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# The Predictive Value of First Trimester Fibrinogen-Albumin Ratio for Late Onset Fetal Growth Restriction

İlk Trimester Fibrinojen-Albumin Oranının Geç Fetal Gelişim Kısıtlılığı Öngörüsündeki Değeri

Osman Onur Özkavak, Dilek Şahin

Department of Perinatology, Ankara Bilkent City Hospital, Ankara, Türkiye

***ORCID ID of the authors***
OOÖ. 0000-0001-9259-7825
DŞ. 0000-0001-8567-9048

**Correspondence / Sorumlu yazar:**
Osman Onur ÖZKAVAK

Department of Perinatology, Ankara Bilkent City Hospital, Ankara, Türkiye

**e-mail:** onurozkavakdr@gmail.com

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**Abstract:** Fetal growth restriction (FGR) is a common cause of adverse pregnancy outcomes, with two main categories: early and late onset.The standard cut-off gestational age is 32 weeks.There's no accepted screening method for early pregnancy prediction. Maternal inflammation is a key factor in FGR development. In the context of inflammation, fibrinogen levels increase and albumin levels decrease, resulting in an elevated fibrinogen albumin ratio (FAR). FAR has been shown to be a valuable prognostic marker for various inflammation-related diseases. This retrospective study aimed to investigate the value of first trimester FAR in predicting the development of late-onset FGR. The study found that first trimester CRP, fibrinogen, and FAR values were statistically significantly higher in the FGR group ($p<0.001$ for all). ROC curve analyses demonstrated that both CRP and FAR exhibited significant predictive capabilities for the development of late FGR. However, the performance of the conventional inflammatory marker “CRP” (sensitivity:61%, specificity:60%) in predicting FGR was found to be inferior to that of FAR (sensitivity:73%, specificity:71%). Also, the FGR group demonstrated significantly elevated rates of adverse neonatal outcomes and neonatal intensive care unit hospitalization. The prediction of FGR risk in early pregnancy is crucial for the implementation of appropriate pregnancy follow-ups and the administration of necessary preventive strategies.This study underscores the potential value of FAR as a prognostic instrument to estimate the probability of late FGR.
**Keywords:** Fetal growth restriction, inflammation, fibrinogen-albumin ratio

**Özet:** Fetal büyüme kısıtlılığı (FGR), erken ve geç başlangıçlı olmak üzere iki ana gruba ayrılır ve olumsuz perinatal sonuçların yaygın bir nedenidir. İki grup arasında ayrım 32. gebelik haftasına göre yapılmaktadır. Erken gebelik döneminde FGR öngörüsü için yaygın olarak kabul gören bir tarama yöntemi yoktur. Maternal inflamasyon, FGR gelişiminde önemli bir faktördür. İnflamasyon varlığında, fibrinojen seviyeleri artar ve albümin seviyeleri azalır, bu da fibrinojen albümin oranının (FAR) yükselmesine neden olur. FAR'ın inflamasyonla ilişkili çeşitli hastalıklar için değerli bir prognostik belirteç olduğu gösterilmiştir. Bu retrospektif çalışma, geç başlangıçlı FGR gelişimini öngörmede ilk trimester FAR'ın değerini araştırmayı amaçlamıştır. Çalışmada ilk trimester CRP, fibrinojen ve FAR değerlerinin FGR grubunda istatistiksel olarak anlamlı derecede yüksek olduğu bulunmuştur (tümü için $p<0,001$). ROC eğrisi analizleri, hem CRP hem de FAR'ın geç FGR gelişimi için istatistiksel olarak anlamlı şekilde prediktif performans sergilediğini göstermiştir. Bununla birlikte, konvansiyonel bir inflamatuar belirteç olan “CRP ”nin FGR'yi öngörme performansı (duyarlılık:%61, özgüllük:%60) FAR değerinden (duyarlılık:%73, özgüllük:%71) daha düşük bulunmuştur. Ayrıca, FGR grubunda olumsuz yenidoğan sonuçları ve yenidoğan yoğun bakım ünitesine yatış oranları anlamlı şekilde yüksek bulunmuştur. Erken gebelikte FGR riskinin öngörülmesi, uygun gebelik takiplerinin planlanması ve gerekli önleyici stratejilerin uygulanması için çok önemlidir. Bu çalışma ile FAR değerinin geç FGR gelişimini öngörmek için potansiyel bir prognostik belirteç olduğu gösterilmiştir..
**Anahtar Kelimeler:** Fetal büyüme kısıtlılığı, inflamasyon, fibrinojen-albümin oranı.

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## 1. Introduction

Fetal growth depends on a variety of factors, including but not limited to maternal disease, uteroplacental function, nutrition, smoking, infection, and genetics. Fetal growth restriction (FGR) signifies the failure of the fetus to achieve its genetically determined growth capacity. The underlying causes of FGR can be classified into three categories: placental, fetal, and maternal. While the underlying mechanisms may differ, these conditions generally result in similar impairments to fetal growth. This phenomenon is referred to as inadequate uteroplacental perfusion (1). Two primary phenotypes of FGR exhibit significant disparities in numerous domains, including gestational age at onset, sonographic observations, placental histopathologic findings, the severity of uteroplacental insufficiency, and adverse perinatal consequences. These include early and late-onset FGR. The consensus cutoff gestational age for this distinction is 32 weeks and is widely accepted on a global scale (2). FGR is considered one of the most prevalent etiologies of unfavorable pregnancy outcomes, affecting an approximate range of five to ten percent of all pregnancies (3). Despite its significance as a major obstetric concern, the prediction of FGR in the early stages of pregnancy remains a challenging endeavor. The predictive performance of existing methods remains suboptimal (4).

Maternal immunologic balance is of great importance in the healthy development and continuation of pregnancy. It has been established that some proinflammatory biomarkers and cytokines contribute to endothelial impairment and placental dysfunction during pregnancy, which can lead to conditions such as preeclampsia and FGR associated with placental insufficiency. A multitude of studies have examined the role of inflammation in FGR, with a particular focus on various hematologic parameters that reflect an individual's inflammatory status. Among these, hemogram-derived combined inflammatory markers, such as systemic immune-inflammation index (SII) and neutrophil-to-lymphocyte ratio (NLR), have been the focus of frequent investigation (5,6). These parameters have been shown to be more sensitive than conventional laboratory tests for inflammation and are easily accessible. Fibrinogen, a protein synthesized in the liver, serves as an acute-phase reactant. During periods of infection, tissue damage, or inflammation, there is an increase in fibrinogen synthesis, influenced by proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (7). Albumin, another protein synthesized in the liver, has reparative, antioxidant, and anti-inflammatory roles in the body. Conversely, albumin levels tend to decrease in chronic inflammation, malnutrition, or liver diseases (8). Low albumin levels are associated with the severity and prolonged duration of inflammation. In inflammatory conditions, fibrinogen levels increase while albumin levels decrease, resulting in an increase in the fibrinogen-albumin ratio (FAR).

It has been shown that FAR can be used as a useful prognostic marker in the diagnosis and severity assessment of various diseases such as placental abruption, pre-eclampsia and hyperemesis gravidarum, as well as neonatal sepsis, cancer, cerebrovascular diseases, and heart diseases (9–13). To the best of our knowledge, however, there are no studies on the use of FAR in the prediction of FGR. Therefore, the present study aimed to investigate the value of first trimester FAR values in predicting the development of late-onset FGR.

## 2. Materials and Methods

The present study was designed retrospectively in a single tertiary care hospital. The sample included patients with a diagnosis of FGR who were monitored and delivered in the High Risk Pregnancies Department of Ankara Bilkent City Hospital between January 2024 and December 2024. The study was reviewed and approved by the ethics committee of the hospital (E2-22-1923), and it adhered to the ethical guidelines outlined in the Declaration of Helsinki at every stage. The gestational age of the patients was determined according to the crown-to-rump length measured in the first trimester. For each patient included in the study, clinicodemographic and obstetric data including age, parity, gravida, body mass index, gestational week at the time of laboratory tests, gestational week at delivery, hemoglobin, white blood cell (WBC), C-reactive protein (CRP), fibrinogen and albumin values at the first trimester (11-14 gestational weeks) controls, neonatal weight, neonatal intensive care unit (NICU) admission, first and fifth minute APGAR scores were retrospectively recorded from the hospital database. FAR was computed by the division of the fibrinogen level by the albumin level. The diagnosis of FGR was made in accordance with the guidelines established by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) (14). For each patient with FGR, a control group was established

by identifying the first healthy pregnant woman who delivered after the patient and had a similar gestational age from the birth registry. Additionally, control group participants were selected to match the FGR group in terms of maternal age (±2 years), and body mass index (BMI) (±2 kg/m²) ensuring better comparability and reducing potential confounding effects.

The following subjects were excluded from the study: pregnant women with known major fetal chromosomal and structural anomalies; patients with active or chronic viral hepatitis and autoimmune hepatitis; diabetic patients; hypertensive patients; multiple gestations; individuals diagnosed with FGR before 32 weeks of gestation; and subjects with missing or inaccessible data. The presence of any of the following was taken to indicate a composite adverse neonatal outcome: delivery before 34 weeks of gestation, neonatal weight less than 2500 grams, first or fifth minute APGAR score less than 5, or admission to the NICU.

The statistical program SPSS v. 22.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to analyze the conformity of the data to normal distribution. Mann Whitney U test was used to compare continuous variables and Pearson Chi-Square test was used to compare categorical variables. A receiver operating characteristic (ROC) curve analysis was used to determine the cut-off value of FAR and CRP to predict FGR. Continuous variables are presented as median and quartile range (IQR), and categorical variables are presented as percentages (%) and numbers. Results of the ROC curve analysis were presented as the area under the curve (AUC), standard deviation, and 95% confidence interval (CI). The cut-off value providing optimum sensitivity and specificity values was calculated using Youden's index. A p value less than 0.05 was considered statistically significant.

## 3. Results

The study encompassed a total of 124 patients, categorized into two groups: 62 cases of FGR and 62 controls. The study found no significant differences between the groups in terms of age, gravidity, parity, BMI, first trimester hemoglobin, WBC count, and albumin values. Conversely, the FGR group demonstrated significantly elevated first trimester CRP, fibrinogen, and FAR mean values ($p<0.001$ for all).

A subsequent analysis of obstetric outcomes revealed that gestational week at delivery and newborn weight were significantly lower in the FGR group ($p=0.002$ and $p<0.001$, respectively). While there was no significant difference in first- and fifth-minute APGAR scores, the NICU hospitalization rate was 25.8% in the FGR group and 10.9% in the control group ($p=0.031$). The composite adverse neonatal outcome rate was 27.4% in the FGR group and 12.5% in the control group ($p=0.036$). The results of the comparison of clinicodemographic data and obstetric outcomes for the groups are presented in Table 1.

**Table 1.** The results of the comparison of clinicodemographic data and obstetric outcomes for the groups

| Variable | FGR (n:62) Median (IQR) | Control (n:62) Median (IQR) | p value |
|---|---|---|---|
| Age (year) | 28 (6) | 29 (9) | 0.108 |
| BMI (kg/m$^2$) | 27 (2) | 28 (2) | 0.587 |
| Gravidity | 2 (2) | 2 (3) | 0.359 |
| Parity | 1 (2) | 1 (2) | 0.274 |
| Hemoglobin (g/dL) | 12.3 (1.7) | 11.9 (1.6) | 0.265 |
| WBC (x10$^9$/L) | 9455 (3507) | 9390 (3120) | 0.467 |
| CRP (mg/L) | 5.6 (8.1) | 0.7 (6.8) | <0.01 |
| Fibrinogen (g/L) | 4.32 (1.35) | 3.5 (0.5) | <0.01 |
| Albumin (g/L) | 39 (5) | 39 (4) | 0.682 |
| FAR | 0.111 (0.04) | 0.088 (0.01) | <0.01 |
| Gestational age at birth (week) | 38 (1) | 38 (2) | <0.002 |
| Newborn weight (gram) | 2515 (518) | 3080 (590) | <0.01 |
| APGAR 1 | 7 (1) | 7 (1) | 0.905 |
| APGAR 5 | 9 (1) | 9 (1) | 0.774 |
| NICU | % 25.8 | % 10.9 | 0.031[a] |
| CANO | % 27.4 | % 12.5 | 0.036[a] |

*Pearson Chi-Square Test, FGR: fetal growth restriction, BMI: body mass index, WBC: white blood cell count, CRP: C-reactive protein, FAR: fibrinogen-albumin ratio, NICU: neonatal intensive care unit, CANO: composite adverse neonatal outcomes, p<0.05 accepted as statistically significant*

ROC curve analyses were performed to investigate the value of first trimester CRP and FAR in predicting late FGR, and it was determined that both variables significantly predicted this condition. The AUC for FAR was 0.764 (95% CI: 0.673-0.855, p<0.001), while the AUC for CRP was 0.684 (95%CI: 0.591-0.777, p<0.001). The cut-off values for optimal sensitivity and specificity were determined to be 0.094 (sensitivity: 73%, specificity: 71%) for FAR and 4.55 (sensitivity: 61%, specificity: 60%) for CRP. The results of the ROC curve analysis are presented in Table 2 and Figure 1.

**Table 2.** Results of ROC curve analysis evaluating the performance of first trimester CRP and FAR in predicting late onset FGR

| Variable | AUC | 95%CI | Cut-Off | Sensitivity | Specificity | p value |
|---|---|---|---|---|---|---|
| FAR | 0.764 | 0.673-0.855 | 0.094 | %73 | %71 | <0.01 |
| CRP | 0.684 | 0.591-0.777 | 4.55 | %61 | %60 | <0.01 |

*CRP: C-reactive protein, FAR: fibrinogen-albumin ratio, AUC: area under the curve, CI: confidence interval, p<0.05 accepted as statistically significant*

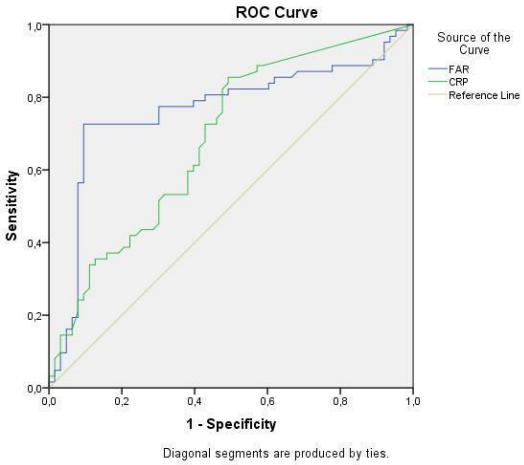


**Figure 1.** ROC curve analysis evaluating the performance of first trimester CRP and FAR in predicting late FGR

## 4. Discussion

The ability to predict FGR in the early stages of pregnancy has the potential to identify pregnancies that are at risk, to plan for close follow-up with these patients, and to implement prophylactic strategies when necessary. However, there is currently no universally accepted protocol for predicting FGR or adverse perinatal outcomes. The objective of this study was to examine the role of the first trimester level of FAR, a recently developed marker of inflammation, in predicting late-onset FGR and its potential as a predictor of poor neonatal outcomes. The findings of the study indicate that FAR, calculated during the first trimester, demonstrates considerable promise in the prediction of late-onset FGR.

A number of ultrasound findings and biochemical markers in early pregnancy have been examined for their potential to predict FGR.In the first trimester sonographic examination, increased resistance on uterine artery Doppler is an important indicator of impaired placental perfusion and indicates a high risk of FGR (15). Furthermore, an array of biochemical markers, including free beta-human chorionic gonadotropin (β-hCG), pregnancy-associated plasma protein A (PAPP-A), soluble fms-like tyrosine kinase-1 (sFlt-1), and soluble endoglin (sEng), have been assessed for their capacity to predict FGR in early pregnancy (16,17). These markers are recognized as crucial indicators of maternal-fetal health and placental function. Consequently, the objective is to assess the mechanisms that may contribute to the development of FGR. While these biomarkers are useful, their predictive performance is limited, and they can be cost-prohibitive. The optimal prediction instrument should be characterized by ease of implementation, cost-effectiveness, and standardization.

Placental insufficiency plays a pivotal role in the pathogenesis of FGR, and inflammation can either cause or exacerbate this deficiency by altering the

structure and function of the placenta. Increased levels of proinflammatory cytokines have been demonstrated in cases of FGR, and this is thought to contribute to impaired angiogenesis, incomplete trophoblast invasion, and activation of pathways leading to endothelial dysfunction (18,19). Furthermore, inflammatory mediators such as sFlt-1 have been shown to promote the release of anti-angiogenic factors, which further impairs placental vascular development (20). In addition, studies have demonstrated an elevation of pro-inflammatory Th1 cells in pregnant women with FGR, compared to the anti-inflammatory Th2 cells that typically predominate during pregnancy (21). This imbalance in the maternal immune system, coupled with the heightened inflammatory response in the mother, has the potential to impede placental development, directly impacting its functionality, and thereby contributing to the onset of FGR (22).

A paucity of studies have been conducted that investigate the role of fibrinogen or albumin levels in pathophysiologic processes in pregnancy, and the results of these studies are contradictory. In the context of preeclampsia, a condition characterized by placental insufficiency, studies have observed elevated fibrinogen levels compared to healthy pregnancies (23,24). This increase is believed to be a consequence of an exaggerated inflammatory response and vascular endothelial activation, which are considered the mechanisms underlying the pathogenesis of preeclampsia. However, contrary to this, Chen et al. observed that women with preeclampsia had lower fibrinogen levels compared to healthy pregnant and non-pregnant women in the third trimester (25). In the initial study of two investigations exploring the relationship between fibrinogen levels and FGR, no statistically significant differences were identified between the FGR and control groups (26). However, in a subsequent study with a larger sample size, the FGR group exhibited higher fibrinogen levels (27). In the context of pregnancy-associated hypertension, a decline in serum albumin levels has been observed, suggesting its potential as a prognostic indicator (28). Furthermore, lower serum albumin levels have been observed in cases of recurrent pregnancy loss and threatened miscarriage compared to healthy pregnant women (29,30). The findings of studies examining the association between fetal growth and albumin levels are inconsistent. Some studies have indicated that high maternal albumin levels are associated with low birth weight and FGR, suggesting that the underlying reason for this association may be a lack of adequate hemodulation during pregnancy (31,32). Conversely, in low socioeconomic status pregnant women, low serum albumin levels have been associated with low birth weight (33). In a separate study that identified an inverse correlation between maternal serum albumin levels at 18 weeks of gestation and birth weight, the researchers noted that there was a negative association between albumin and BMI. They further observed that the correlation between albumin levels and birth weight vanished when the impact of BMI was adjusted for (34). The observed discrepancy in the outcomes related to the impact of albumin on birth weight can be attributed to the varying levels of albumin in pregnant women with different BMI categories. Specifically, low albumin levels in pregnant women with high BMI do not necessarily indicate malnutrition, in contrast to the situation observed in pregnant women with low BMI.

FAR is a biomarker that can be measured by the ratio of fibrinogen and albumin values evaluated in laboratory tests in routine prenatal care. It does not incur additional costs. A substantial body of research has emerged from the scientific literature, demonstrating a correlation between elevated FAR levels and a variety of chronic inflammatory diseases, including ankylosing spondylitis, acute coronary syndrome, systemic lupus erythematosus, and obstetric complications such as threatened abortion, hyperemesis gravidarum, and severe preeclampsia (9,13,30,35–37). Consistent with these findings, FAR has been demonstrated to serve as a valuable prognostic marker in breast cancer cases (38). Elevated plasma FAR has also been demonstrated to serve as an independent risk factor for unfavorable prognoses, including reduced disease-free survival times and early recurrence in cases of esophageal squamous cell carcinoma (39). A comprehensive analysis of these studies suggests that FAR may emerge as a promising prognostic marker in the context of inflammatory processes.

In the present study, fibrinogen levels in the first trimester were elevated in the FGR group, while albumin levels did not demonstrate a significant difference. In conjunction with the relatively modest patient sample size in the present study, the conflicting data observed in previous studies limits the ability to draw definitive conclusions regarding the relationship between these two parameters and FGR. Furthermore, the present study observed an elevated first trimester FAR value in the FGR group. The potential implications of maternal inflammatory status in early pregnancy on the development of FGR are further underscored by the observed elevation of this inflammatory marker.

The maternal immune system undergoes a series of changes during pregnancy to ensure the health of both the mother and the fetus. In this process, acute-phase reactants and cytokines play a crucial role (40). CRP, in particular, has been observed to increase as early as the fourth week of gestation (41). Elevated maternal CRP levels have been associated with an increased risk of preterm labor (42). Increased WBC in maternal peripheral blood may serve as an indicator of an inflammatory environment, which has been observed in pregnancy complications such as preeclampsia (43). However, the results of studies investigating the relationship between FGR and CRP remain inconsistent. Some studies have indicated that elevated CRP in early pregnancy predicts low birth weight, while others have found no association between CRP and birth weight (44–46).

The present study demonstrated that the FGR group exhibited elevated CRP levels during the early stages of pregnancy, in comparison to healthy pregnant individuals. However, the performance of the conventional inflammatory marker "CRP" in predicting FGR was inferior to that of FAR, as evidenced by the results of the ROC curve analyses.

The retrospective nature of the study and its single-center design are limitations that should be noted. Additionally, the number of cases included in the sample is limited, which may impact the generalizability of the results. Further clinical trials are necessary to substantiate the efficacy in clinical practice.

## 5. Conclusion

The identification of pregnancies deemed to be at risk of FGR is of paramount importance to healthcare providers, as it enables the planning of appropriate fetal monitoring and the implementation of necessary precautions. This study underscores the potential value of FAR as a prognostic instrument for anticipating the likelihood of FGR, with the earliest detection occurring as early as the first trimester. The current study is the first to examine the value of FAR, a recently identified marker of inflammation, in predicting FGR.

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