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The significance of Systemic Immune Inflammation Index (SII) and Systemic Inflammation Response Index (SIRI) in fetuses with fetal growth restriction

ABSTRACT

Objectives: Our aim was to investigate the significance of parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune inflammatory index (SII), and systemic inflammatory response index (SIRI) in late fetal growth restriction (FGR) cases.

Methods: After applying the exclusion criteria, 70 late FGR cases and 70 healthy pregnant cases matched by maternal age and week of gestation were included in the study. In addition to demographic characteristics, neonatal outcomes, and peripheral blood parameters, we examined whether there were differences between groups in NLR, PLR, MLR, SII, and SIRI scores. We also investigated the association between systemic inflammatory markers and neonatal intensive care unit (NICU) admission. P-values < 0.05 were interpreted as statistically significant.

Results: The FGR group had higher leukocyte, neutrophil, NLR, and SII values than the control group (p=0.019; p=0.007; p=0.011; p=0.005, respectively). For the diagnosis of FGR, an optimal cut-off value of ⩾4.7946 was found for NLR (with 54.7% sensitivity and 85.7% specificity) and a value of ⩾918.15 for SII (with 67.1% sensitivity and 60% specificity). PLR and SII were higher in the FGR group with NICU admission than in the FGR group without NICU admission (p=0.024; p=0.012, respectively).

Conclusion: SII, in addition to other clinical data, may contribute to both the diagnosis of FGR and the prediction of NICU admission in FGR cases. This finding is supported by randomized controlled trials with large series of prospective subgroup analyses.

Keywords: FGR, PLR, SII, SIRI

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Fetal growth restriction (FGR) is characterized by the inability of the fetus to reach its genetic growth potential and is a significant cause of perinatal complications and prematurity (1-3). It is associated with long-term complications such as metabolic syndrome, cardiovascular disease, and diabetes, as well as short-term complications like low birth weight, prematurity, neonatal exit, and a high number of neonates in the intensive care unit (1-4). The pathogenesis is multifactorial, involving genetic factors, maternal inflammation, immune system abnormalities, infections, oxidative stress, defects in spiral artery remodeling, and endocrine causes (4-11).

It is well-known that inflammation plays a major role in tissue homeostasis (12). To prevent tissue rejection at the beginning of pregnancy, there is a physiological rearrangement of the innate immune system and cytokine network (6,7,11,12). Changes occur in the inflammatory and infectious balance, especially in the activity of T cells, with the goal of maintaining the fetomaternal relationship in balance. However, if excessive aggregation in the placenta and intervillous space is triggered by various mechanisms during this activation, diseases such as preeclampsia and FGR may result, which are referred to as chronic inflammatory placental diseases (13-16).

Many inflammatory and anti-inflammatory markers have been studied in maternal circulation and cord blood in cases diagnosed with FGR (8-10,15,16,17,18). Cytokines such as interleukin 1β (IL-1β), IL-6, and tumor necrosis factor α (TNF-α), interferon-γ (INF-γ), IL-8, IL-10, as well as neutrophils, white blood cells, myeloperoxidase, and many molecules such as C-reactive protein (CRP) and neutrophil/monocyte-derived substances were the

main subjects of these studies (8-10,16,17,18). However, the results regarding the relationship between inflammation and FGR in the literature are contradictory and inconclusive.

Parameters such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), systemic immune inflammation index (SII), and systemic inflammatory response index (SIRI), which determine systemic inflammation, are novel markers that have prognostic value in evaluating the immune system. Alterations in these inflammatory markers, which can be easily obtained from simple peripheral blood parameters, have been found to be associated with diseases such as malignancies, cardiovascular disease, inflammatory and autoimmune diseases, and some obstetric pathologies (11,19,20-24). This situation is likely related to the active role of cells such as neutrophils and platelets in the immune system, which play a role in the activation of inflammatory cells and the release of cytokines and autoantibodies.

In accordance with this information, we aimed to investigate the significance of parameters such as NLR, PLR, MLR, the systemic immune inflammatory index (SII), and the systemic inflammatory response index (SIRI) in cases diagnosed with late FGR.

METHODS

This retrospective case-control study was conducted in the Department of Perinatology at the Ministry of Health, Etlik City Hospital in Ankara. The protocol of this study was approved by the hospital's Ethics Committee (Date: 01.11.2023, Decision number: AEŞH-EK 1-2023-667). The study was conducted in accordance with the universal ethical principles of the Declaration of Helsinki.

Ninety-seven single pregnant women diagnosed with FGR at 32 to 41 weeks of gestation who presented to the perinatology clinic between April 2023 and September 2023 participated in the study. Study participants with chronic systemic diseases, gestational diabetes, multiple gestations, congenital anatomic and genetic anomalies, hematologic diseases, and clinical and laboratory findings of systemic infection or with additional pregnancy complications such as preterm delivery, chorioamnionitis, or gestational hypertension were excluded from the study. Cases whose data could not be accessed, who delivered at another hospital, or who had additional pregnancy complications were also excluded. Thus, 70 pregnant women diagnosed with FGR and 70 randomly selected healthy individuals matched for gestational week and maternal age were included in our study. All cases were diagnosed with late FGR (n≥32 weeks' gestation at diagnosis), and the diagnosis of FGR was made using the following criteria based on the Delphi consensus (2):

EFW <3rd percentile or EFW <10th percentile with Doppler evidence of placental dysfunction [Umbilical artery Doppler (UA) pulsatility index (PI) >95th percentile, absence of umbilical artery end-diastolic flow (UAEDF), or reverse-UAEDF and/or cerebroplacental ratio (CPR) <5th percentile].

Data such as maternal age, gravidity, parity, abortion history, BMI, maternal peripheral blood parameters, week of gestation when blood parameters were studied, amniotic fluid values, estimated fetal weight, week of birth, birth weight, mode of delivery, Apgar scores, and neonatal intensive care unit admission rate were taken from the records.

Blood parameters studied were based on hemogram data of routinely examined peripheral maternal blood in the period of 1 month before delivery in the 3rd trimester. This process includes the period when no drugs are administered and labor does not begin. Parameters such as maternal hemoglobin (Hb)(g/dl), leukocytes (10^3/μL), lymphocytes (10^3/μL), neutrophils (10^3/μL), platelets (10^3/μL), NLR: absolute neutrophil count (ANC)/absolute lymphocyte count (ALC); PLR: platelets/lymphocytes, MLR: absolute monocyte count/ALC; SII: neutrophil count × platelet count/lymphocyte count, SIRI: monocyte count × neutrophil count/lymphocyte count were obtained and recorded from the hemogram values, and the indices were calculated according to the formulas.

Statistical analysis was performed using the Statistical Package for Social Sciences version 24.0 software (IBM Corp., Armonk, NY, USA). The distribution of variables was determined using the Kolmogorov-Smirnov method. Numerical variables were expressed as standard deviation and median (min-max). The independent-samples t-test and Mann-Whitney U test were used to analyze parametric and nonparametric variables. Receiver operating characteristic (ROC) analysis was performed to determine the predictive value of the indices. Statistical significance was interpreted when the p-value was less than 0.05.

RESULTS

The demographic and clinical characteristics and perinatal outcomes of the study groups are presented in Table 1. There were no statistically significant differences in maternal age, gravidity, parity, or abortion rates (p=0.251; p=0.619; p=0.180; p=0.728, respectively). BMI, amniotic fluid volume, gestational age at birth, birth weight, and Apgar scores at 1 minute and 5 minutes were lower in the FGR group than in the control group (p<0.001 for each). There were no differences between the groups in primary C-section rate and fetal heart rate tracing (p=0.699; p=0.196, respectively). NICU admission was higher in the FGR group than in the control group (p=0.002).

A comparison of complete blood parameters and systemic inflammatory indices between the groups is shown in Table 2. Statistically, no differences were found in the values of lymphocytes, monocytes, platelets, hemoglobin, PLR, MLR, or SIRI between the two groups (p=0.375; p=0.574; p=0.327; p=0.314; p=0.216; p=0.732; p=0.299, respectively). Higher leukocyte, neutrophil, NLR, and SII levels were observed in the FGR group than in the control group (p=0.019; p=0.007; p=0.011; p=0.005, respectively).

The ROC curve analysis of systemic inflammatory indices for predicting the diagnosis of FGR is shown in Table 3. The optimal cut-off value of ≥4.7946 for NLR (with 54.7% sensitivity and 85.7% specificity) and a value of ≥918.15 for SII (with 67.1% sensitivity and 60% specificity) were found for the diagnosis of FGR.

As shown in Table 4, PLR and SII were higher in the FGR group with NICU admission than in the FGR group without NICU admission (p=0.024; p=0.012, respectively). There were no differences in NLR, MLR, and SIRI values between these subgroups (p=0.149; p=0.082; p=0.111, respectively).

Table 1. Demographic, clinical characteristics and perinatal outcomes of study groups

	FGR (n=70)	Control group (n=70)	P
Maternal Age, years	26.5 [17.0-41.0]	26.0 [19.0-41.0]	0.251
Gravidity (number)	2.0 [1.0-7.0]	2.0 [1.0-8.0]	0.619
Parity (number)	0.0 [0.0-3.0]	1.0 [0.0-4.0]	0.180
Abortion (number)	0.0 [0.0-4.0]	0.0 [0.0-3.0]	0.728
BMI (kg/m^2)	26.0 [19.0-40.0]	30.0 [22.0-49.0]	**p<0.001**
Amniotic fluid volume SDVP (mm)	41.5 [5.0-100.0]	55.0 [35.0-70.0]	**p<0.001**
Gestational age at delivery (week)	37.4 [33.0-40.5]	39. [34.0-41.0]	**p<0.001**
Birth weight (gr)	2302.58±407.34	3321.29±479.91	**p<0.001**
Apgar score at 1 minute	8.5 [2.0-9.0]	9.0 [6.0-9.0]	**p<0.001**
Apgar score at 5 minutes	10.0 [4.0-10.0]	10.0 [7.0-10.0]	**p<0.001**
Primary C/S rate	19 (27.1%)	17 (24.3%)	0.699
Non-reassure fetal heart rate tracing	11 (15.7%)	6 (8.6%)	0.196
NICU admission	27 (38.6%)	11 (15.7%)	**0.002**

Data are expressed as mean ± standard deviation, median (minimum-maximum), or number where appropriate. p-Value < 0.05 indicates significant difference. FGR: Fetal growth restriction, BMI: Body mass index, EFW: Estimated fetal weight, SDVP: Single deepest vertical pocket, C/S: Cesarean section, NICU: Neonatal İntensive care unit

Table 2. A comparison of complete blood parameters and systemic inflammatory indices between the groups

	FGR group (n=70)	Control group (n=70)	P
Leukocytes (10^3/μL)	10.92±3.01	9.83±2.35	**0.019**
Lymphocytes (10^3/μL)	1.86±0.61	1.94±0.53	0.375
Neutrophils (10^3/μL)	8.23±2.72	7.17±1.76	**0.007**
Monocytes (10^3/μL)	0.68±0.23	0.70±0.22	0.574
PLT (10^3/μL)	249.5 [96.0-455.0]	233.0 [137.0-465.0]	0.327
Hb (g/dL)	11.83±1.39	11.60±1.31	0.314
NLR	4.13 [1.7-20.5]	3.73 [1.87-13.2]	**0.011**
PLR	129.1 [48.4-333.3]	128.9 [66.4-266.0]	0.216
MLR	0.36 [0.0-0.9]	0.37 [0.2-0.8]	0.732
SII (×10^9/L)	1076.7 [259.2-4710.0]	849.1 [383.5-2504.2]	**0.005**
SIRI (×10^9/L)	2.58 [0.4-10.4]	2.58 [0.9-5.7]	0.299

Data are expressed as mean ± standard deviation, median (minimum-maximum), 5. p-Value < 0.05 indicates significant difference. FGR: Fetal growth restriction, PLT: Platelets, Hb: Hemoglobin, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelets-Lymphocyte Ratio, MLR: Monocytes-Lymphocyte Ratio, SII: Systemic immune-inflammation index, SIRI: systemic inflammatory response index.

Table 3. ROC curve analysis of systemic inflammatory indices in predicting the diagnosis of FGR

Variables	Area	Std. Error	p	Sensitivity	Specificity	Cut-off
NLR	0.624	0.048	**0.011**	54.7%	85.7%	≥4.7946
PLR	0.561	0.049	0.216	-	-	-
MLR	0.517	0.049	0.723	-	-	-
SII	0.638	0.047	**0.005**	67.1%	60,0%	≥918.15
SIRI	0.551	0.049	0.299	-	-	-

FGR: Fetal growth restriction, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelets-Lymphocyte Ratio, MLR: Monocytes-Lymphocyte Ratio, SII: Systemic immune-inflammation index, SIRI: systemic inflammatory response index

Table 4. Comparison of the parameters by NICU Status in FGR group

	NICU admission	Absent NICU admission	p
NLR	4.55 [2.1-20.5]	3.97 [1.7-7.3]	0.149
PLR	137.9 [77.2-333.3]	120.7 [48.4-291.6]	**0.024**
MLR	0.40 [0.1-0.9]	0.31 [0.2-0.7]	0.082
SII (×109/L)	1215.0 [474.0-4710.0]	972.1 [259.2-2271.1]	**0.012**
SIRI (×109/L)	2.77 [0.4-10.4]	2.46 [0.7-6.9]	0.111

Data are expressed as mean ± standard deviation, median (minimum-maximum), or number where appropriate. p-Value < 0.05 indicates significant difference. FGR: Fetal growth restriction, NICU: Neonatal İntensive care unit, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelets-Lymphocyte Ratio, MLR: Monocytes-Lymphocyte Ratio, SII: Systemic immune-inflammation index, SIRI: systemic inflammatory response index

DISCUSSION

In this retrospective case-control study, we observed higher leukocyte, neutrophil, NLR, and SII values in the FGR group compared to the control group. However, no statistically significant differences were found in lymphocyte, monocyte, platelet, hemoglobin, PLR, MLR, and SIRI values between the two groups. Our findings also indicate that an optimal cut-off value of ⩾4.7946 for NLR (with 54.7% sensitivity and 85.7% specificity) and of ⩾918.15 for SII (with 67.1% sensitivity and 60% specificity) can be used for the diagnosis of FGR. Additionally, PLR and SII were higher in the FGR group with NICU admission compared to the FGR group without NICU admission.

Many etiological factors have been identified in the pathogenesis of FGR, encompassing various pathways (5-18). Among the most significant are inflammation, inadequate angiogenesis, and oxidative stress. Although adaptive changes in the physiological cellular and humoral immune systems occur during pregnancy, severe inflammation, where homeostatic balance cannot be maintained, plays a role in diseases such as FGR (11-14). Numerous inflammatory and proinflammatory markers, including monocytes, neutrophils, MPO, IL6, IL1, IL10, have been studied in FGR. In addition to elevated leukocyte and monocyte levels, neutrophil/monocyte-derived substances have been found to be increased in FGR (16-18). In situations triggered by hypoxia, B cell-mediated nuclear factor kappa light chain enhancer (NFkB) causes the release of proinflammatory cytokines due to increased oxidative stress and decreased antioxidant molecules (9). In a study conducted on rats by He et al., it was shown that the levels of TNF alpha, IL-1b, IL-6, and MPA were higher in rats with tumors than in the control group (17).

Cornish et al., (25) in their review evaluating adverse pregnancy outcomes in chronic inflammatory placental disease, noted that villous inflammation of unknown etiology, chronic histiocytic intervillitis, and massive perivillous fibrin deposition occur as a result of activation by maternal immune cells, and this situation can lead to intervillous disruption and interrupt gas and nutrient transport to the fetus. They suggest that this situation may lead to FGR and intrauterine fetal death. In addition to inflammation in the placenta, the effects of systemic inflammation on FGR have also been studied (10,11). While levels of interferon alpha, lymphocytes, TNF alpha, and IL8 were high in both cord blood and maternal blood in FGR cases, low levels of the anti-inflammatory IL10 were found (10,11). These factors are thought to act through vasoconstriction in the fetomaternal circulation to cause placental dysfunction. The concentration of calprotectin, a molecule released by active neutrophils whose concentration increases during inflammatory and apoptotic processes, has been studied in the cord blood of patients with FGR (26). However, no significant difference was found between the groups. In the study by Kara et al. that examined the importance of Hs-CRP, sialic acid, and IL-6 in preeclampsia and FGR, no statistically significant difference was found between them and healthy individuals, although there were differences in inflammatory markers in FGR and preeclampsia (18). A review of the literature shows that the relationship between inflammation and FGR is still not clear.

The importance of peripheral blood cell parameters in the diagnosis and prognosis of inflammatory diseases has been the focus of recent studies (11,19-24). Neutrophils, platelets, lymphocytes, monocytes, and indices such as SIRI, SII, PLR, NLR, and MLR, including various combinations thereof, have been studied in cancers, inflammatory and immune diseases, and many inflammation-related obstetric pathologies. Studies have shown that SII and SIRI are more effective indicators of local inflammation and systemic immune responses (27). Based on the studies in the literature showing the association between FGR and inflammation, in FGR cases, we investigated the peripheral blood parameters SIRI, SII, NLR, MLR, PLR values, which are markers of systemic inflammation in recent studies. In their study examining inflammation levels to determine the risk of preterm birth, Hruboru et al. (21) found that white blood cell and monocyte levels were high and lymphocyte, platelet, and hemoglobin levels were low in the preterm group. While PLR, MLR, and NLR were higher in the preterm group, no difference was found in SIRI and SII indices between the groups. Akgün et al. (22) investigated whether there was a correlation between birth weight and NLR and PLR and found that there was a negative correlation between maternal PLR and NLR and birth weeks and weights. Similarly, Can et al. (23) found that NLR and PLR levels were higher in the cord blood of neonates with fetal malnutrition than in healthy term infants. In another study examining adverse perinatal outcomes and systemic inflammatory index and blood parameters in PPROM cases, Tanacan and colleagues (24) found that SII and platelet levels were higher in cases with adverse outcomes. They showed that SII and platelet levels were better predictors of unfavorable outcomes compared with NLR. In our study, although we did not demonstrate a significant difference between SIRI values in FGR cases, leukocyte, neutrophil, NLR, and SII values were higher in FGR cases. Furthermore, we determined cutoff values at which NLR and SII values could additionally contribute to the prediction of FGR disease. The fact that NLR and SII values were higher in fetuses with NICU admission in FGR cases

suggests that these parameters, in addition to other clinical data, may be helpful in predicting the severity of this condition.

This study has some drawbacks, although to our knowledge it is the first study in the literature to examine the association between FGR and SIRI. Limitations of our study include the fact that it is a retrospective study, includes only a small number of cases, and addresses only late FGR cases.

In conclusion, our study highlights the association between peripheral blood parameters, particularly the new systemic inflammatory markers, and the diagnosis and prognosis of late FGR. The significance of these parameters, which can be readily obtained in peripheral maternal blood, will be further clarified with the support of prospective randomized trials that include more comprehensive neonatal data, including blood gas analysis with two subgroups as early and late FGR.

Ethics Committee Approval: The protocol of this study was approved by the Etlik City Hospital Ethics Committee (Date: 01.11.2023, Decision number: AEŞH-EK 1-2023-667).

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