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RESEARCH ARTICLE

The value of the second trimester glucose-to-lymphocyte ratio in predicting fetal loss at late preterm and term pregnancies

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Abstract

Introductıon: This study aimed to determine whether the second-trimester glucose-to-lymphocyte ratio (GLR) can predict intrauterine fetal demise (IUFD) at late preterm and term gestations.

Methods: A retrospective cross-sectional design was employed. Pregnant women aged 18–45 who delivered at our tertiary hospital between January 2023 and December 2024 were screened. Those diagnosed with IUFD at or beyond 34 weeks of gestation comprised the case group, while two healthy pregnant women of similar age and body mass index for each case served as the control group. Laboratory parameters from the 20th–24th weeks, including hemoglobin, white blood cell (WBC) count, neutrophil count, lymphocyte count, random blood glucose, and GLR, were analyzed.

Results: Data from 105 patients (35 IUFD, 70 controls) were included. The IUFD group had significantly lower WBC, neutrophil, and lymphocyte counts but higher glucose and GLR than controls ($p<0.01$). Receiver operating characteristic analysis showed an area under the curve of 0.876 ($p<0.01$) for GLR, with 80% sensitivity and 79% specificity at a cutoff of 0.604.

Conclusion: Elevated GLR in the second trimester may reflect subclinical inflammation and serve as a practical, cost-effective predictor of IUFD. Further large-scale studies are warranted to validate these findings.

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Introduction

Intrauterine fetal demise (IUFD) is defined as the cessation of fetal cardiac activity after the 20th week of gestation and prior to delivery.[1] It is one of the most dramatic complications of pregnancy, occurring in approximately 5 per 1000 births in developed countries, whereas the incidence is considerably higher in developing nations.[2] Although many risk factors have been identified, such as maternal diseases, fetal genetic or structural anomalies, or intrauterine infections, IUFD is not always confined to high-risk pregnancies.

An association between increased maternal inflammatory response in early pregnancy and fetal loss has been suggested. In acute or chronic inflammatory conditions, cells such as macrophages and neutrophils require a hyperglycemic environment to meet their elevated energy demands.[3] Furthermore, lymphopenia is a component of the acute severe inflammatory response, driven by corticosteroid-induced lymphocyte apoptosis and migration, along with the movement of lymphocytes to the inflammation site and the action of cytokines such as TNF-α.[4] While lymphopenia is more frequent and severe in acute inflammation, it may also occur in chronic inflammation due to suppressed lymphocyte production and prolonged consumption.

The glucose-to-lymphocyte ratio (GLR) has recently been proposed as a novel index reflecting this hyperglycemia and lymphopenia observed in inflammatory states. Its clinical utility in detecting inflammation and monitoring therapeutic response has been highlighted in various disorders.

Based on the hypothesis that subclinical inflammation in the second trimester is related to the subsequent development of IUFD, this study aimed to investigate the utility of the second-trimester GLR in predicting IUFD at term.

Material and Methods

This retrospective cross-sectional study included pregnant women aged 18–45 who were admitted to our tertiary training and research hospital between January 2023 and December 2024 with a diagnosis of IUFD at or beyond 34 weeks of gestation. Data were obtained from the hospital's electronic medical records and patient files. The study was approved by the local ethics committee under the approval number TABED-2-25-916.

Inclusion criteria required that all prenatal follow-ups and deliveries had taken place at our center, and that complete blood count (CBC) and biochemical tests had been performed between the 20th and 24th weeks of gestation. Patients diagnosed with IUFD after 34 weeks of gestation comprised the case group. The following criteria guided the selection of subjects for the control group: From the birth registry, for each patient in the case group, the first two patients of similar age, BMI, and gestational age who delivered live births subsequent to her were selected.

Patients were excluded if they met any of the following criteria: multiple pregnancies, chronic inflammatory disease, suspected or established malignancy, fetal genetic or major structural anomalies, any history of smoking, alcohol, or substance abuse, congenital infections, pregestational or gestational diabetes mellitus, chronic hypertension, or placental abruption.

The two groups were compared regarding age, gravidity, parity, number of abortions, BMI; and laboratory parameters obtained between the 20th and 24th weeks of gestation: hemoglobin, white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, random blood glucose level, and the glucose/lymphocyte ratio (GLR).

Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess the normality of data distribution. Continuous variables without normal distribution were presented as median (interquartile range, IQR), and comparisons between groups were made using the Mann–Whitney U or Kruskal–Wallis tests. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive power of GLR, and the cut-off value that provided the highest sensitivity and specificity was calculated. Youden's index was used to determine the optimal cut-off value. Statistical significance was accepted as $p<0.05$. All analyses were performed using SPSS software (version 24, IBM Corp., Armonk, NY).

Results

A total of 105 patients (35 IUFD, 70 controls) were included. There was no significant difference between the groups regarding age, gravidity, parity, number of abortions, BMI, hemoglobin, and monocyte count.

In the IUFD group, WBC, neutrophil count, and lymphocyte count were significantly lower than in the control group ($p=0.03$, $p=0.02$, and $p<0.01$, respectively). The median values for glucose and GLR were significantly higher in the IUFD group ($p<0.01$,

p<0.01). Table 1 presents the clinical and laboratory characteristics of both groups.

Table 1. Comparison of clinical characteristics, laboratory results, birth outcomes, and combined inflammatory indices between IUFD and control groups

Variable	Control (n: 70) Median (IQR)	IUFD (n:35) Median (IQR)	p-value
Age (years)	29 (7)	27 (9)	0.05
Gravidity	2 (2)	2 (2)	0.40
Parity	1 (2)	1 (2)	0.91
Abortus	0 (1)	0 (0)	0.09
BMI	28.4 (12)	29.6 (14.1)	0.36
Hemoglobin (g/dL)	12 (2)	12.3 (2)	0.06
WBC (x109/L)	9.27 (2.5)	7.81 (3.2)	0.03
Neutrophil count (x109/L)	6.63 (2.3)	5.49 (2.5)	0.02
Lymphocyte count (x109/L)	1.79 (0.59)	1.35 (0.93)	<0.01
Monocyte Count (x109/L)	0.45 (0.17)	0.36 (0.23)	0.15
Glucose (mg/dL)	82.5 (17)	111 (16)	<0.01
GLR	0.048 (0.024)	0.083 (0.068)	<0.01

IUFD: intra uterine fetal demise, IQR: interquartile range, WBC: white blood cells, GLR: glucose-lymphocyte ratio, p values less than 0.05 accepted as statistically significant

ROC curve analysis for GLR in predicting IUFD showed an area under the curve (AUC) of 0.876 (95% CI: 0.802–0.949, p<0.01). The cut-off value for GLR providing optimal sensitivity and specificity was determined to be 0.604 (80% sensitivity, 79% specificity). Figure 1 and Table 2 show the ROC analysis results.

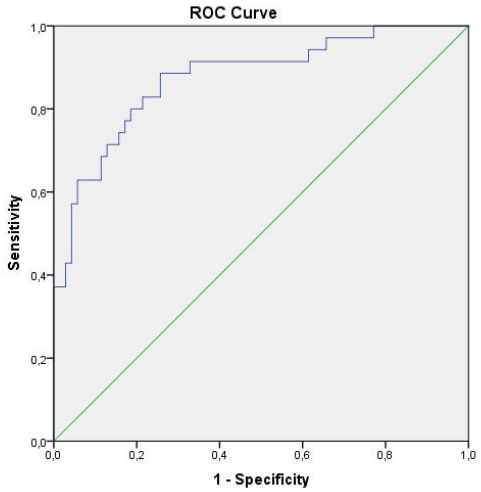

Figure 1 ROC curve evaluating the performance of GLR in predicting IUFD

Table 2. Predictive Performance of GLR for IUFD Based on ROC Curve Analysis

Variable	AUC	95% CI	Cut-off value	Sensitivity	Specificity	p-value
GLR	0.876	0.802-0.949	0.604	80%	79%	<0.01

GLR: glucose-lymhocyte ratio, AUC: area under the curve, CI: confidence interval, p<0.05 accepted as statistically significant

Discussion

Numerous factors have been implicated in the etiology of IUFD, such as antepartum hemorrhage, fetal chromosomal or structural anomalies, intrauterine infections, fetal growth restriction, and preeclampsia-related placental insufficiency.[5] Several mechanisms have been proposed in its pathophysiology, among which acute or chronic fetal hypoxia is the most recognized. Evidence also suggests a strong link between inflammation and fetal demise.[6,7]

The relationship between IUFD and inflammation arises from the balanced functioning of maternal and fetal immune systems. Inflammation can compromise the intrauterine environment through maternal infections and proinflammatory responses. During maternal infections, proinflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) can alter placental vasculature, reducing uteroplacental blood flow and leading to fetal hypoxia.[8] These cytokines may also induce oxidative stress and apoptotic pathways in fetal tissues, causing direct fetal damage. At the placental level, an inflammatory response can hinder trophoblast invasion and result in placental insufficiency, potentially culminating in fetal growth restriction or death.[9] Moreover, hyperactivation of the maternal immune system may recognize the fetus as a foreign antigen and mount an immunologic attack.[10] Together, these mechanisms underscore the critical role of poorly regulated inflammation in IUFD.

GLR reflects the hyperglycemic environment in inflammatory states and the lymphopenia observed particularly during acute inflammation. Its use as a sensitive marker to diagnose inflammation and monitor therapeutic response is increasingly recognized in various clinical scenarios. Elevated GLR levels have been linked to higher mortality rates in septic patients admitted to intensive care units.[11] Similarly, in a large-scale retrospective study on adult patients with respiratory distress syndrome, an elevated GLR was identified as a readily accessible predictor of morta-

lity. [12] This marker has also attracted attention in malignancies characterized by increased inflammation, with studies suggesting that GLR is a cost-effective, useful prognostic indicator in pancreatic and breast cancers.[13–15] Furthermore, GLR has been associated with prognostic outcomes in acute conditions such as myocardial infarction and hemorrhagic cerebrovascular events.[16,17]

In obstetrics, reduced pregnancy-associated plasma protein-A (PAPP-A) and human chorionic gonadotropin (hCG), along with increased nuchal translucency in first-trimester aneuploidy screening, have been linked to a higher fetal demise risk, even in the absence of aneuploidy.[18] Additionally, combined inflammatory markers such as the systemic immune-inflammation index (SII) and the neutrophil-to-lymphocyte ratio (NLR) have been associated with conditions related to placental insufficiency and fetal death, including fetal growth restriction and severe preeclampsia.[19,20]

The findings of this study indicate that GLR, an emerging prognostic marker in various inflammatory diseases, could also be beneficial in predicting IUFD—a condition intimately related to inflammation. Specifically, elevated GLR levels in otherwise uncomplicated pregnancies at 20–24 weeks could predict IUFD with a promising sensitivity (80%) and specificity (79%). These results not only strengthen the association between inflammation and IUFD but also highlight GLR as a potential early warning marker.

The limitations of this study include its retrospective design and single-center data. Its strength lies in being, to our knowledge, the first study in the literature to investigate the association between GLR and IUFD.

Conclusion

Inflammation plays a pivotal role in the pathophysiology of late-onset IUFD, one of the most devastating pregnancy complications. GLR, a recently identified prognostic marker for several inflammatory conditions, has the potential to serve as a practical, cost-effective tool for early prediction of this unexpected obstetric complication. Recognizing inflammation early and implementing appropriate interventions could be beneficial. However, further large-scale studies are needed to substantiate these findings.

Statements & Declarations

Funding

The authors declare that no funds, grants, or other support were received.

Declaration of Conflict Interests

The authors have no competing interests to declare.

Ethics approval

The study protocol was approved by the Ankara City Hospital Clinical Research Ethics Department and was performed in line with the Declaration of Helsinki. The ethics committee approval was obtained with the decision number TABED-2-25-916.

Author Contribution

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by OOO, DS. The first draft of the manuscript was written by OOO and DS commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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