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Research Article

Inflammatory markers as predictors of late-onset fetal growth restriction: a focus on neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios

Geç başlangıçlı fetal gelişim geriliğini öngörmede inflamatuar belirteçlerin rolü: nötrofil-lenfosit ve trombosit-lenfosit oranlarına odaklanma

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Abstract

Aim: This study evaluates the role of hematologic inflammatory markers, specifically neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), in predicting late-onset fetal growth restriction (FGR).

Material and Methods: A retrospective comparative analysis was conducted on 76 pregnancies complicated by late-onset FGR and 100 healthy pregnancies as controls. Maternal blood samples were collected, and hematologic parameters, including NLR and PLR, were recorded. Data analysis compared inflammatory markers between the FGR and control groups to assess the relationship between maternal inflammatory profiles and FGR.

Results: NLR was significantly higher in the FGR group compared to the control group ($p<0.001$), suggesting increased systemic inflammation in pregnancies complicated by FGR. PLR, although elevated in the FGR group, did not show significant differences between groups. Additionally, white blood cell and neutrophil counts were significantly elevated in the FGR group ($p<0.001$), while Apgar scores at 1 and 5 minutes were notably lower in FGR cases ($p<0.01$), indicating compromised neonatal outcomes.

Conclusion: Our findings suggest that elevated NLR may serve as a valuable inflammatory marker for identifying pregnancies at risk for late-onset FGR. Although PLR showed no significant association, the overall inflammatory profile indicates systemic maternal inflammation's role in FGR pathogenesis. The use of NLR as a cost-effective and accessible predictive tool could enhance early identification and monitoring of at-risk pregnancies, supporting timely intervention strategies. Further studies are needed to validate these findings and explore the integration of inflammatory markers into routine prenatal care.

Keywords: Fetal growth restriction, Inflammation, Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio

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Öz

Amaç: Bu çalışma, geç başlangıçlı fetal gelişim geriliğinin (FGR) öngörülmesinde hematolojik inflamatuar belirteçlerden özellikle nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranının (PLR) rolünü değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: u retrospektif çalışmada, geç başlangıçlı FGR ile komplike 76 gebelik ve 100 sağlıklı gebelik kontrol grubu olarak incelenmiştir. Anne kan örnekleri alınarak NLR ve PLR dahil olmak üzere hematolojik parametreler kaydedilmiştir. FGR ve kontrol grubu arasında inflamatuar belirteçler karşılaştırılarak anne inflamasyon profili ile FGR arasındaki ilişki değerlendirildi.

Bulgular: NLR, FGR grubunda kontrol grubuna kıyasla anlamlı olarak daha yüksekti ($p<0.001$), bu da FGR ile komplike gebeliklerde artmış sistemik inflamasyonu göstermektedir. FGR grubunda PLR yüksek olmasına rağmen gruplar arasında anlamlı bir fark görülmemiştir. Ayrıca, beyaz kan hücresi ve nötrofil sayıları FGR grubunda anlamlı olarak daha yüksekti ($p<0.001$), ve 1. ve 5. dakikadaki Apgar skorları FGR vakalarında anlamlı olarak düşüktü ($p<0.01$), bu da neonatal sonuçların etkilendiğini göstermektedir.

Sonuçlar: Bulgularımız, yüksek NLR'nin geç başlangıçlı FGR riski taşıyan gebeliklerin tespitinde değerli bir inflamatuar belirteç olabileceğini düşündürmektedir. PLR anlamlı bir ilişki göstermemekle birlikte, genel inflamatuar profil, FGR patogenezinde sistemik anne inflamasyonunun rolünü desteklemektedir. NLR'nin düşük maliyetli ve erişilebilir bir öngörü aracı olarak kullanılması, risk altındaki gebeliklerin erken tespit ve takibini güçlendirebilir ve zamanında müdahalelere destek olabilir. Bu bulguların doğrulanması ve inflamatuar belirteçlerin rutin prenatal bakıma entegrasyonunun araştırılması için ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Fetal Gelişim Geriliği, İnflamasyon, Nötrofil-Lenfosit Oranı, Trombosit-Lenfosit Oranı

Introduction

Fetal growth restriction (FGR) is a complex obstetric condition characterized by the inability of the fetus to achieve its genetically determined growth potential. Affecting approximately 5–10% of all pregnancies, FGR is a leading contributor to perinatal morbidity and mortality worldwide, underscoring the critical need for effective diagnostic and predictive strategies [1,2]. FGR can be broadly classified into early- and late-onset types, with late-onset FGR generally presenting after 32 weeks of gestation. This distinction is important, as early-onset FGR is often associated with severe placental pathology and preeclampsia, while late-onset FGR tends to involve more subtle placental insufficiency that can be challenging to detect [2,3].

The primary pathophysiological mechanism underlying FGR is thought to be placental insufficiency, which compromises the transfer of essential nutrients and oxygen from the mother to the fetus. This condition is multifactorial, with contributions from maternal, fetal, and placental factors, including genetic anomalies, maternal health conditions, and placental dysfunction. Among these, inflammation has emerged as a potential contributor to FGR, as inflammatory processes can disrupt placental function, impacting fetal growth and development [4,5].

Inflammatory markers like the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have gained attention as potential indicators of systemic inflammation and immune status [6,7,8]. These hematologic markers are inexpensive, accessible, and can reflect ongoing inflammation in the body. Recent studies have suggested that elevated NLR and PLR levels are associated with adverse pregnancy outcomes, including FGR, potentially due to their impact on placental health [6,7,9]. The use of these hematologic ratios as part of antenatal assessment may offer a practical approach to identifying pregnancies at risk of FGR, particularly in settings where advanced diagnostic resources are limited.

However, the utility of NLR and PLR in predicting FGR, especially late-onset FGR, still needs to be explored. Studies by Aydogan et al. and Seyhanli et al. have investigated the relationship between inflammatory markers and FGR, providing evidence that elevated NLR and WBC counts are more pronounced in FGR cases, which might reflect underlying placental inflammation and compromised fetal growth [7,8]. Given the potential of these markers as predictive tools, further research is warranted to clarify their role in FGR pathogenesis and assess their predictive value in clinical practice.

This study aims to evaluate the inflammatory profiles of pregnancies complicated by late-onset FGR, specifically focusing on NLR and PLR as potential markers of systemic inflammation. By comparing these markers between late-onset FGR and control groups, we hope to contribute to the growing body of evidence on the role of maternal inflammation in FGR and explore the feasibility of integrating these markers into routine antenatal care for early identification of at-risk pregnancies.

Material and Methods

This single-center, retrospective case-control study evaluated the medical records of patients who delivered at our clinic between January 2021 and October 2024. The study population included patients with idiopathic late-onset FGR after 32 weeks of gestation. The control group compromised pregnant individuals who gave birth at term without complications.

Exclusion criteria included the presence of any of the following: (i) multiple pregnancies, (ii) co-existing maternal diseases such as hypertension, metabolic disorders, systemic diseases, or infection, (iii) obstetric complications, including preterm premature rupture of membranes (iv) fetal anomaly, (v) placenta previa, (vi) placental abruption, or (vii) any history of glucocorticoid treatment or blood transfusion. Ethical approval for the study was obtained from the Ethics Committee of the University of Health Science, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital (Approval number: 327-23.10.2024), in compliance with the principles outlined in the Helsinki Declaration.

Maternal demographics, body mass index (BMI), gestational age at diagnosis, amniotic fluid levels, delivery type, timing of delivery, fetal gender, birth weight, Apgar scores at the 1st and 5th minutes, and hemogram values taken between 24th and 28th weeks of gestation were extracted from electronic health records. Sysmex XT-2000i Automated Hematology Analyzer (GMI, MN, USA) was used for hemogram evaluations.

FGR was defined based on ultrasound findings: estimated fetal weight (EFW) or abdominal circumference (AC) below the 3rd percentile, or EFW or AC below the 10th percentile with UA-PI>95th percentile or cerebroplacental ratio less than 5th percentile [3].

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean ± standard deviation (SD) or median with interquartile range (IQR) based on the data distribution. Categorical variables were expressed as frequencies and percentages. Comparative analyses between groups were conducted using independent t-tests or Mann-Whitney U tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables, as appropriate. A p-value of less than 0.05 was considered statistically significant.

Results

Initially, 143 cases of FGR were identified within the study period. Of these, 67 cases were excluded for various reasons (Figure 1). This left a final cohort of 76 FGR fetuses. For comparison, the control group included 100 singleton pregnancies without complications.

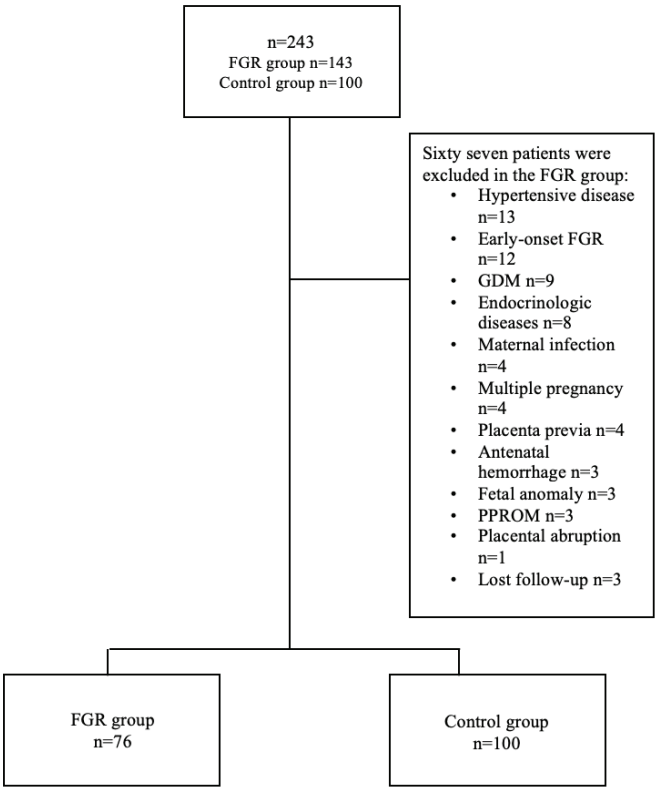

Figure 1. The flowchart of the study group.

Maternal age was similar across both groups, with a mean of 27.4 ± 5.8 years in the FGR group and 28.1 ± 7.6 years in the control group (p=0.08). Likewise, there was no significant difference in BMI at the beginning of pregnancy between the two groups (26.9 ± 5.1 kg/m^2 for the FGR group vs. 27.1 ± 3.4 kg/m^2 for controls, p=0.22). However, nulliparity was significantly more prevalent in the FGR group (53.9%) compared to the control group (28%, p<0.001). The average gestational age at delivery was significantly earlier in the FGR group, at 36.4 ± 1.0 weeks, compared to 38.5 ± 0.8 weeks in the control group (p<0.01). Additionally, birth weights were significantly lower in the FGR group, averaging 2179.3 ± 440.7 grams, while the

control group had an average birth weight of 3408 ± 411.6 grams (p<0.001). The mode of delivery and neonatal gender distribution were similar between groups (p=0.28 and p=0.26, respectively). Apgar scores were significantly lower in the FGR group at both the 1st and 5th-minute assessments (7.1 ± 1.6 and 7.9 ± 1.3, respectively) than in the control group (8.7 ± 0.8 and 9.1 ± 0.7, respectively, p<0.01 for both) (Table 1).

The comparison of hematologic parameters between the FGR and control groups was given in Table 2. Hemoglobin levels were similar between the groups, with the FGR group showing a mean of 12.1 ± 1.3 g/dL compared to 12.4 ± 1.6 g/dL in the control group (p=0.09). However, the white blood cell (WBC) count was significantly higher in the FGR group (10.5 ± 3.2 $x10^9$/L) than in the control group (9.1 ± 2.8 $x10^9$/L, p<0.001). Similarly, the neutrophil count was significantly elevated in the FGR group (7.6 ± 2.5 $x10^9$/L) compared to the control group (6.3 ± 1.9 $x10^9$/L, p<0.001). Lymphocyte and monocyte counts did not differ significantly between the groups (p=0.21 and p=0.33, respectively). Platelet counts were also comparable, with a mean of 261.8 ± 60.1 $x10^9$/L in the FGR group and 254.6 ± 71.5 $x10^9$/L in the control group (p=0.15). In terms of ratios, the neutrophil-to-lymphocyte ratio (NLR) was significantly higher in the FGR group (3.6 ± 0.8) than in the control group (2.8 ± 0.5, p<0.01). Additionally, the platelet-to-lymphocyte ratio (PLR) was significantly elevated in the FGR group (124.2 ± 35.9) compared to the control group (115.4 ± 37.2, p=0.02).

Table 1. Demographic and clinical characteristics of the study groups.

Characteristics	FGR group (n=76)	Control group (n=100)	p
Maternal age (years)	27.4±5.8	28.1±7.6	0.08
BMI at the beginning of pregnancy (kg/m2)	26.9±5.1	27.1±3.4	0.22
Nulliparity n (%)	41 (53.9)	28 (28)	<0.001
Gestational week at diagnosis (week)	34.1±1.1	-	-
Gestational week at delivery (week)	36.4±10	38.5±0.8	<0.01
Birth weight (grams)	2179.3±440.7	3408±411.6	<0.001
Delivery type			0.28
Vaginal birth n (%)	28 (36.8)	45 (45)	
Cesarean section n (%)	48 (63.2)	55 (55)	
Gender			0.26
Female n (%)	40 (52.6)	53 (53	
Male n (%)	36 (47.4)	47 (47)	
Apgar score 1st minute	7.1±1.6	8.7±0.8	<0.01
Apgar socre 5th minute	7.9±1.3	9.1±0.7	<0.01

BMI: Body mass index.

Table 2. Comparison of laboratory data of the study groups.

	FGR group (n=76)	Control group (n=100)	p
Hemoglobin (g/dL)	12.1±1.3	12.4±1.6	0.09
Wbc (x109/L)	10.5±3.2	9.1±2.8	<0.001
Neutrophil (x109/L)	7.6±2.5	6.3±1.9	<0.001
Lymphocyte (x109/L)	2.1±0.9	2.2±0.7	0.21
Monocyte (x109/L)	0.6±0.6	0.6±0.8	0.33
Platelet (x109/L)	261.8±60.1	254.6±71.5	0.15
NLR	3.6±0.8	2.8±0.5	<0.01
PLR	124.2±35.9	115.4±37.2	0.02

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, Wbc: White blood cell.

Discussion

Our findings indicate a significant association between elevated inflammatory markers, specifically the neutrophil-to-lymphocyte ratio (NLR) and white blood cell (WBC) counts, with late-onset FGR. Compared to controls, elevated NLR and WBC in the FGR group point to a systemic inflammatory state that may contribute to the pathogenesis of FGR. Similar inflammatory pathways have been highlighted in previous studies, where increased maternal inflammatory markers have been linked to placental insufficiency, leading to compromised fetal growth [7,8].

Inflammation has been increasingly recognized as a critical factor in the development of FGR, with research showing elevated cytokine levels, such as IL-6, IL-1β, and TNF-α, in FGR cases. These cytokines are known to impact placental function, leading to impaired nutrient and oxygen transfer essential for fetal growth. Studies have reported elevated levels of TNF-α in amniotic fluid during mid-pregnancy among FGR cases, and IL-6 has been linked to growth restriction in newborns [4,10,11]. Our study's findings on elevated NLR align with these studies, as NLR is a readily accessible marker reflecting maternal systemic inflammation. Elevated NLR has been shown to correlate with adverse pregnancy outcomes, including preeclampsia and growth restriction, likely due to its role in mediating inflammatory processes within the uteroplacental unit [12].

Additionally, our study observed no significant difference in platelet-to-lymphocyte ratio (PLR) between the FGR and control groups. While PLR is sometimes considered a marker of vascular inflammation, our results align with those of Aydogan et al., who found that PLR may not be as strongly associated with FGR as NLR [8]. This distinction may suggest that FGR is more closely linked to inflammation affecting immune cell responses rather than to endothelial activation, which would typically involve platelets more directly. Studies on preeclampsia and early-onset FGR, where vascular inflammation is more prominent, have shown greater changes in PLR; however, late-onset FGR, as studied here, may involve a different inflammatory profile [13,14].

Furthermore, our study demonstrated significantly lower Apgar scores in the FGR group, consistent with other studies that associate inflammation with compromised neonatal outcomes [7,8]. Seyhanli et al. observed that systemic inflammation, reflected in parameters like NLR and WBC, correlates with poor neonatal outcomes in FGR cases, further underscoring the role of maternal inflammation in affecting neonatal health [7]. Low Apgar scores may result from chronic fetal exposure to inflammatory states, which could influence fetal development and neonatal adaptation [15].

In conclusion, this study highlights the potential of using inflammatory markers, such as NLR and WBC counts, as cost-effective and accessible tools for assessing the risk of FGR and makes an important contribution to understanding the role of these markers in late-onset fetal growth restriction. Given the challenges in predicting FGR, these findings contribute to a growing body of evidence that inflammatory markers could be useful in identifying pregnancies at risk, aiding in early intervention strategies. The use of inflammatory markers in routine antenatal care could potentially improve the management of high-risk pregnancies, although further research is necessary to standardize their application in clinical practice.

Conflict of Interest Statement and Funding

There is no financial support from any individual or organization for this study, and the authors have no conflicts of interest.

Statement of Non-Submission

We declare that none of the material within this study, in whole or in part, has been previously published elsewhere and is not currently under consideration for publication elsewhere. This includes, except for abstracts up to 400 words, symposiums, information transfers, books, invited articles, electronic submissions, and all types of preprints.

Scientific Responsibility Statement

Conception and design of the experiments, or collection of data; OK, KG

Analysis or interpretation of data; OK

Drafting of the manuscript or revising its scientific content; OK

Approval of the final version of the manuscript for publication; KG

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