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Is the use of first-trimester systemic inflammation markers predictive in fetal growth restriction?

Birinci trimester sistemik inflamasyon belirteçleri fetal büyüme kısıtlılığı prediksiyonunda kullanılabilir mi?

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ABSTRACT

Aim: To predict fetal growth restriction (FGR) and its effect on prognosis according to changes in systemic inflammation indexes, such as the neutrophil-to-lymphocyte ratio (NLR), the systemic immune-inflammation index (SII), and the systemic inflammation response index (SIRI).

Materials and Methods: The study group consisted of 200 women with singleton pregnancies diagnosed with FGR, and the control group comprised 280 obstetrically and demographically matched healthy pregnant women. The NLR, SII, and SIRI were compared between the groups according to the first-trimester complete blood count results.

Results: When the groups were compared in terms of systemic inflammation indexes, the NLR, SII, and SIRI were found to be statistically lower in the FGR group ($p<0.001$, $p=0.01$, and $p=0.03$, respectively).

Conclusion: We found that the NLR, SII, and SIRI were lower in pregnant women with FGR compared to the control group, according to the first-trimester complete blood count analysis.

Keywords: fetal growth restriction, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index

ÖZ

Amaç: Çalışmanın amacı, nötrofil-lenfosit oranı (NLR), sistemik immün-inflamasyon indeksi (SII) ve sistemik inflamasyon yanıt indeksi (SIRI) gibi sistemik inflamasyon indekslerindeki değişikliklerin, fetal büyüme kısıtlılığı (FGR) ve prognoz üzerindeki etkisini tahmin etmekti.

Gereç ve Yöntemler: Çalışma grubu FGR tanısı almış tekil gebeliği olan 200 kadın, kontrol grubu ise obstetrik ve demografik olarak eşleştirilmiş 280 sağlıklı gebe kadın oluşturmaktaydı. Birinci trimester tam kan sayımı sonuçlarına göre gruplar arasında NLR, SII ve SIRI karşılaştırıldı.

Bulgular: Gruplar sistemik inflamasyon indeksleri açısından karşılaştırıldığında, NLR, SII ve SIRI'nin FGR grubunda istatistiksel olarak daha düşük olduğu bulundu (sırasıyla $p<0,001$, $p=0,01$ ve $p=0,03$).

Sonuç: FGR'li gebelerde birinci trimester tam kan sayımı analizine göre NLR, SII ve SIRI'nin kontrol grubuna göre daha düşük bulunmuştur.

Anahtar Kelimeler: fetal büyüme kısıtlılığı, nötrofil-lenfosit oranı, sistemik immün-inflamasyon indeksi, sistemik inflamasyon yanıt indeksi

INTRODUCTION

Fetal growth restriction (FGR) is defined as an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile according to the week of gestation in a standard population growth curve on an ultrasonographic examination (1). Since FGR is associated with high perinatal morbidity and mortality, early diagnosis and management are extremely important (2). The etiology of FGR includes maternal, fetal, and placental causes (1). Although the use of some ultrasound and biomarkers is recommended to predict pregnant women with FGR in the first trimester, there is not yet any marker that has been introduced into clinical use (3).

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The first stage of pregnancy begins with the attachment of the embryo to the endometrium, known as implantation. Increased maternal immune responses during implantation may lead to failure in blastocyst-endometrium interactions (4). In the first trimester, neutrophils are located in an area that is involved in the physiological decidual implant reaction, shows high resistance to apoptosis, and expresses fibro/angiogenic factors (5). Immune cells play a fundamental role in successful pregnancy outcomes, and changes in the immune response may lead to complicated pregnancies (6). Disruptions in the implantation process can cause the abnormal development of the spiral arteries, which may lead to preeclampsia or FGR (7).

Systemic inflammation is a response of the immune system to stimuli such as infection, stress, and physical trauma (8). Inflammation markers can be used to detect the presence of systemic inflammation and as early markers of potential disease (9). Among the systemic inflammation markers that can be simply calculated using a complete blood count analysis are the neutrophil-to-lymphocyte ratio (NLR), the systemic immune-inflammation index (SII), and the systemic inflammation response index (SIRI).

The primary aim of this study was to predict FGR based on changes in systemic inflammation markers, namely the NLR, SII, and SIRI. Second, we divided the FGR cases into two groups according to the onset of disease [early-onset (EO) FGR and late-onset (LO) FGR] and compared the systemic inflammation markers between these subgroups (10). Lastly, we compared the first-trimester systemic inflammation markers of the FGR cases with and without neonatal intensive care unit (NICU) requirements.

MATERIAL AND METHOD

This retrospective, case-control study was conducted at Perinatology Department of Ankara City Hospital from January 1, 2020, through September 1, 2022, in accordance with the tenets of the Declaration of Helsinki. The study was approved by the Medical Research Ethics Unit of the hospital (E2-22-2848).

Study design

Since this study aimed to evaluate pregnant women with a diagnosis of FGR, we screened all births with FGR that occurred during the study period and included cases eligible for the study. Incomplete digital or paper records, incomplete laboratory analyses, and underage patients were excluded from the study. Cases presenting with infection or inflammatory disease were excluded from the study in order to avoid confounding factors. In addition, pregnant women who received corticosteroid and anti-inflammatory treatment, which could affect their inflammation scores during the sampling period, were excluded from the study. Other exclusion criteria were the presence of multiple pregnancies, imminent abortion, autoimmune diseases, diabetes, chronic hypertension, or major anomalies and chromosomal abnormalities in the fetus during the following gestational weeks.

The gestational ages of all pregnant women were confirmed by first-trimester ultrasound recordings. The ultrasonographic evaluation was performed using a Voluson E8 (GE Medical Systems, Solingen, NRW, Germany) device with a GE C2-9-D probe. Fetal biometry was evaluated by measuring the biparietal diameter, head circumference, abdominal circumference, and femur length. EFW and percentile values were calculated according to the formula of Hadlock et al. (11). The diagnosis of FGR was made using the guidelines of the American College of Obstetricians and Gynecologists (1). The cases diagnosed with FGR before 32 weeks of gestation were included in the EO-FGR group, and those diagnosed after 32 weeks were included in the LO-FGR group.

The sample consisted of a total of 480 participants, including 200 women with singleton pregnancies diagnosed with FGR and 280 obstetrically and demographically matched healthy pregnant women. Systemic inflammation markers were calculated using the results of complete blood count analysis performed during the first trimester as follows (12):

NLR = absolute neutrophil count / absolute lymphocyte count

SII = (absolute neutrophil count × absolute platelet count) / absolute lymphocyte count

SIRI = (absolute neutrophil count × absolute monocyte count) / absolute lymphocyte count

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v. 25, IBM, SPSS for Windows, NY: IBM Corp.). Visual and analytical methods (Kolmogorov-Smirnov test) were used to determine whether the variables were normally distributed. Descriptive statistics were presented as median and interquartile range values for non-normally distributed variables. Since continuous variables were not normally distributed, the Mann-Whitney U-test was conducted to compare median values between groups. Using the receiver operating characteristic (ROC) curve method, the predictive performance of inflammation markers for FGR risk was evaluated by calculating the area under the curve (AUC) values and their associated significance values. The optimal cut-off values of inflammation markers were obtained using Youden's index. A p value of <0.05 was considered statistically significant in comparisons between groups.

RESULTS

The study included a total of 480 pregnant women, of whom 200 were diagnosed with FGR and 280 had uncomplicated pregnancies. The demographic and perinatal characteristics and systemic inflammation markers of all participants are presented in Table 1. The cases in both groups were found to be similar in terms of maternal age, body mass index, gravida, and parity (p>0.05). Week of birth, fetal birth weight, first-minute APGAR score, and fifth-minute APGAR score were found to be lower in the FGR group (p<0.001). When the groups were compared in terms of systemic inflammation markers, the NLR, SII, and SIRI were statistically significantly lower in the FGR group (p<0.001, p=0.01, and p=0.03, respectively).

A ROC analysis was performed to evaluate the predictive power of systemic inflammation markers for FGR cases (Table 2). When the cut-off value for the NLR was taken as 3.31, it had 39% specificity and 43% sensitivity for this prediction [AUC: 0.384, 95% confidence interval (CI): 0.334-0.435, p<0.001). At a cut-off value of 806, the SII had a specificity of 40% and a sensitivity of 45% (AUC: 0.413, 95% CI: 0.362-0.465, p = 0.01). Lastly, the specificity and sensitivity values of the SIRI were found to be 45% and 49%, respectively, at a cut-off value of 1.47 (AUC: 0.442, 95% CI: 0.390-0.494, p=0.03).

The comparison of the EO-FGR and LO-FGR cases according to systemic inflammation markers is presented in Table 3. The two groups were statistically similar in terms of the NLR, SII, and SIRI (p=0.760, p=0.546, and p=0.737, respectively).

Table 1. Comparison of the demographic, perinatal, and systemic inflammation markers of the study and control groups

	FGR (n = 200)		Control (n = 280)		
	Median	IQR	Median	IQR	P
Maternal age (years)	28	7	28	7	0.612
BMI (kg/m²)	27.29	7.21	26.22	5.88	0.199
Gravidity	2	2	2	2	0.509
Parity	1	1	1	1.75	0.374
Gestational age at birth (weeks)	37	1	39	1	**<0.001**
Fetal birth weight (grams)	2350	506	3150	510	**<0.001**
First-minute APGAR score	7	1	7	1	**<0.001**
Fifth-minute APGAR score	9	1	9	0	**<0.001**
NLR	3.10	1.63	3.63	1.83	**<0.001**
SII	787	553	907	568	**0.01**
SIRI	1.44	0.96	1.58	1	**0.03**

Mann-Whitney U test, FGR: Fetal growth restriction, IQR: Interquartile range, BMI: Body mass index, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index
p<0.05 was considered statistically significant.

Table 2. Results of the receiver operating characteristic analysis on the ability of systemic inflammation markers to predict FGR cases

	Cut-off	AUC	P	95% CI	Sensitivity	Specificity
NLR	3.31	0.384	<0.001	0.334-0.435	43%	39%
SII	806	0.413	0.01	0.362-0.465	45%	40%
SIRI	1.47	0.442	0.03	0.390-0.494	49%	45%

FGR: Fetal growth restriction, AUC: Area under the curve, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index
p<0.05 was considered statistically significant.

Table 3. Comparison of systemic inflammation markers in groups of early onset-FGR and late onset-FGR

	Early-onset FGR (n = 34)		Late-onset FGR (n = 166)		
	Median	IQR	Median	IQR	P
NLR	3.19	1.32	3.09	1.71	0.760
SII	838	398	773	561	0.546
SIRI	1.45	0.97	1.45	0.94	0.737

Mann-Whitney U test, FGR: Fetal growth restriction, NLR: Neutrophil lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, IQR: Interquartile range
p<0.05 was considered statistically significant.

Table 4. Comparison of systemic inflammation markers according to NICU requirements

	Admission to NICU				
	Present (n = 51)		Absent (n = 149)		
	Median	IQR	Median	IQR	P
NLR	3.09	1.72	3.15	1.53	0.897
SII	771	693	778	534	0.822
SIRI	1.32	1.39	1.47	0.89	0.717

Mann-Whitney U test, NICU: Neonatal intensive care unit, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, IQR: Interquartile range
p<0.05 was considered statistically significant.

Table 4 presents the results of the comparison of systemic inflammation markers according to NICU requirements among the FGR cases. The NLR, SII, and SIRI values were statistically similar between the patients with and without NICU requirements (p = 0.897, p = 0.822, and p = 0.717, respectively).

DISCUSSION

This retrospective case-control study found that systemic inflammation markers, namely the NLR, SII, and SIRI, which can be simply calculated using the first-trimester complete blood count analysis, were lower in pregnant women with FGR than in the control group. On the other hand, these markers were statistically similar when compared between the EO-FGR and LO-FGR cases and between the FGR cases with and without NICU requirements.

The maternal immune system undergoes major adaptations during pregnancy to protect both the mother and the fetus from pathogenic damage, while maintaining fetal allograft tolerance (13). The interface between the maternal decidua and trophoblasts is a dynamic microenvironment in which interactions between cells of fetal and maternal origin occur (14). Maternal immune cells accumulate in this area in response to foreign tissues of the fetus. These immune cells play an important role in decidualization, trophoblast invasion, and remodeling mechanisms, forming the basis of a healthy pregnancy, and their imbalance can lead to pregnancy complications (6).

Systemic inflammation indexes have frequently been the subject of investigation for many researchers. It has been suggested that these indexes can predict the prognosis of some cancer types and can be used to indicate exacerbations in autoimmune diseases (15-17). In recent years, researchers have reported that the use of these indexes may be beneficial in complicated pregnancies, such as preeclampsia, FGR, and preterm delivery (9, 18-20).

In a study in which complete blood count analyses were undertaken during the first trimester of pregnancy to evaluate the prediction of preeclampsia, the NLR and the platelet-to-lymphocyte ratio (PLR) were found to be higher in the preeclampsia group, and the authors suggested that increased NLR and PLR might be a risk factor for this condition (21). In another study, the NLR and SII determined during the first trimester could predict miscarriage, with these markers being higher in women who experienced pregnancy loss (22). Another study reported that the NLR and SII were higher in severe cases of hyperemesis gravidarum (HEG) and claimed that systemic inflammation markers could be used to predict HEG severity (23).

Harita et al. examined the leukocyte and neutrophil counts of pregnant women diagnosed with FGR based on the results of a complete blood count analysis performed in the first or third trimester and compared these values to those of a control group. The authors found that both groups had similar results in the first trimester, but the FGR group had higher leukocyte and neutrophil counts in the third trimester, suggesting that increased maternal inflammation might be a factor in the development of FGR (24). In another study examining the relationship between the NLR and fetal birth weight, no such relationship was observed (25). Levy et al. reported that women who gave birth to small-for-gestational-age neonates had higher NLR values than controls according to the first-trimester complete blood count results (20). In contrast, our results revealed lower inflammation markers in pregnant women with FGR. In a study conducted in China to determine the reference ranges of systemic inflammation markers, such as the SII and NLR, in healthy pregnant women and non-pregnant women, the NLR and SII values of the former were found to be approximately twice those of the latter. Furthermore, the median NLR value was 3.53 (1.76-6.76), and the SII median value was 754 (302-1,603) among pregnant women during their first trimester (26). These results show that systemic inflammation markers evaluated in the first trimester can vary widely. In addition, in a study on neutrophil heterogeneity in inflammation, it was demonstrated that neutrophils could exhibit

different functions and phenotypes in the presence of a disease (27). In a healthy pregnancy series, the balance of neutrophils of different phenotypes was reported to be more important than the quantitative number of neutrophils (6). Our study, conducted with the highest number of pregnant women diagnosed with FGR in the literature, suggests that the contribution of systemic inflammation markers to the clinical evaluation of FGR may be limited.

This study has some limitations that should be discussed. First, since the study was planned at a single center, our sample size was small. Therefore, multicenter, randomized, controlled studies with larger samples are needed. Second, only one blood sample was taken from the participants. Further studies can be designed to collect repeated blood samples to report changes in systemic inflammation markers. The strength of our study is that it is the largest study in the literature evaluating pregnant women with a diagnosis of FGR.

We found that the NLR, SII, and SIRI were lower in pregnant women with FGR compared to the control group, according to first-trimester complete blood count results. However, the NLR, SII, and SIRI did not statistically significantly differ according to the onset of FGR or NICU requirements.

Conflict of interest statement
None

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Author contribution
ZA: methodology, data collection, writing, editing, AT: technical assistance, data collection, correction, analysis, RD: methodology, writing, editing, analysis, BS: technical assistance, data collection, correction, analysis, NF: technical assistance, writing, editing, analysis, MH: technical assistance, writing, editing, analysis, OK: technical assistance, data collection, correction, analysis, DS: methodology, design, correction, analysis

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