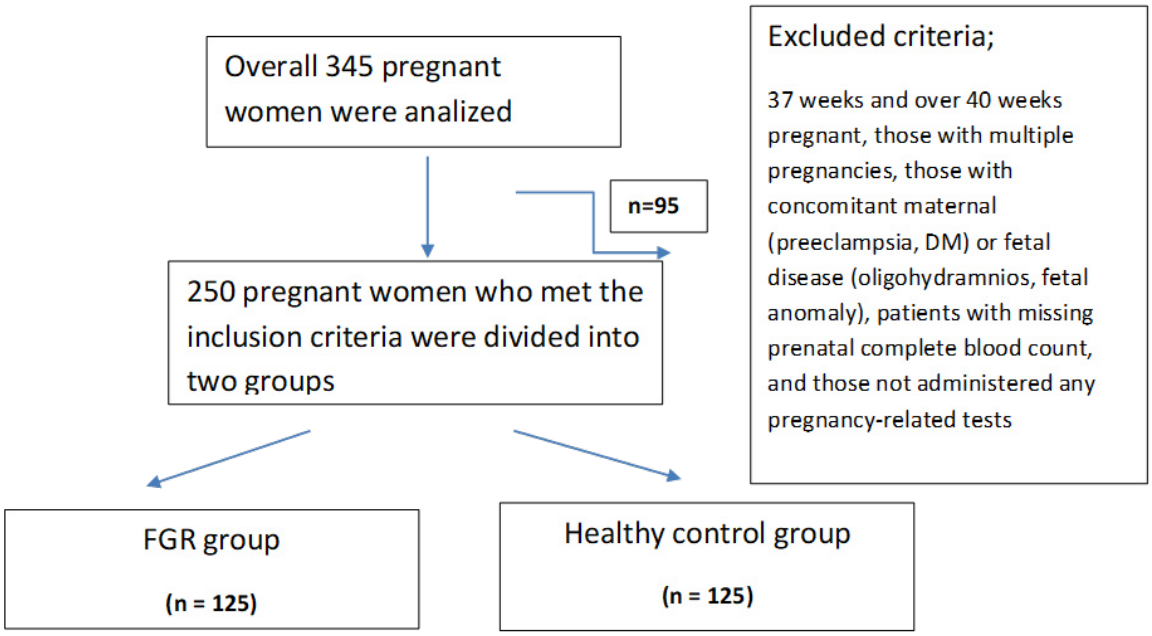

Fig 1. Patient flow chart.

cording to the LMP, tobacco use, regular pregnancy monitoring, type of delivery, birth weight, maternal complications (bleeding, dysuria, etc.), 1- and 5-min. Apgar scores, and hospitalization in the neonatal intensive care unit (NICU)]. Then, we stored about 2 ml of cord blood obtained from each patient at delivery in hemogram tubes with ethylenediaminetetraacetic acid (EDTA) to measure leukocyte, neutrophil, and lymphocyte counts, MPV, PDW, and RDW.

Statistical Analysis

The data are presented descriptively, and we utilized the Kolmogorov-Smirnov test to check whether the data showed a normal distribution. While the normally-distributed data were compared pair-wise using independent samples t-test, we utilized the Mann-Whitney U test to compare non-normally distributed data. The categorical variables were compared using the Chi-square and Fischer's exact tests. We performed all statistical analyses on the SPSS 26.0 program and accepted a p value of < 0.05 as statistically significant.

RESULTS

Our findings showed no significant difference between the FGR and healthy control groups by age ($p = 0.142$), BMI ($p = 0.54$), stillbirth ($p = 0.625$), abortion ($p = 0.56$), tobacco use ($p = 0.92$), and regular pregnancy monitoring ($p = 0.88$). While we found that the control group had significantly higher gravida ($p = 0.01$), parity ($p = 0.003$), gestational week ($p = 0.003$), birth weight ($p = 0.002$), and the number of surviving children ($p = 0.005$) than the FGR group. The number of male newborns was significantly higher ($p < 0.001$), while 1- and 5-minute Apgar scores were significantly lower in the FGR group ($p < 0.001$ for both). (Table 1).

Besides, NLR and PLR values ($p = 0.008$ and 0.001) and neutrophil and platelet counts ($p = 0.002$ and 0.001) were found to be significantly increased in the FGR group. Nevertheless, leukocyte ($p = 0.95$) and lymphocyte counts ($p = 0.08$), MPV ($p = 0.33$), PCT ($p = 0.88$), and PDW ($p = 0.64$) values were similar between the groups (Table 2).

Table 1. Patients' demographic characteristics and obstetric findings

	FGR group	Control group	*p* value
Age (years)	27.5 ± 6.3	26.3 ± 5.1	0.142
BMI (kg/m^2)	24.5 ± 4.5	25.6 ± 4.3	0.540
Gravida	2.2 ± 1.5	2.4 ± 1.3	**0.010**
Gestational week	37.1 ± 2.1	39.6 ± 1.1	**0.003**
Parity	0.9 ± 1.2	1.2 ± 1.3	**0.003**
Surviving children	0.8 ± 1.2	1.1 ± 1.1	**0.005**
Previous stillbirth	1.6 ± 1.1	2.1 ± 1.0	0.625
Previous abortion	0.9 ± 1.0	1.2 ± 1.1	0.560
Tobacco use	13 (10.4%)	12 (9.6%)	0.920
Regular pregnancy monitoring	110 (88%)	108 (86.4%)	0.880
Birth weight (g)	2,350 ± 450	3,240 ± 400	**0.002**
1-min. Apgar score	6.5 ± 0.7	8.9 ± 0.6	**< 0.001**
5-min. Apgar score	8.1 ± 0.6	9.2 ± 0.7	**< 0.001**
Gender			**< 0.001**
Female	45 (36%)	65 (52%)	
Male	80 (64%)	60 (48%)	
NICU admission (days)	11 (8.8%)	7 (5.6%)	0.260

Data are shown as mean ± standard deviation or n (%). FGR = Fetal growth restriction, BMI = Body mass index, NICU = Neonatal intensive care unit

Table 2. Patients' hematological and biochemical findings

	FGR group	Control group	*p* value
Leukocyte (×10^3 /mm^3)	34.7 ± 1.5	36.2 ± 1.3	0.950
Neutrophil (×10^3/mm^3)	7.5± 0.9	8.4 ± 1.1	**0.002**
Lymphocyte (×10^3/mm^3)	1.9 ± 0.6	1.8 ± 0.7	0.080
Platelet (×10^3/mm^3)	197 ± 51	278 ± 43	**0.001**
NLR	3.94 ± 1.1	4.66 ± 0.9	**0.008**
PLR	103.6 ±1.7	154.4 ± 1.2	**0.001**
MPV	9.2 ± 0.8	9 ± 0.9	0.330
PCT	0.35 ± 0.04	0.34 ± 0.03	0.880
PDW	11.7 ± 2.1	11.5 ± 1.9	0.640

Data are shown as mean±standard deviation. FGR = Fetal growth restriction, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, MPV = mean platelet volume, PCT = plateletcrit, PDW = platelet distribution width

DISCUSSION

Described as the inability of the fetus to reach its growth potential, FGR may be the most accurate description of the fetus [13]. Although a plethora of research on the subject adopted different criteria to describe it, there is still no consensus on a standard definition of FGR. Yet it is defined as a birth weight below 3%, 5%, or 10% or 2SD of mean gestational age or a birth weight of 2500 g or less in gestational age of 37 weeks and above [14]. In this study, we included those whose birth weight was 3% lower than the gestational age.

Overlapping with previous findings, our findings showed significantly lower gravida and parity and higher male fetuses among the patients with fetal distress. Pregnancy is likely to bring multiple changes in the hematological system. For example, hematological findings of the pregnant may yield an increase in blood volume by 30-40%, erythrocyte, and plasma levels by 30%, and reticulocyte erythropoietin levels by 2-3 times. While the absolute lymphocyte count is within normal limits, platelet half-life is shortened, and MPV and PDW values are increased [15]. It was previously reported that whole blood parameters can be adopted to predict specific diseases during pregnancy and reveal their prognosis. In this regard, many studies previously attempted to predict preeclampsia and its severity through some whole blood parameters [16-19]. It was documented that first and second-trimester NLR values may be considered a helpful marker to predict preeclampsia [20, 21]. Accordingly, NLR and PLR are often calculated to be higher among pregnant women with preeclampsia [16-22]. Moreover, the previous research showed that increased second-trimester NLR, PLR, and MPV values may be independent risk factors for GDM [23]. Moreover, it is known that pregnant women with hyperemesis gravidarum are likely to have elevated PLR and NLR values secondary to metabolic changes and inflammation [24]. The relevant research also concluded high MPV and RBC values and low PLR values among those with early pregnancy loss and miscarriage threat in the first trimester [8]. The literature also hosts studies reporting significantly higher NLR and PLR values in ectopic pregnancy cases with tubal abortion [25]. In contrast, Bullens *et al*. could not conclude any relationship between maternal hemoglobin levels and fetal distress and neonatal outcomes [26]. In our study, MPV values and hematocrit and lymphocyte counts were significantly lower, while neutrophil counts and PDW, NLR, and PLR values were significantly higher among patients with FGR. Meconium aspiration and infections, in particular, may have caused fetal and maternal systemic inflammatory response, leading to elevated neutrophil counts and NLR, PDW, and PLR values.

To our knowledge, this is the first study to explore the relationship between umbilical cord NLR and PLR values and FGR. The previous research that traced maternal inflammation with NLR indicated that inflammation causes disorganization of the placental vascular bed. In these studies, the mother's existing

inflammatory response was found to be related to low birth weight in the ongoing process [15-27].

Limitations

It should be noted that the present study is not free of a few limitations. The small sample size may be considered a significant limitation of our findings. In addition, the study did not include the findings of small-for-gestational-age (SGA) infants since we preferred to exclude the effects of SGA on inflammatory processes.

CONCLUSION

In our study, our findings suggested that NLR and PLR, two notable inflammatory markers, would likely be elevated in the presence of FGR. It can be used daily as screening biomarkers in the detection of FGR. These results should be supported by studies using larger samples.

Authors' Contribution

Study Conception: MA, ŞÇ; Study Design: MA, MBD; Supervision: MA, CRC, MBD; Funding: ŞÇ, MBD; Materials: CRC, MBD; Data Collection and/or Processing: MA, CRC; Statistical Analysis and/or Data Interpretation: MA, CRC; Literature Review MA, ŞÇ, CRC, MBD; Manuscript Preparation: MA, CRC, and Critical Review: MA, ŞÇ, CRC, MBD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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