



The relationship between the low Apgar scores of the newborns and hematologic parameters which are inflammatory markers

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Abstract

Objective: To investigate the relationship between the 5-minute Apgar scores of the newborns checked in the cases induced due to prolonged pregnancy and neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), and to investigate the contributions of these parameters as prognostic markers in the low Apgar scores.

Methods: A total of 169 primigravida cases for which delivery by induction was decided due to prolonged pregnancy after they completed 41 weeks of gestation between 2017 and 2018 were included in the study. The detailed previous histories of all cases were obtained at admission and they underwent cervicovaginal examination, obstetric ultrasonography for the assessment of fetal biometry and amniotic fluid, and complete blood count including hemoglobin level, total white blood cell count, differential leukocyte number and platelet count. NLR and PLR were calculated as the ratio of neutrophil number to lymphocyte number and the ratio of platelet number to lymphocyte number, respectively. The Apgar scores in the newborn assessment were determined according to the usual criteria 1 and 5 minutes after the birth. The independent samples t-test, Mann-Whitney U test and chi-square test were used for the analysis of the data.

Results: The mean NLR and PLR values of the cases were calculated 4.8±2.8 and 148.8±74.9, respectively. While 108 (64%) patients delivered vaginally, 61 (36%) patients delivered by cesarean section. The Apgar score was >7 in 142 (84%) patients and <7 in 27 (16%) patients. NLR and PLR values were significantly higher in the group with Apgar score <7 than the group with Apgar score ≥7 (p<0.05).

Conclusion: The elevations in NLR and PLR is the usual part of a health pregnancy; however, excessively elevated inflammation has been associated with poor prenatal and developmental outcomes in various populations. In conclusion, these markers can be used as the parameters helping clinicians to predict poor obstetric outcomes.

Keywords: Inflammation, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio.

Özet: İnflamatuar belirteç olan hematolojik parametrelerin yenidoğan düşük Apgar skorları ile ilişkisi

Amaç: Uzamış gebelik nedeni ile indüklenen olgularda bakılan yenidoğan 5. dakika Apgar skoru ile nötrofillerin lenfositlere oranı (NLR) ve trombositlerin lenfositlere oranı (PLR) arasındaki ilişkiyi araştırmak ve bu parametrelerin düşük Apgar skorlarında prognostik belirteç olarak katkılarını incelemektir.

Yöntem: 2017–2018 yılları arasında 41. gebelik haftasını tamamlayarak uzamış gebelik nedeniyle induksiyon ile doğum kararı alınan 169 primigravid olgu çalışmaya dahil edildi. Tüm olgular kabul anında ayrıntılı öykü alma, servikovajinal muayene, fetal biyometri ve amniyotik sıvı değerlendirmesi için obstetrik ultrason ve hemoglobin düzeyi, toplam beyaz küre sayımı, diferansiyel lökosit sayısı ve trombosit sayımı dahil tam kan sayımlarına tabi tutuldu. NLR ve PLR sırasıyla nötrofil sayısının lenfosit sayısına oranı ve trombosit sayısının lenfosit sayısına oranı olarak hesaplandı. Yenidoğanın değerlendirilmesinde Apgar skorları doğumdan bir ve beş dakika sonra olağan kriterlere göre tayin edildi. Verilerin analizinde bağımsız örneklem t testi, Mann-Whitney U ve ki-kare testleri kullanıldı.

Bulgular: Hastaların ortalama NLR değerleri 4.8±2.8, PLR değerleri 148.8±74.9 olarak saptandı, 108 (%64) hasta vajinal yolla doğum yaparken, 61 (%36) hastada sezaryen ile doğum gerçekleşti. 142 (%84) hastada Apgar skoru >7 iken, 27 (%16) hastada <7 olarak belirlendi. Apgar <7 olan grupta NLR ve PLR değerleri Apgar ≥7 olan gruptan anlamlı (p<0.05) olarak daha yüksekti.

Sonuç: NLR ve PLR'deki yükselmeler, sağlıklı gebeliğin olağan bir parçasıdır ancak aşırı artmış inflamasyon, çok çeşitli popülasyonlarda olumsuz doğum ve gelişimsel sonuçlarla ilişkili bulunmuştur. Sonuç olarak, bu belirteçler kötü obstetrik sonuçları öngörmeye klinisyenlere yardımcı olan parametreler olarak kullanılabilir.

Anahtar sözcükler: İnflamasyon, nötrofil lenfosit oranı, trombosit lenfosit oranı.

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Introduction

The post-term pregnancy is defined as the pregnancy that takes more than 294 days or 42 weeks as of the beginning of the last menstrual period, and the prolonged pregnancy is defined as the pregnancy that takes more than 287 days or 41 weeks. The prolonged pregnancy is associated with the increase in the fetal and neonatal morbidity and mortality risks.^[1] Therefore, the international guidelines recommend inducing labor at 41–41 weeks of gestation.^[2]

The Apgar test is a simple and reproducible method used to evaluate the physical condition and health of a newborn right after the birth and to determine any urgent need for the extra care. Five factors are used to evaluate the newborn condition, and each factor is scored between 0 and 2, where 2 is the best score for each of them. The scoring is based on the heart rate, ventilatory effort, skin color, muscle tone and reflex irritability measurements.^[3] The final score is between 0 and 10, and 10 is the maximum possible score. Total score between 7 and 10 is considered “normal”, and the low Apgar score indicates the depressed vitality. Apgar scoring is done twice, where the first one is done one minute after the birth and second one is five minutes after the birth. If, rarely, there are concerns about the condition of newborn and first two scores are below 7, the scoring is done 10, 15 and 20 minutes after the birth as well.^[4,5] 1-minute Apgar score may indicate sudden resuscitation need, and 5-minute Apgar score is an indication of the newborn mortality and various neurological outcomes. There are many factors affecting Apgar score such as the sedation and anesthesia of mother, gestational age during delivery, breech presentation, low birth weight, congenital malformation, presence of comorbid conditions such as maternal hypertensive disorders and different assessments between observers.^[6]

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are the inflammatory ratios that can be calculated easily through a simple blood count. In various medical disciplines, they are frequently reported and tested as the prognostic factors. Many studies investigated these rates in cardiology, oncology, surgery and gastroenterology fields and usually included them into prognostic algorithms.^[7–10] In a gynecology-related literature, NLR and PLR were evaluated in gynecologic cancers and reproduction morbidities such as ovarian hyper-

stimulation syndrome, premature ovarian insufficiency and endometriosis.^[11–14] In the obstetrics, it was reported that NLR elevated in hyperemesis gravidarum, gestational diabetes, preeclampsia, pregnancy-related intrahepatic cholestasis and other diseases.^[15–18] Based on these studies, the interpretation of the elevated values during pregnancy has become important.

The objective of this study is to investigate the relationship between NLR and PLR values calculated by the simple blood count parameters and 5-minute Apgar scores of newborns in the cases induced due to the prolonged pregnancy and their contributions as prognostic markers in the low Apgar scores.

Methods

The primigravida cases for which delivery by induction was decided due to prolonged pregnancy after they completed 41 weeks of gestation between 2017 and 2018 were included in our study. The gestational age was calculated based on the first day of the last menstrual period, and it was confirmed by measuring crown-rump length (CRL) in the ultrasonography examination performed before 14 weeks of gestation.

The cases whose weeks of gestation were unclear, those with irregular cycles, the cases who did not undergo first-trimester ultrasonography examination, and the patients who were classified under high risks due to various reasons such as multiple pregnancy, fetal anomaly, fetal growth restriction, positive indirect Coombs test, documented exposure to an infectious disease that may be transmitted to fetus, hypertension and gestational diabetes during the current pregnancy were excluded from the study.

The detailed previous histories of all cases were obtained at admission and they underwent cervicovaginal examination, obstetric ultrasonography for the assessment of fetal biometry and amniotic fluid, and complete blood count including hemoglobin level, total white blood cell count, differential leukocyte number and platelet count. All blood counts were conducted by a single laboratory using the same automatic computed technology (Autoslide and Siemens ADVIA 2120i Hematology System, Erlangen, Germany). NLR and PLR were calculated as the ratio of neutrophil number to lymphocyte number and the ratio of platelet number to lymphocyte number, respectively.

The sex and weight of newborn, delivery type, reasons for performing cesarean section, and the need for neonatal intensive care were recorded. The Apgar scores in the newborn assessment were determined according to the usual criteria 1 and 5 minutes after the birth. The cases with high fever and suspected chorioamnionitis during the labor induction, the cases for which emergency cesarean section was preferred due to the indications such as fetal distress and ablatio previa that may affect Apgar score and the cases which underwent general anesthesia during the cesarean section were excluded from the study. The informed consents of all cases included in the study, which was approved by the local ethics committee (ethics committee no: 07.01.2017-01), were obtained.

The statistical method: The descriptive statistics of the data were presented by mean values, standard deviation, median values, the minimum and maximum values, frequency and percentage values. The distribution of the variables were analyzed by Kolmogorov-Smirnov test. The independent samples t-test and Mann-Whitney U test were used for the analysis of quantitative independent data. The qualitative independent data were analyzed by the chi-square test. SPSS (Statistical Package for the Social Sciences) version 22.0 (SPSS Inc., Chicago, IL, USA) was used for the analyses.

Results

A total of 236 patients were evaluated. After applying the exclusion criteria, 169 patients could be included in the

study. The mean NLR and PLR values of the patients were 4.8 ± 2.8 and 148.8 ± 74.9 , respectively. While 108 (64%) patients delivered vaginally, 61 (36%) patients delivered by cesarean section. The cephalopelvic disproportion and non-progressive labor were the indications of cesarean section. The Apgar score was >7 in 142 (84%) patients and <7 in 27 (16%) patients (Table 1). 33.3% of 27 cases with Apgar score <7 were observed in the newborns delivered vaginally and 66.7% of them in the newborns delivered by cesarean section. There was no significant difference between the groups in terms of newborn weight, newborn sex, and the cervical dilation procedure used ($p > 0.05$). The rate of cesarean section was significantly higher in the group with Apgar score <7 than the group with Apgar score ≥ 7 ($p < 0.05$). NLR and PLR values were significantly higher in the group with Apgar score <7 than the group with Apgar score ≥ 7 ($p < 0.05$) (Table 2 and Fig. 1).

Discussion

In the recent years, various studies have focused on neutrophil-lymphocyte ratio (NLR) which shows the ratio of the neutrophils which initiate the first defense line and represent the active non-specific inflammatory mediator to the lymphocytes representing the regulatory or protective component of inflammation.^[19] It provides prognostic and diagnostic information about the sub-clinical inflammation beyond conventional risk factors. It is a reliable indicator of the low level inflammation under various clinical conditions. The platelets and lymphocytes are the significant blood parameters about

Table 1. Demographic data.

	Min-max	Median	Mean \pm SD / n (%)
Birth weight (gram)	2330-4190	3380	3405 \pm 317
NLR	1.8-22.7	4.2	4.8 \pm 2.8
PLR	22.4-744.4	129.3	148.8 \pm 74.9
Procedure	Vaginal prostaglandin		120 (71.0%)
	Balloon dilation		49 (29.0%)
Delivery type	Vaginal delivery		108 (63.9%)
	Cesarean section		61 (36.1%)
Sex	Male		77 (45.6%)
	Female		92 (54.4%)
Apgar	≥ 7		142 (84.0%)
	<7		27 (16.0%)

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.

Table 2. The comparison of the data by Apgar scores.

		Apgar ≥ 7 Mean \pm SD / n (%)	Apgar < 7 Mean \pm SD / n (%)	p-value
Weight (g)		3400 \pm 325	3433 \pm 271	0.617
NLR		4.2 \pm 2.2	7.7 \pm 3.9	0.000
PLR		144.0 \pm 73.6	174.6 \pm 78.1	0.007
Procedure	Vaginal prostaglandin	101 (71.1%)	19 (70.4%)	0.937
	Balloon dilation	41 (28.9%)	8 (29.6%)	
Delivery type	Vaginal delivery	99 (69.7%)	9 (33.3%)	0.000
	Cesarean section	43 (30.3%)	18 (66.7%)	
Sex	Male	63 (44.4%)	14 (51.9%)	0.474
	Female	79 (55.6%)	13 (48.1%)	

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.

the immunity surveillance, and platelet-lymphocyte ratio (PLR) has a significant role in the cytokine-dependent immune response.^[16] It was claimed that PLR is a sensitive marker for systemic inflammation in various cases.^[17] In a study performed in South Korea, NLR and PLR values were calculated 1.73 \pm 1.55 and 133.7 \pm 85.6, respectively in the women who are in healthy reproductive period.^[20] In another study performed to generate a nomogram during pregnancy,

NLR and PLR values were found 2.6 \pm 1 and 136.3 \pm 44.3 during the first trimester, 4.0 \pm 1.4 and 144.6 \pm 47.1 during the second trimester, and 3.5 \pm 1.2 and 118.1 \pm 42 during the third trimester, respectively. It was shown that both NLR and PLR reached the maximum values during the second trimester and that they had a positive correlation with the gestational age.^[19] As seen in the previous studies, slight elevations in NLR and PLR values during pregnancy are the part of natural course.

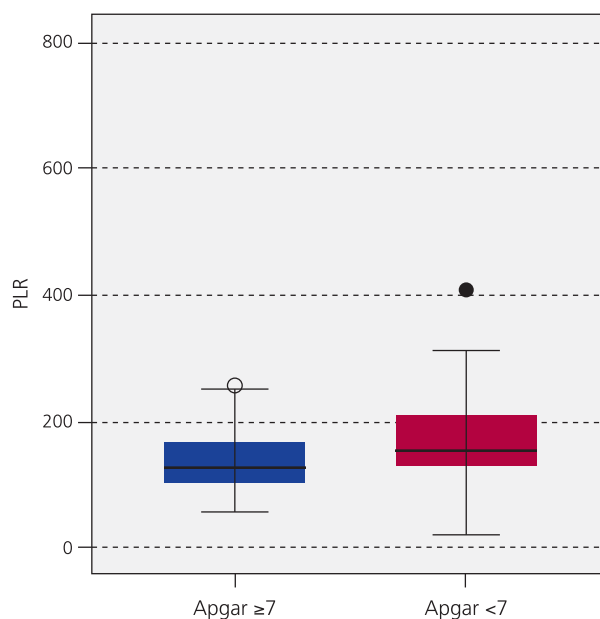
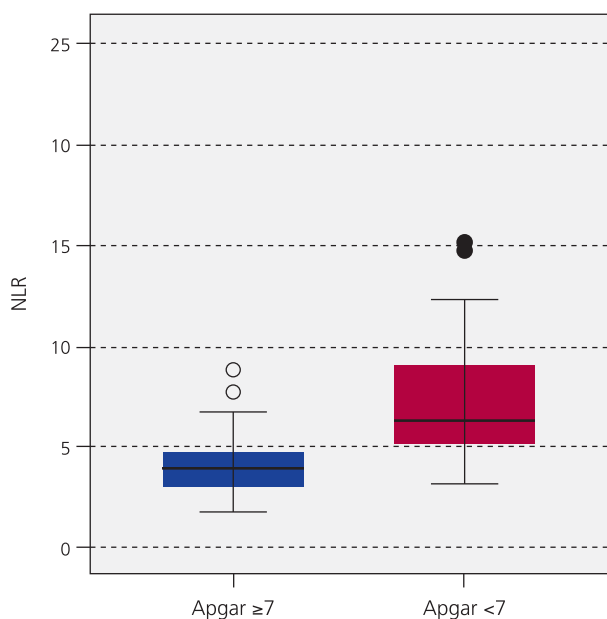


Fig. 1. The distribution graph of NLR-PLR.

Previously, NLR and PLR were tested as the predictors of common gestational complications; however, it was seen that there were inconsistencies between the results.^[16,17,21,22] For instance, it was found that NLR was not predictive for pregnancy-related hypertension,^[22] but increased significantly in the preeclamptic patients. Similar inconsistencies were also reported in the studies testing NLR and PLR in the pregnant women with gestational diabetes.^[16,21] NLR was also evaluated in the inflammatory conditions complicating pregnancy and was suggested as an early indicator of acute pancreatitis during pregnancy and a potential marker for disease severity.^[23] It was shown that NLR has a better diagnostic performance than maternal serum C-reactive protein (CRP) in case of placental inflammatory response. High NLR helped to predict preterm labor even at normal CRP levels.^[24] These studies highlight the potential contribution of evaluating NLR in diagnostic difficulties during pregnancy.

Slight elevations in the inflammation is the usual part of a healthy pregnancy, but higher inflammation levels during pregnancy are associated with poor gestational outcomes.^[25,26] For instance, CRP concentrations in the circulation elevate slightly in healthy pregnant women;^[27,28] however, the concentrations higher than normal during the third trimester may help to predict low birth weight, preterm labor, chronic placental villitis and preeclampsia.^[29-32] Elevated inflammation during pregnancy is also associated with gestational diabetes^[33] and neonatal neurobehavioral disorder.^[34] In our study, we found that inflammatory indicators such as NLR and PLR elevated in the newborns with Apgar score <7 in cases induced due to prolonged pregnancy although they did not have any comorbid condition. We believe that it may be secondary to a low level inflammation which is non-predicting clinically.

The mechanisms of action of the chronic inflammation leading to the development of gestational complications have been investigated. Primarily, the condition of low level chronic inflammation may be the expression of an abnormal immunity regulation during pregnancy which allows trophoblastic invasion and placentation in the women with polycystic ovary syndrome (PCOS), decreases maternal immunological suppression and increases the frequency and level of immune-mediated placental pathologies.^[35,36] In this sense, an increase has been observed recently in the placental lesion incidence in the microscopic analysis such as chronic villitis and

intervillositis in the women with PCOS.^[36] Palomba et al. found that elevated WBC, CRP and ferritin levels in the pregnant women with PCOS were secondary to the low level chronic inflammation, and that it was an increased risk for the obstetric/neonatal complications such as pregnancy-related hypertension, preeclampsia, gestational diabetes, antepartum hemorrhage and birth weight being large and/or small for gestational age in the presence of these indicators.^[36] It is believed that obesity also results in the poor obstetric effects and neonatal complications by causing chronic inflammation as in PCOS patients. In the study of Çintesun, the authors found that WBC, neutrophil and lymphocyte values which are directly associated with inflammation were significantly higher in the obese group during early pregnancy period.^[37] It was reported that the elevated WBC is associated with the impaired glucose metabolism, insulin resistance and type 2 diabetes, and high WBC levels lead to gestational diabetes.^[38] There are also other factors initiating and maintaining a low level inflammatory response than PCOS and obesity. These include aging, malnutrition and smoking. These factors may be the reasons in our patient group with elevated NLR and PLR levels. The clinical results of our findings are not clear and additional studies are needed.

The most important limitation of our study can be the failure of ruling out every variable that may affect Apgar score. We did not include the neonatal results and maternal data for the factors such as obesity and PCOS which may affect maternal NLR and PLR value. Other than that, we did not investigate the advanced maternal age, nutritional conditions and cholesterol levels as well as smoking habits which may be associated with the chronic inflammation of patients. We did not evaluate the relationship between NLR and PLR values and the duration from collecting blood samples to delivery, and did not perform any additional hemogram measurement.

The elevations in NLR and PLR values is the usual part of a healthy pregnancy,^[19] but extremely increased inflammation was found to be associated with poor postpartum and developmental outcomes in various populations.^[25,26]

Conclusion

In conclusion, these markers may help clinicians to predict poor obstetric outcomes, and they are also cheap and practicable parameters technically. However, fur-

ther analyses are needed with a wider population before reaching a final decision.

Conflicts of Interest: No conflicts declared.

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