Original Article

An Assessment of the Relationship Between Fetal Growth Restriction and Maternal Serum Markers of Systemic Inflammation (NLR, SIRI, SII, and PIV)

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Abstract

Background: The processes involved in inflammatory regulation are crucial during pregnancy. **Aim:** This study aims to identify the association between fetal growth restriction (FGR) and neutrophil-to-lymphocyte ratio (NLR), systemic inflammatory response index (SIRI), Systemic immune-inflammatory index (SII), and pan-immune inflammatory value (PIV). **Methods:** This retrospective case-control study was conducted between 2015 and 2021. The study group comprised cases diagnosed with FGR, while the control group was randomly selected from a healthy cohort of pregnancies. The levels of inflammatory markers were calculated from the blood count results of the cases. A comparison was conducted between the two groups' obstetric and neonatal outcomes and serum inflammatory markers. **Results:** A total of 1052 cases were included in the study, with 526 (50%) belonging to the FGR group. The mean age was found to be similar in both groups ($P = .311$). A significant increase in neutrophils, NLR, SIRI, SII, and PIV was observed in the FGR group ($P < .05$). The multivariate logistic regression analysis results demonstrated that elevated neutrophil, NLR, and SII values were independent risk factors for FGR ($P < .001$). No notable discrepancy was observed in these markers between the early and late FGR ($P > .05$). A significant inverse relationship was observed between neutrophils, NLR, and SII, and gestational age and fetal weight at birth ($P < .05$). **Conclusion:** The findings indicated that elevations in neutrophils, NLR, and SII are independent risk factors for FGR. These markers reflecting maternal systemic inflammation, have been linked to FGR and associated poor neonatal outcomes.

Keywords: *Fetal growth restriction (FGR), neutrophils, neutrophil-to-lymphocyte ratio (NLR), pan-immune inflammatory value (PIV), systemic immune-inflammatory index (SII)*

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Introduction

Fetal growth restriction (FGR) is a challenging condition with an incidence of 5-10% in pregnancies.[1] Fetal growth is influenced by the interplay between maternal metabolism and substrate availability, placental function and inflammation, and fetal adaptability.[2-4] The systemic inflammatory response index (SIRI), systemic immune-inflammatory index (SII), and pan-immune inflammatory value (PIV) have been the subject of recent studies.[5,6]

There is a paucity of studies comprising a substantial number of cases that have investigated the relationship between FGR and novel inflammatory markers, including SIRI, SII, and PIV. This study aims to determine the association between FGR and systemic

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inflammatory processes, focusing on SIRI, SII, and PIV.

Methods

This retrospective case-control study was conducted between January 2015 and December 2021, utilizing data from pregnant women at our hospital. The study was approved by Etlik Zubeyde Hanim Women's Health Education and Research Hospital (approval number 10, dated 19/10/2023), and written informed consent was obtained from all participants during their period of hospitalization.

- The study group comprised cases diagnosed with FGR at the perinatology clinic and delivered at our hospital. In the diagnosis of FGR, the following criteria were accepted before (AC) <3 (rd) centile or EFW < 3 (rd) centile or contributory AC or EFW < 10 (th) centile and a pulsatility index (PI) >95 (th) centile in either the umbilical artery (UA).
- The control group was selected at random from a cohort of healthy pregnant women who had followed up and delivered at our hospital without any maternal-fetal high-risk conditions.

Large-for-gestational-age and small-for-gestational-age pregnancies that did not meet the Delphi criteria according to Gordijn *et al*.[7] were excluded from both groups of the study. The study excluded pregnancies with pregnancy-induced hypertensive diseases (PIHD), multiple pregnancies, cholestatic diseases of pregnancy, gestational and prediabetes mellitus, placental pathologies, fetal anomalies, users of anticoagulants, smokers, and drug users. Furthermore, cases with immunodeficiency, chronic inflammatory disease, hematological disease, connective tissue diseases (systemic lupus erythematosus, etc.), liver and kidney dysfunction, acute or chronic infection diseases, and prenatal blood transfusion were excluded from the study.

The following data were extracted from the patient record system: maternal age, body mass index (BMI), gravida, parity, abortion, obstetric features, presence of oligohydramnios, rate of corticosteroid administration, gestational age at birth, delivery method, newborn weight, 1st and 5th minute Apgar scores, neonatal gender, and rates of neonatal intensive care unit (NICU) admission. The count of white blood cells (WBC), neutrophils, monocytes, basophils, eosinophils, lymphocytes, platelet (PLT), hemoglobin (HB), hematocrit (HCT), and mean platelet volume (MPV) were obtained retrospectively from the patient's blood count conducted during their hospitalization in the delivery room. The following formulas are used to calculate various ratios of blood cell counts: SII = neutrophils × platelets/lymphocytes; PIV = neutrophils × platelets × monocytes/lymphocytes; neutrophil-to-lymphocyte ratio (NLR) = neutrophils/lymphocytes; platelet-to-lymphocyte ratio (PLR) = platelets/lymphocytes; monocyte-to-lymphocyte ratio (MLR) = monocytes/lymphocytes.

All data were subjected to comparison between the two groups. Furthermore, the FGR group was divided into two subgroups, designated as early and late FGR, and the resulting differences between the three groups were then revealed.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 29 (IBM, Armonk, NY, USA). The numerical data are presented as either the mean ± SD or the median (interquartile range), depending on whether a normal distribution is present. Categorical variables were expressed as numbers (percentages) and analyzed using the Chi-square test, with odds ratios (OR) provided with 95% confidence intervals (CI). Mann-Whitney U test or *t*-test was employed for variables from two independent groups, depending on a normal distribution. A receiver operating characteristic (ROC) curve analysis was conducted to determine the 95% CI values, cut-off values with sensitivity, and specificity values of immune markers with an area under the curve (AUC) greater than 0.5. Moreover, a multivariate logistic regression analysis was conducted to identify serum inflammatory markers that are independent risk factors for FGR. The relationship between serum inflammatory markers and obstetric and neonatal outcomes was evaluated using correlation tests. For parametric variables with three groups (control, early, and late FGR groups), the analysis of variance (ANOVA) test was employed, and the significant results were evaluated pairwise with *post hoc* analyses in the subgroups. The threshold for statistical significance was set at $P < 0.05$.

Results

This case-control study included a total of 1,052 cases, with an equal number of cases in each group. The mean maternal age was found to be similar between the two groups (27.7 ± 5.86 vs. 27.9 ± 5.00 years, $P = .311$). The number of gravida was found to be similar in both groups, with a mean of 2.1 ± 1.39 and 2.0 ± 1.29, respectively ($P = .235$). Likewise, parity and previous miscarriage exhibited no statistical difference, with means of 0.7 ± 1.01 and 0.7 ± 0.96, and 0.3 ± 0.67 and 0.2 ± 0.69, respectively ($P > .05$).

A comparative analysis of obstetric characteristics and neonatal outcomes in both cohorts is presented in Table 1.

Table 1: A comparative analysis of obstetric, neonatal, and serum inflammatory markers outcomes for the groups

Variables	Control Group, *n*=526	FGR Group, *n*=526	*P*
Maternal age (year), mean±SD	27.7±5.86	27.9±5.00	0.311[a]
Pregestational BMI (kg/m^2), mean±SD	24.6±5.23	23.1±5.09	<.001[a]
BMI at birth (kg/m^2), mean±SD	29.6±4.67	28.0±4.81	<.001[a]
Gravidae (*n*), mean±SD	2.1±1.39	2.0±1.29	0.253[a]
Parity (*n*), mean±SD	0.7±1.01	0.7±0.96	0.414[a]
Previous miscarriages (*n*), mean±SD	0.3±0.67	0.2±0.69	0.111[a]
Birth Age (week), median (IQR)	39 (2)	37 (1)	<.001[b]
Presence of oligohydramnios, (*n*, %)			
No	513 (97.5)	390 (74.1)	<.001[c]
Yes	13 (2.5)	136 (25.9)	
Administration of corticosteroids before 34 week, (*n*, %)			
No	515 (97.9)	447 (85.0)	<.001[c]
Yes	11 (2.1)	79 (15.0)	
Birth way, (*n*, %)			
Vaginal	310 (58.9)	221 (42)	<.001[c]
Cesearean	216 (41.1)	305 (58.)	
Newborn gender (*n*, %)			
Female	241 (46)	333 (63.1)	<.001[c]
Male	284 (54)	194 (36.9)	
Fetal weight at birth (g), mean±SD	3319.9±403.93	2300.4±393.21	<.001[a]
NICU admission, (*n*, %)			
No	507 (96.4)	416 (79.1)	<.001[c]
Yes	19 (3.6)	110 (20.9)	
APGAR Score (1st-minute), median (IQR)	9 (0)	10 (0)	<.001[b]
APGAR Score (5th-minute), median (IQR)	9 (0)	10 (0)	<.001[b]
WBC (×10^9/L), mean±SD	8.6±2.42	9.5±2.87	0.007[a]
HB (gr/dl), mean±SD	12.4±1.21	11.7±1.39	<.001[a]
HCT (%), mean±SD	37.6±3.39	35.5±3.77	<.001[a]
PLT (×10^9/L), mean±SD	261.4±65.68	240.2±65.23	<.001[a]
Neutrophil (×10^9/L), mean±SD	6.2±2.13	8.1±2.70	<.001[a]
Monocyte (×10^9/L), mean±SD	0.4±0.15	0.5±0.18	<.001[a]
Lymphocyte (×10^9/L), mean±SD	1.8±0.54	1.7±0.60	0.013[a]
MPV (fL), mean±SD	8.5±0.96	8.8±1.18	<.001[a]
MLR, mean±SD	0.2±0.08	0.3±0.12	<.001[a]
NLR, mean±SD	3.6±1.48	5.1±3.63	<.001[a]
PLR, mean±SD	152.0±53.38	148.9±56.52	0.177[a]
SIRI, mean±SD	1.6±0.97	2.5±1.68	<.001[a]
PIV, mean±SD	444.0±300.72	622.1±444.57	<.001[a]
SII, mean±SD	943.0±451.22	1224.2±668.69	<.001[a]

[a]Independent *t*-test, [b]Mann-Whitney U Test, [c]Chi-Square test. $P<0.05$ is statistically significant. BMI: body mass index, HB: hemoglobin, HCT: hematocrit, IQR: interquartile range, MPV: mean platelet volume, MLR: monocyte-lymphocyte ratio, n: number, NICU: newborn intensive care unit, NLR: neutrophil-lymphocyte ratio, PIV: pan-immune inflammatory value, PLT: platelets, PLR: platelet-lymphocyte ratio, SD: standard deviation, SII: systemic immune-inflammatory index, SIRI: systemic inflammatory response index, WBC: white blood cells

The FGR group exhibited a lower mean gestational age at birth and lower mean fetal weight (P < .001). The analysis revealed a significantly higher prevalence of oligohydramnios in the FGR group (2.5% vs. 25.9%, P < .001), with a 13.7-fold increase (95% CI: 7.67-24.67). A significantly higher rate of corticosteroid application was observed in the FGR group before 34 weeks, with a prevalence of 15% compared to the control group (P < .001). This resulted in an 8.27 OR (95% CI: 4.34-15.74). The cesarean section rate was found to be 1.98 times higher in the FGR group (95% CI: 1.55-2.53, P < .001). A significantly higher rate of female fetuses was observed in the FGR group (63.1% vs. 46%, P < .001). Furthermore, the rate of NICU admission was found to be 7.05 times higher in the FGR group (95% CI: 4.26-11.67, P < .001).

The levels of HB, HCT, PLT, and lymphocytes were observed to be markedly diminished in the FGR cohort,

Table 2: The results of the receiver operating characteristic (ROC) curve analysis of serum inflammatory markers

Variables	Cut-off values	Sensitivity (%)	Specificity (%)	Youden index	Area under curve	*P*	95% Confidence interval	
							Lower bound	Upper bound
WBC	8.27	60.1	50.2	0.10	0.59	<.001	0.55	0.62
Neutrophil	6.39	73	60.8	0.33	0.72	<.001	0.69	0.75
Monocyte	0.44	57.8	54	0.11	0.57	<.001	0.54	0.61
MPV	8.35	54.8	51.1	0.05	0.55	0.009	0.52	0.59
MLR	0.25	61.2	55.7	0.16	0.61	<.001	0.57	0.64
NLR	3.73	71.3	60.3	0.31	0.72	<.001	0.69	0.75
SIRI	1.61	71.1	60.1	0.31	0.70	<.001	0.67	0.73
PIV	380.81	67.7	54	0.21	0.64	<.001	0.61	0.67
SII	856.47	69.2	53.4	0.22	0.64	<.001	0.61	0.68

ROC curve analysis. MPV: mean platelet volüme, MLR: monocyte-lymphocyte ratio, NLR: neutrophil-lymphocyte ratio, PIV: pan-immune inflammatory value, SII: systemic immune-inflammatory index, SIRI: systemic inflammatory response index, WBC: white blood cells

Table 3: The results of neutrophil, neutrophil-lymphocyte ratio (NLR), systemic immune-inflammatory index (SII), pan-immune inflammatory value (PIV), and systemic inflammatory response index (SIRI) between groups according to cut-off values

	Cut off values	Control Group *n* (%)	FGR Group *n* (%)	*P*	Odds Ratio	95% Confidence Interval
Neuthrophil	<6.39	320 (60.8%)	142 (27.0%)	<.001	4.20	3.23−5.44
	≥6.39	206 (39.2%)	383 (73.0%)			
NLR	<3.73	310 (58.9%)	151 (28.7%)	<.001	3.56	2.75−4.60
	≥3.73	216 (41.1%)	375 (71.3%)			
SIRI	<1.61	314 (59.7%)	145 (27.6%)	<.001	3.89	3.00−5.04
	≥1.61	212 (40.3%)	381 (72.4%)			
PIV	<380.81	284 (54.0%)	170 (32.3%)	<.001	2.45	1.91−3.15
	≥380.81	242 (46.0%)	356 (32.3%)			
SII	<586.47	281 (53.4%)	163 (31.0%)	<.001	2.55	1.98−3.28
	≥586.47	245 (46.6%)	363 (69.0%)			
Total		526 (50%)	526 (50%)			

Chi-Square test, $P<0.05$ is statistically significant. NLR: neutrophil-lymphocyte ratio, PIV: pan-immune inflammatory value, SII: systemic immune-inflammatory index, SIRI: systemic inflammatory response index

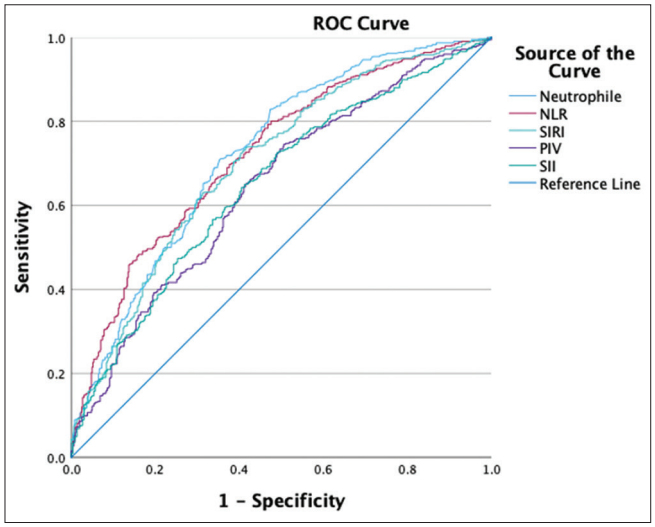

Figure 1: ROC curve of neutrophils, neutrophil-lymphocyte ratio (NLR), systemic immune-inflammatory index (SII), pan-immune inflammatory value (PIV), and systemic inflammatory response index (SIRI)

whereas WBC, neutrophils, monocytes, MLR, NLR, SIRI, PIV, and SII were identified to be elevated, as illustrated in Table 1 ($P < .05$). The results of the ROC curve analysis of the markers obtained from the blood count are presented in Table 2, together with the corresponding cut-off values. Additionally, the ROC curve graphs for neutrophil, NLR, SIRI, PIV, and SII are presented in Figure 1. Furthermore, Table 3 presents the evaluation of serum inflammatory markers, including neutrophil, NLR, SIRI, PIV, and SII, between groups according to established cut-off values, with an accompanying OR with 95% CI.

Upon examination of Tables 2 and 3 in this study, the optimal neutrophil cut-off value was determined to be 6.39, with an OR of 4.20 for cases with FGR, a sensitivity of 70%, and a specificity of 60.8% ($P < .001$). The optimal NLR cut-off value was identified as 3.73, with an OR of 3.56 for cases with FGR, a sensitivity of 71.3%, and a specificity of 60.3% ($P < .001$). In cases with FGR, the optimal cut-off value for SIRI was identified as 1.61, with an OR of 3.89, a sensitivity of 71.1%, and a specificity of 61.1% ($P < .001$). The optimal cut-off value for PIV was 380.81, with an OR

Table 4: The results of a multivariate logistic regression analysis of neutrophil, the neutrophil-to-lymphocyte ratio (NLR), systemic inflammation response index (SIRI), platelet-to-lymphocyte ratio (PIV), and systemic inflammation index (SII)

Variables in the equation							
		B	S. E.	Wald	df	Sig.	Exp (B)
Step 1[a]	Neutrophil	0.29	0.05	33.85	1	<0.001	1.33
	NLR	0.55	0.18	8.56	1	0.003	1.73
	SIRI	–0.03	0.36	0.01	1	0.914	0.96
	PIV	0.000	0.001	0.000	1	0.986	1.00
	SII	–0.001	0.001	3.62	1	0.057	0.99
	Constant	–2.90	0.27	113.62	1	<0.001	0.05
Step 2[a]	Neutrophil	0.29	0.05	34.17	1	<0.001	1.33
	NLR	0.55	0.08	44.45	1	<0.001	1.74
	SIRI	–0.04	0.11	0.16	1	0.683	0.95
	SII	–0.001	0.000	26.64	1	<0.001	0.99
	Constant	–2.90	0.27	114.18	1	<0.001	0.05
Step 3[a]	Neutrophil	0.28	0.04	43.43	1	<0.001	1.32
	NLR	0.54	0.07	48.93	1	<0.001	1.72
	SII	–0.001	0.000	27.09	1	<0.001	0.99
	Constant	–2.86	0.25	129.85	1	<0.001	0.05

[a]Variable(s) entered in Step 1: Neutrophil, NLR, SIRI, PIV, SII. Multivariate logistic regression, backward stepwise (Wald).
NLR: neutrophil-lymphocyte ratio, PIV: pan-immune inflammatory value, SII: systemic immune-inflammatory index, SIRI: systemic inflammatory response index

of 2.45 for cases with FGR, a sensitivity of 67.7%, and a specificity of 54% ($P < .001$). In cases with FGR, the optimal SII cut-off value was identified as 856.47, with an OR of 2.55, a sensitivity of 69.2%, and a specificity of 53.4% ($P < .001$). Furthermore, the multivariate logistic regression analysis [Table 4] revealed that neutrophil, NLR, and SII were independent risk factors for FGR ($P < .001$ and $R^2 = 0.24$).

Furthermore, the present study identified 489 cases (92.97%) as late FGR, while 37 cases (7.03%) were classified as early FGR. A comparison of the control, early FGR, and late FGR groups revealed no statistically significant difference in PLR across all three groups ($P = .081$). Nevertheless, notable discrepancies were evident in the neutrophil count, NLR, SIRI, PIV, and SII between the three groups ($P < .001$). The present study revealed that the neutrophil and NLR values in the early and late FGR groups were 8.15 ± 2.41 and 8.18 ± 2.72, respectively, and 4.6 ± 2.22 and 5.1 ± 2.26, respectively. The SIRI was found to be 2.2 ± 1.52 and 2.1 ± 1.44, the PIV was found to be 546.6 ± 418.31 and 627.8 ± 446.38, and the SII was found to be 1090.1 ± 625.26 and 1234.3 ± 671.38 for the early and late FGR groups, respectively. Nevertheless, no significant differences were identified in the subsequent *post hoc* analyses for these markers between the early and late FGR groups (P = 1.,310.,603.,630, and. 415, respectively).

Additionally, an inverse relationship was observed between neonatal weight and neutrophils, NLR, and SII ($P < .001$, r = –0.330, –0.325, and –0.202, respectively). Similarly, a negative correlation was identified between gestational age at birth and neutrophils, NLR, and SII ($P < .001$, r = –0.205, –0.214, and –0.118, respectively). However, a positive correlation was observed between the incidence of admission to the NICU and the levels of neutrophils and NLR ($P < .001$, r = 0.143 and 0.087, respectively).

Discussion

FGR represents a significant obstetric issue, with a high incidence of morbidity, mortality, and developmental delay during infancy.[1,7] The rationale for this study is to gain further insight into the relationship between maternal systemic inflammation and FGR and to assess the impact of maternal inflammation during pregnancy on neonatal outcomes. This study found that the levels of neutrophil, NLR, SIRI, PIV, and SII were significantly higher in the FGR group ($P < .05$). Moreover, the findings demonstrated that an elevation in neutrophil, NLR, and SII levels were independent risk factors for FGR.

As with many other obstetric complications, such as pre-eclampsia (PE), premature birth, and fetal death, the pathogenesis of FGR is generally associated with abnormal maternal inflammation.[8] In their study on rat models, Cotechini *et al*.[9] indicate that inflammation-induced FGR is associated with alterations in placental morphometrics. The release of proinflammatory cytokines and other antiangiogenic factors from the ischemic placenta is associated with both PIHD and FGR.[10] Furthermore, Sauder *et al*.[11] demonstrated that birth weight is inversely correlated with chronic inflammation during pregnancy. Additionally, there is a negative correlation between NLR and PLR and both birth weight and gestational age.[3,4] Consequently, in cases of FGR, it is worth investigating the potential utility of NLR, SII, SIRI, and PIV, which are novel biomarkers obtained from blood counts and provide reflections of systemic inflammation.[5,6,12]

Firatligil *et al*.[13] demonstrated that elevated levels and fluctuations of SII in maternal blood are indicative of an inflammatory process that contributes to late FGR, and also established that the cut-off value for ΔSII (>586) with 90% specificity can be employed as a screening test for late FGR. Furthermore, SII, SIRI, and PIV levels are more indicative of systemic inflammation than NLR, MLR, and PLR, as they reflect the combined

effect of thrombocytosis, neutrophilia, monocytosis, and lymphopenia.[5,6,12-14] In a study, the NLR, PLR, MLR, and SII were found to be insignificant in predicting preeclampsia, however, the SIRI and PIV demonstrated significantly higher values in preeclampsia.[5] The optimal cut-off values for SIRI and PIV were identified as 1.5 and 394.4, respectively, with 56.2% and 55.2% sensitivity and 55.6% and 55% specificity for preeclampsia cases.[5]

The results of several studies conducted on late FGR cases indicated that the NLR was significantly higher compared to the control group.[4,15] However, no difference was observed in PLR values, as seen in our study. The lack of a notable shift in PLR may suggest that there is no associated process related to endothelial damage in cases of late-onset FGR; this condition is also known to be frequently associated with pre-eclampsia.[15,16] However, in our study, PLR was found to be similar in late and early FGR (150.2 ± 56.13 vs. 131.1 ± 59.36, $P = .123$). Furthermore, the study did not reveal any notable discrepancies in neutrophil, NLR, SIRI, PIV, and SII values between the early and late FGR ($P > .05$).

In the present study, an increase in neutrophils, NLR, and SII was associated with a reduction in gestational age and fetal weight at birth ($P < .05$). Akgün *et al*.[3] demonstrated that maternal NLR and PLR were negatively correlated with gestational age and fetal weight at birth. Nevertheless, a different study on late FGRs revealed that this relationship could not be substantiated.[15] Additionally, a study has demonstrated that an increase in maternal PLR is associated with several adverse outcomes, including low Apgar scores, and perinatal death.[17] Nevertheless, no notable correlation was identified between PLR and neonatal and obstetric outcomes in the present study ($P > .05$).

In this case-control study, factors that could affect systemic inflammation were strictly excluded and the number of participants was more than a thousand. We contend that this is the inaugural study to examine the correlation between FGR and serum markers indicative of maternal systemic inflammation. Nevertheless, as this study was conducted at a single center, it would be prudent to replicate these findings in different settings to reach a definitive conclusion. A further limitation of the study is its retrospective design. To gain a more comprehensive understanding of this subject, it would be beneficial to conduct randomized controlled studies with larger case numbers.

In conclusion, healthcare professionals must be able to identify FGR at high risk for poor neonatal outcomes to provide effective counseling. The case-control study revealed that maternal serum inflammatory markers, including neutrophil, NLR, SIRI, PIV, and SII, were significantly elevated in the FGR group. The results demonstrated that higher neutrophil, NLR, and SII values were found to be independent risk factors for FGR. The results of this study indicate that the use of neutrophils, NLR, and SII may prove beneficial as predictive and diagnostic markers for cases of FGR and as prognostic markers for neonatal outcomes in FGR cases, including fetal weight, gestational age at birth, and NICU rates. However, no significant difference was observed in the serum inflammatory markers between the early and late onset of FGR. To reduce the incidence of FGR with poor neonatal outcomes, further studies are recommended to investigate the obstetric and neonatal effects of maternal systemic inflammation, to develop effective prevention strategies.

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Ethical approval

This study was approved by the local hospital ethics committee (numbered 10, dated 19/10/2023, Etlik Zubeyde Hanim Women's Health Education and Research Hospital, Ankara, Turkiye).

Declaration of patient consent

All human subjects provided written informed consents with guarantees of confidentiality.

Helsinki declaration

All authors and the study protocol respected the World Medical Association Declaration of Helsinki on the ethical conduct of studies involving human subjects.

Author contributions

AA, YAR, and YEÜ conceptualized and designed the study. AA, YAR, SYE, and KH were involved in data collection/acquisition and statistical analysis. All authors were involved in the writing and revising of the manuscript for intellectual content. All authors read, and approved the final manuscript and agreed to be accountable for all aspects of the work.

Data availability statement

Authors are available and ready to supply the data upon any requests through the corresponding author.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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