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Evaluation of the leukoglycemic index in preeclampsia: Could it have diagnostic value?

Ahmet Zeki Nessar[1], Yusuf Dal[1], Şebnem Karagün[1], Sefanur Gamze Karaca[1], Mürşide Çevikoğlu Kıllı[2], Ayhan Coşkun[1]

[1]Mersin University, Faculty of Medicine, Department of Perinatology, Mersin, Türkiye
[2]Mersin University, Faculty of Medicine, Department of Gynecological Oncology, Mersin,Türkiye

Abstract

Objective: The aim of the study is to investigate the diagnostic performance of the leukoglycemic index (LGI) in the diagnosis of preeclampsia (PE).

Methods: The study included 176 pregnant women meeting inclusion criteria, with 69 in the study group and 107 in the control group. Obstetric and demographic data, gestational weeks, newborn birth weights, 1st and 5th minute Apgar scores, umbilical cord pH levels, and NICU admission information were recorded and compared between both groups. LGI was calculated from the laboratory results of the study group at the time of diagnosis and compared with the control group. LGI was calculated by multiplying leukocyte count by blood glucose and dividing by 1,000.

Results: LGI was statistically significantly higher in the PE group compared to the control group (1421.06 vs. 997.32, p = 0.001). LGI correctly identified 65.22% of PE patients and 84.96% of healthy pregnant women (p = 0.001).

Conclusion: LGI was higher in the PE group. The sensitivity of LGI, which is an easily calculated marker in the diagnosis of PE, was 65.22%, and the specificity was 84.96%. In conclusion, we believe that it is a useful marker that can help in the diagnosis of this disease.

Keywords: Inflammation, leucoglycemic index, preeclampsia

Introduction

Hypertensive disorders of pregnancy, including gestational hypertension, preeclampsia (PE), eclampsia, chronic hypertension, and superimposed PE, affect approximately 10% of pregnancies and are the main cause of fetal and maternal mortality and morbidity.[1] Preeclampsia complicates 2-8% of pregnancies. It is a systemic disease that occurs after the 20th week of pregnancy and is characterized by hypertension, with or without proteinuria, and involves multi-organ damage, including the liver, kidneys, and central nervous system.[2] PE that develops before the 32nd week of pregnancy is defined as early-onset PE, and PE that occurs after the 32nd week of pregnancy is defined as late-onset PE.[3] Early-onset PE may show more severe clinical features than late-onset PE.

The cause of PE is still not fully understood. It is believed that endothelial dysfunction, insufficient trophoblast invasion, and impaired spiral artery remodeling play a role in the pathogenesis of the disease.[4] In normal pregnancy, the balance between T helper (Th)1 and Th2 immune cells, which are in a delicate balance, is disrupted in favor of Th1 in preeclamptic pregnancies. The increased Th1 cells lead to excessive release of certain cytokines, resulting in chronic inflammation and oxidative stress.[5] The findings that systemic lupus erythematosus (SLE), obesity, diabetes, and chronic hypertension, all conditions associated with chronic inflammation, increase the risk of preeclampsia, lend credence to the notion that chronic inflammation plays a significant role

Correspondence: Ahmet Zeki Nessar, Mersin University, Faculty of Medicine, Department of Perinatology, Mersin, Türkiye, **e-mail:** zekinessar@gmail.com , **Received:** February 12, 2024 **Accepted:** April 16, 2024

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ORCID ID: AZ Nessar 0000-0003-2985-0212; Y Dal 0000-0001-7162-4644; Ş Karagün 0000-0003-2339-1609; SG Karaca 0000-0003-1595-2621; M Çevikoğlu Kıllı 0000-0003-0007-2816; A Coşkun 0000-0002-2887-9649

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in the pathogenesis of preeclampsia.[6]

The leukogycemic index (LGI) is a systemic inflammation marker that has been identified in recent years. It is an index that can be easily and quickly calculated by multiplying the number of white blood cells by the blood glucose.[7] It has been determined that it is an independent mortality indicator in patients with coronary artery disease.[6] There is no data in the literature regarding the relationship between LGI and PE.

The increase in the number of leukocytes in PE is greater than in normal pregnancies.[8] Based on this, we thought that it might be useful to investigate the diagnostic performance of a systemic inflammatory marker such as LGI in the diagnosis of PE. Our study is the first study in the literature on this subject.

Methods

The ethics committee of our university approved the inclusion of pregnant women diagnosed with PE who were followed up and treated in our hospital, a tertiary care center, between January 1, 2021 and June 1, 2023, with the decision numbered 2023/692. The electronic records of the patients were retrospectively reviewed. Pregnant women who met the inclusion and exclusion criteria were enrolled in the study and divided into two groups. Singleton pregnant women diagnosed with PE were selected for the study. The absence of additional obstetric pathologies was taken into consideration. Exclusion criteria included diabetes, multiple pregnancies, premature preterm membrane rupture (PPROM), fetal anomalies, collagenous connective tissue or autoimmune disease history, systemic diseases (liver, kidney, heart, lung, psychiatric disorders), alcohol, tobacco, or substance addiction, the presence of active local or systemic infection, and a history of immunodeficiency. As a control group, healthy pregnant women with matched gestational ages were selected. Similarly, the absence of any additional systemic or obstetric conditions was considered in the control group. The diagnosis of PE was based on the criteria of the American College of Obstetricians and Gynecologists (ACOG). Accordingly, after 20 weeks of pregnancy, newly diagnosed hypertension (measured at intervals of 4 hours and systolic 140 mm Hg, diastolic 90 mmHg, and/or higher arterial blood pressure) and signs of organ damage regardless of the presence of proteinuria (more than twice the liver enzymes, thrombocyte count less than 100000×10^9 /liter (L), pulmonary edema, newcomers and non-reacting to analgesics, persistent upper right membrane pain, double serum creatine levels or 1.1 milligrams/desiliter (mg/dL) in milk without known kidney disease, visual impairment) were accepted as criteria for diagnosis .[3]

Patient data including age, gravidity, parity, height, weight, body mass index, hemoglobin, haematocrit, leukocytes, glucose levels, platelet count, average thrombocyte volume (MPV), platecrites (PCT), aspartate aminotransferase (AST), alanine amino transferase (ALT), birth weeks, newborn birth weight, 1st and 5th minute Apgar scores, umblical cord pH, and newborn intensive care unit (NICU) admissions were collected from electronic hospital records. LGI was calculated by multiplying the leukocyte count ($\times10^3$/ microliter (µl)) by the blood glucose level (mg/dl) and dividing the result by one thousand. [9] Laboratory data of both the study and control groups were obtained from hospital records and represent laboratory values at the gestational week when PE was diagnosed. No medication was administered prior to collection of laboratory data for evaluation.

Statistical Analysis

Data analysis was conducted using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normality using Kolmogorov-Smirnov, Shapiro-Wilk tests, and histograms. Mean differences between the two groups were compared using the independent sample t-test or Mann-Whitney U test, depending on the normality of the distribution. Continuous variables were presented as mean ± standard deviation (SD) or median (IQR). The best way to tell the difference between the groups was found using Receiver Operating Characteristic (ROC) analysis by LGI. The area under the curve (AUC) was used to find the maximum Youden index, which is (sensitivity + specificity - 1). A P-value less than 0.05 was considered statistically significant.

Results

A total of 176 pregnant women were included in the study based on inclusion and exclusion criteria. The PE group consisted of 69 women, while the control group consisted of 107 pregnant women. When evaluating the demographic data of the groups, the groups were similar in terms of age (29.9±7.36 vs. 30.19±5.61, p = 0.676) and BMI (26.32±4.48 vs. 25.73±4.20, p = 0.270). The median numbers of gravidity (2 (1-3) vs. 3 (2-4), p = 0.003) and parity (1 (0-1.5) vs. 1 (0-2), p = 0.014) were significantly lower in the PE group.

A comparison of the birth and neonatal outcomes of the groups is presented in Table 1. The birth-week control group had a significantly lower birth weight than the PE group (p = 0.001). The median birth weights in the PE group were lower than those in the control group (2300 grams vs. 3210, p = 0.001). The median Apgar scores at 1 and 5 minutes and

umbilical cord blood pH values were all significantly lower in the PE group (p = 0.001). The NICU admission rate was 76.8% in the PE group and 9.7% in the control group, and this difference was statistically significant (p = 0.001).

When comparing the laboratory parameters of the groups (Table 2), there was no significant difference between the groups in terms of hemoglobin, hematocrit, platelet, PCT, and MPV values (p-values were 0.408, 0.104, 0.243, 0.151, and 0.120, respectively). The leukocyte values were lower, and the AST, ALT, and blood glucose levels were higher in the PE group compared to the control group (p = 0.001 for all). The LGI was statistically significantly higher in the PE group compared to the control group (1421.06 vs. 997.32, p = 0.001).

ROC analysis was used to evaluate the success of LGI in diagnosing PE (Figure 1). The analysis showed that LGI has a significant diagnostic value for PE. The cut-off point for LGI in distinguishing between groups was calculated to be >1193.01. It was found to show 65.22% sensitivity and 84.96% specificity for the diagnosis of PE at this cut-off point. The area under the curve (AUC) value was found to be 0.800 (0.735-0.856) (p=0.001).

Table 1. Comparison of the delivery and neonatal outcomes of the groups

Parameters	PE group (n=69)	Control group (n=107)	p value
	Median (IQR)	**Median (IQR)**	
Birth week	35 (32-37)	38 (37-39)	0.001*
Birth weight (gram)	2300 (1507.5-2845)	3210 (2950-3520)	0.001*
Apgar score 1st minute	7 (5-8)	8 (6-9)	0.001*
Apgar score 5th minute	8 (7.5-9)	9 (8-10)	0.001*
	n(%)	**n(%)**	
NICU	53(76.8%)	11(9.7%)	0.001**
	mean±SD	**mean±SD**	
Umblikal cord blood pH	7.25±0.13	7.33±0.06	0.001***

*Mann -Whitney U test, **Chi-Squared test, ***Independent Sample t testi. A value of p<0.05 is significant. Bold p values indicate statistical significant.

Table 2. Comparison of laboratory parameters of the groups

Parameters	PE group (n=69)	Control group (n=107)	P value
	mean±SD	**mean±SD**	
Hemoglobin (g/dl)	10.78±1.6	10.99±1.64	0.408*
Hematocrit (%)	31.28±4.27	32.07±4.2	0.104*
Leukocyte (×10³/µl)	13.940±5.297	11.525±2.243	0.001*
Platelets (×10³/µl)	200.890±90.937	215.991±71.948	0.243*
PCT (%)	0.21±0.09	0.23±0.07	0.151*
MPV (fl)	11.21±1.24	10.9±1.18	0.120*
AST (U/L)	77.21±201.11	21.67±21.75	0.001*
ALT (U/L)	45.33±91.89	14.97±35.51	0.001*
Blood glucose (mg/dl)	101.94±15.65	87.06±12.05	0.001*
LGI	1421.06±588.31	997.32±203.87	0.001*

***Independent Sample t test. A value of p<0.05 is significant. Bold p values indicate statistical significant.

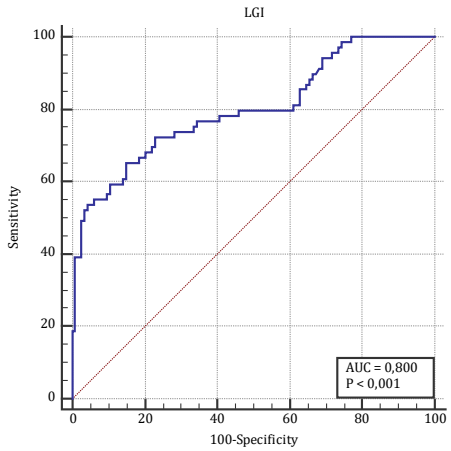

Fig 1. ROC analysis of LGI for the diagnostic value of preeclampsia

Discussion

Our findings determined that LGI in PE was significantly higher than in healthy controls and also had a significant diagnostic value for LGI in PE.

It has long been debated that inflammation plays an important role in the pathogenesis of PE. Due to the excessive release of cytokines in the fetoplacental unit, an increase in mononuclear phagocytic system activity, oxidative stress, and impaired inflammatory response led to the development of PE syndrome.[10] In a study conducted by Bu et al., it was found that cyncytin-1, a modulator of inflammation, plays a role in regulating vascularization, hypoxia, immunity, and infection that contribute to systemic inflammation in preeclamptic pregnant women.[11] One reason for the increased risk of PE in obese women is

the release of cytokines such as tumor necrosis factor-alpha (TNF-) and interleukin-6 (IL-6) into circulation from adipose tissue, which contribute to inflammation.[12] In a study conducted by Wang et al., an increase in inflammation-related proteins was detected in the plasma of women with PE using Olink technology. The increase was most notable in cysteine-cysteine chemokine ligand 20 (CCL20) and fibroblast growth factor 21 (FGF-21). The authors suggest that CCL20 may have predictive value in the diagnosis of PE.[13] Van Rijn et al. (year) found that an increased susceptibility to PE and HELLP syndrome was more frequently observed in women with certain genetic variants and a pro-inflammatory phenotype.[14]

Early diagnosis of preeclampsia is crucial for maternal and fetal health. Therefore, various sonographic markers and biomarkers in the blood have been investigated for their predictive value. An ideal marker should have high sensitivity and specificity, be easily calculable or accessible, and be cost-effective. In a study by Van Rijn et al., levels of inflammation markers such as C-reactive protein and fibrinogen were found to be associated with recurrent preeclampsia.[15] A study by Mannaerts et al. found that MPV was higher in pregnant women who later developed PE as a marker of inflammation in the first half of pregnancy.[16] Similarly, Artunç-Ülkümen et al. observed that neutrophil gelatinase-associated lipocalin (NGAL) and procalcitonin levels were higher in pregnant women with PE.[17] LGI was first used as a systemic inflammatory biomarker to predict prognosis in patients with myocardial infarction.[9] This was followed by a series of studies on coronary artery disease. Kilic et al. found that LGI was higher in patients with critical coronary artery disease and concluded that LGI may predict the severity of coronary artery disease.[18] In another study, Sadeghi et al. found that LGI had a sensitivity and specificity of 90% in diabetic patients and 93.14% in non-diabetic patients in predicting in-hospital mortality.[19]

The diagnostic value of LGI as a biomarker in the diagnosis of a disease in which inflammatory processes play a role, such as PE, has not been investigated so far. In our study, which is the first in the literature on this subject, we aimed to investigate this relationship. In our study, we calculated the LGI values of the patients from blood samples taken from women who developed PE. LGI values were found to be significantly higher in the PE group. As a result, we observed that LGI had a diagnostic power of 65.22% sensitivity and 84.96% specificity for PE at a cut-off value of 1193.01. In a study investigating the performance of delta neutrophil index (DNI), an inflammation marker, in the diagnosis of PE, it was stated that it had 47.89% sensitivity and 90% specificity.[20] In a study by Seyhanlı et al. investigating the relationship between PE and inflammatory markers, the systemic inflammation response index (SIRI) was found to provide 56.2% sensitivity and 55.6% specificity.[21] In light of the current findings, we think that LGI may be a useful biomarker along with other markers and findings in the diagnosis of PE.

The most important limitation of our study was that it was a retrospective study conducted at a single center. Therefore, it may not be possible to generalise the results to other populations. The fact that the study was conducted in a tertiary care centre where high-risk pregnancies are followed up and the data from a single laboratory were used is an important feature of the study. The multiplicity of research variables, the application of standard protocols for all patients, and the homogeneity of the study groups are other strengths.

Conclusion

Early diagnosis of PE is vital for maternal and fetal health. The use of biomarkers for this purpose has attracted the attention of researchers for a long time. We think that the use of LGI in the diagnosis of PE may help the diagnosis when used together with other biochemical parameters. However, we think that larger-scale and prospective studies are needed to find a more specific marker.

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