



Comparison of Complete Blood Count Parameters Between Ectopic Pregnancy and Normal Intrauterine Pregnancy

Ektopik Gebelik ile Normal İntrauterin Gebelik Arasında Tam Kan Sayımı Parametrelerinin Karşılaştırılması

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Abstract

Aim: This study aimed to compare complete blood count parameters between patients with ectopic pregnancy and those with normal intrauterine pregnancy and to evaluate the potential utility of inflammation-based indices in the early differential diagnosis of ectopic pregnancy.

Material and Method: This retrospective study included 39 patients diagnosed with ectopic pregnancy and 51 with normal intrauterine pregnancy who presented to the Department of Obstetrics and Gynecology of Aksaray Training and Research Hospital between December 2018 and January 2022. Demographic characteristics, complete blood count parameters, and derived inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio and lymphocyte-to-monocyte ratio, were compared between groups. Receiver operating characteristic (ROC) curve analysis was performed for parameters showing significant differences.

Results: There was no significant difference between the groups in maternal age ($p=0.318$), whereas gestational age at presentation was significantly lower in the ectopic pregnancy group ($p<0.001$). Neutrophil count (median 4.78 vs. $6.44 \times 10^3/\mu\text{L}$; $p=0.023$) and NLR (median 2.28 vs. 2.72; $p=0.013$) were significantly lower in the ectopic pregnancy group. ROC analysis showed an area under the curve of 0.654 ($p=0.013$) for NLR and 0.641 ($p=0.023$) for neutrophil count. At the optimal cut-off values, the corresponding specificities were 78% and 82%, respectively.

Conclusion: Neutrophil count and NLR were significantly lower in women with ectopic pregnancy than in those with normal intrauterine pregnancy. Although these inexpensive and readily available parameters may serve as supportive markers during the initial evaluation of suspected ectopic pregnancy, their discriminative performance was modest and they should not be used as standalone diagnostic markers.

Keywords: Ectopic pregnancy, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, inflammation, complete blood count

Öz

Amaç: Bu çalışmada, ektopik gebelik ile normal intrauterin gebelik hastaları arasındaki tam kan sayımı parametrelerinin karşılaştırılması ve inflamasyon temelli indekslerin ektopik gebeliğin erken ayırıcı tanısındaki potansiyel yararının değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Bu retrospektif çalışmaya, Aralık 2018 ile Ocak 2022 tarihleri arasında Aksaray Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniğine başvuran 39 ektopik gebelik ve 51 normal intrauterin gebelik olgusu dahil edildi. Demografik özellikler, tam kan sayımı parametreleri ve türetilmiş inflamatuvar indeksler [nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı ve lenfosit/monosit oranı] gruplar arasında karşılaştırıldı. Anlamli farklılık gösteren parametreler için ROC eğrisi analizi yapıldı.

Bulgular: Gruplar arasında maternal yaş açısından anlamlı fark yoktu ($p=0,318$), buna karşılık başvuru anındaki gestasyonel yaş ektopik gebelik grubunda anlamlı olarak daha düşüktü ($p<0,001$). Nötrofil sayısı (medyan 4,78'e karşı $6,44 \times 10^3/\mu\text{L}$; $p=0,023$) ve NLR (medyan 2,28'e karşı 2,72; $p=0,013$) ektopik gebelik grubunda anlamlı olarak daha düşüktü. ROC analizinde eğri altında kalan alan NLR için 0.654 ($p=0,013$), nötrofil sayısı için ise 0,641 ($p=0,023$) bulundu. Optimal kesim değerlerinde özgüllük sırasıyla %78 ve %82 idi.

Sonuç: Ektopik gebeliği olan kadınlarda nötrofil sayısı ve NLR, normal intrauterin gebeliği olan kadınlara göre anlamlı olarak daha düşüktü. Bu ucuz ve kolay ulaşılabilir parametreler, şüpheli ektopik gebeliğin ilk değerlendirilmesinde destekleyici belirteçler olarak kullanılabilir; ancak ayırt edici performansları sınırlıdır ve tek başına tanısal belirteç olarak kullanılmamalıdır.

Anahtar kelimeler: Ektopik gebelik, nötrofil/lenfosit oranı, trombosit/lenfosit oranı, inflamasyon, tam kan sayımı



INTRODUCTION

Ectopic pregnancy (EP) is an important gynecological condition that occurs when a fertilized ovum implants at a site outside the uterine cavity, accounting for approximately 1% to 2% of all pregnancies.^[1,2] EP continues to be one of the leading causes of first-trimester maternal mortality and is responsible for a significant proportion of maternal deaths in developing countries.^[3] When left untreated, it can result in life-threatening complications such as tubal rupture, massive intra-abdominal hemorrhage, and consequent hemodynamic deterioration.^[4] Therefore, early and accurate diagnosis has been reported to be critically important for both reducing maternal morbidity and preserving fertility.^[3,4]

The diagnosis of EP is currently based primarily on the combined evaluation of transvaginal ultrasonography and serial serum β -human chorionic gonadotropin (β -hCG) measurements.^[5] However, when the β -hCG level at initial presentation falls below the discriminatory threshold, and an intrauterine gestational sac cannot be clearly demonstrated on ultrasonographic examination, distinguishing between EP, threatened miscarriage, and early normal intrauterine pregnancy becomes considerably difficult.^[6] To overcome this difficulty, numerous biochemical markers have been investigated alongside serial β -hCG monitoring;^[7,8] however, most have failed to achieve sufficient diagnostic accuracy.

Inexpensive, readily accessible markers derived from complete blood count parameters have attracted growing interest in recent years for evaluating inflammatory processes. For this purpose, inflammation-based scoring systems such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been proposed because these indices are associated with angiogenesis and inflammation [9]. Since an increase in NLR reflects neutrophilia developing under inflammatory conditions, accompanied by relative lymphopenia, it is considered a reliable indicator of underlying inflammatory processes.^[10] Similarly, platelet-based indices have also been associated with angiogenesis and inflammation,^[11] supporting the use of markers such as PLR in evaluating the inflammatory response.

Further investigation into the diagnostic value of complete blood count parameters, which are routinely assessed during the initial evaluation of pregnant women, remains clinically relevant. This study aims to compare complete blood count parameters in patients with EP and those with normal intrauterine pregnancy and to investigate their utility in the early differential diagnosis of EP.

MATERIAL AND METHOD

Ethics committee approval was obtained from the Ethics Committee of Aksaray University (approval no: 2022/13-02), and the study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design, patient consent was not required.

Study Design and Participants

This study was conducted between December 15, 2018, and January 15, 2022, at the Department of Obstetrics and Gynecology of Aksaray Training and Research Hospital. EP was diagnosed based on serial serum β -hCG measurements together with transvaginal ultrasonography and was confirmed by surgical findings when applicable or by transvaginal ultrasonographic findings consistent with an EP, with pathological confirmation available for surgically managed cases.^[5,8] The control group included women over 18 years of age with a normally located intrauterine pregnancy of 6–12 weeks confirmed by ultrasonography. Patients younger than 18 years of age, those in whom a definitive diagnosis of EP could not be established, those with a recent history of miscarriage, those with a known hematological disease, those using any medication that could affect anticoagulation or hematological parameters, those with renal or hepatic failure, and those with chronic inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, vasculitis, or connective tissue disorders, as well as patients whose data could not be accessed, were excluded from the study.

Patient age, gestational age, gravidity, parity, singleton or multiple pregnancy status, obstetric ultrasonography findings, and laboratory results were obtained from the hospital's electronic medical database. At initial presentation, all patients underwent serum β -hCG measurement, transvaginal ultrasonography, and complete blood count analysis. Serum β -hCG levels were determined using a UniCel Dxl 800 Access Immunoassay System (Beckman Coulter Inc., Brea, CA, USA) based on a chemiluminescent immunoassay immunoassay. All blood samples were analyzed within 2 hours of collection using a BC-6000 Auto Hematology Analyzer (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). Complete blood count parameters, including neutrophil (Neu), lymphocyte, platelet (Plt), platelet distribution width (PDW), red cell distribution width (RDW) were recorded. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) were calculated and compared between groups.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 27.0 (Armonk, NY: IBM Corp.). The distribution of continuous variables was assessed using the Shapiro-Wilk test, and most variables were not normally distributed; therefore, the Mann-Whitney U test was used for between-group comparisons, while the chi-square test and Fisher's exact test were used for comparisons of categorical variables. Continuous data were presented as mean $\pm$ standard deviation and median (interquartile range), and categorical data were presented as number (percentage). Receiver operating characteristic (ROC) curve analyses were performed to assess the predictive accuracy of selected hematological parameters. The area under the curve (AUC) with 95% confidence intervals (CIs), sensitivity, specificity were calculated.

RESULTS

A total of 90 cases were included in the study: 39 patients diagnosed with EP and 51 patients with normal intrauterine pregnancy. There was no statistically significant difference in age between the groups. In addition, no statistically significant difference was found between the two groups in terms of age group distribution, gravidity, primigravida rate, parity, or nulliparity rate ($p>0.05$ for all values). However, gestational age at presentation was significantly lower in the EP group than in the control group ($p<0.001$). The demographic and obstetric characteristics of the study groups are presented in **Table 1**.

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

Variable	Ectopic pregnancy (n=39)	Control (n=51)	p
Age (years)			
Mean±SD	29.3±6.1	28.3±5.0	0.318
Median (IQR)	31.0 (23.5–33.5)	28.0 (25.0–31.0)	
Min–max	19–40	18–40	
Age group, n (%)			0.237
<25 years	11 (28.2)	10 (19.6)	
25–34 years	20 (51.3)	35 (68.6)	
≥35 years	8 (20.5)	6 (11.8)	
Gestational age (weeks)			
Mean±SD	6.3±1.7	8.7±1.5	<0.001
Median (IQR)	6.0 (5.0–7.0)	8.6 (7.6–9.9)	
Min–max	4–11	6–12	
Gravidity			
Mean±SD	2.8±1.3	2.9±1.4	0.618
Median (IQR)	3.0 (2.0–3.5)	3.0 (2.0–4.0)	
Primigravida, n (%)	7 (17.9)	10 (23.3)	0.596
Parity			
Mean±SD	1.4±0.9	1.5±1.1	0.828
Median (IQR)	1.0 (1.0–2.0)	2.0 (0.5–2.0)	
Nulliparous, n (%)	5 (12.8)	11 (25.6)	0.172

n: number of patients; SD: standard deviation; IQR: interquartile range. Bold values indicate statistical significance ($p<0.05$).

No statistically significant differences were observed between the two groups in hemoglobin, hematocrit, leukocyte, platelet, lymphocyte, monocyte, PDW, RDW, PLR, or LMR (all $p>0.05$). Neutrophil count and NLR were significantly lower in the EP group than in the control group ($p=0.023$ and $p=0.013$, respectively). The comparison of complete blood count parameters and derived inflammatory indices between the groups is shown in **Table 2**.

The diagnostic performance of the neutrophil-based parameters identified in **Table 2** for differentiating EP from normal intrauterine pregnancy was evaluated using receiver operating characteristic (ROC) curve analysis, and the results are presented in **Table 3**. The area under the curve (AUC) for NLR was 0.654 (95% CI 0.530–0.775; $p=0.013$). At a cut-off of ≤ 2.30 , sensitivity was 56%, and specificity was 78%. The AUC for neutrophil count was 0.641 (95% CI 0.519–0.757; $p=0.023$), with a sensitivity of 49% and a specificity of 82% at a cut-off value of $\leq 4.70 \times 10^3/\mu\text{L}$. The AUC for leukocyte count was 0.607 (95% CI 0.483–0.727) but did not reach statistical significance ($p=0.085$).

Table 2. Comparison of complete blood count parameters and derived inflammatory indices between groups.

Parameter	Ectopic pregnancy (n=39)	Control (n=51)	p
Hemoglobin (g/dL)	12.50 (12.05–13.40)	13.00 (12.35–13.50)	0.140
Hematocrit (%)	37.40 (35.15–39.35)	37.80 (36.75–39.75)	0.213
Leukocytes ($\times 10^3/\mu\text{L}$)	8.06 (7.09–9.67)	9.40 (7.73–10.93)	0.085
Platelets ($\times 10^3/\mu\text{L}$)	267.0 (230.0–310.5)	264.0 (233.0–312.0)	0.984
Neutrophils ($\times 10^3/\mu\text{L}$)	4.78 (3.87–6.85)	6.44 (5.13–7.42)	0.023
Lymphocytes ($\times 10^3/\mu\text{L}$)	2.30 (1.64–2.73)	2.15 (1.69–2.70)	0.625
Monocytes ($\times 10^3/\mu\text{L}$)	0.45 (0.35–0.55)	0.47 (0.39–0.59)	0.479
PDW (%)	16.10 (15.65–16.20)	16.10 (15.93–16.30)	0.311
RDW (%)	14.20 (13.55–15.60)	14.00 (13.40–15.10)	0.654
NLR	2.28 (1.69–3.14)	2.72 (2.37–3.54)	0.013
PLR	114.47 (93.81–158.80)	127.37 (103.05–156.66)	0.388
LMR	4.76 (4.07–6.15)	4.56 (3.71–5.57)	0.360

Values are presented as median (interquartile range). NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PDW: platelet distribution width; RDW: red cell distribution width. Bold rows indicate a statistically significant difference ($p<0.05$).

Table 3. ROC analysis of neutrophil-based parameters in distinguishing ectopic pregnancy

Parameter	AUC (95% CI)	p	Cut-off	Sensitivity (%)	Specificity (%)
NLR	0.654 (0.530–0.775)	0.013	≤ 2.30	56	78
Neutrophils ($\times 10^3/\mu\text{L}$)	0.641 (0.519–0.757)	0.023	≤ 4.70	49	82
Leukocytes ($\times 10^3/\mu\text{L}$)	0.607 (0.483–0.727)	0.085	≤ 8.08	56	73

ROC: receiver operating characteristic; AUC: area under the curve; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio. Bold rows indicate statistically significant parameters ($p<0.05$).

DISCUSSION

We found that only the neutrophil count and NLR differed significantly between the groups, with both markers lower in the EP group than in the control group. ROC analysis showed that NLR and neutrophil count had modest discriminative performance, with relatively high specificity but limited sensitivity. These findings suggest that the neutrophil-based systemic inflammatory response may differ between early EP and normal intrauterine pregnancy.

Inflammatory processes are known to play an important role in the pathogenesis of EP. Increased local and systemic inflammatory activity during abnormal tubal implantation has been proposed to influence hematological inflammatory markers, including NLR.^[10,12] Consistent with this hypothesis, Gencdal et al. reported significantly higher NLR but lower mean platelet volume (MPV) values in the EP group than in the control group.^[13] In the study by Eriç Horasanlı et al., no statistically significant differences were found between the EP group and the control group in neutrophil count, leukocyte count, or NLR.^[14] Akkaya et al. found higher baseline NLR values in patients managed medically than in those undergoing surgical treatment and suggested that this difference might be related to inflammatory activity.^[15] More recently, Dereli et al. reported that lower NLR values were associated with successful methotrexate treatment in patients with tubal EP, further suggesting that the magnitude of the systemic inflammatory response may vary according to

the clinical course and treatment outcome of EP.^[16] Turgut et al. reported significantly higher leukocyte counts in patients with ruptured EP than in those with non-ruptured EP and normal intrauterine pregnancy.^[17] However, our findings did not align with this pattern; in our study, NLR and neutrophil count were lower in the EP group than in the control group. This apparent discrepancy may be related to the difference in gestational age between the groups and to the predominance of early-stage, largely non-ruptured ectopic pregnancies in our cohort.

With respect to platelet indices, no significant differences were observed between the groups, including PDW. This finding contrasts with previous studies reporting significantly lower PDW values in EP than in normal intrauterine pregnancy. Eriç Horasanlı et al. found significantly lower PDW values in the EP group. They suggested that lower PDW levels may serve as a useful marker for the early diagnosis of EP.^[14] Similarly, Eskicioğlu et al. reported lower PDW and higher monocyte levels in patients with tubal EP.^[18] Data on mean platelet volume (MPV), an indicator of platelet activation, are conflicting. Artunc et al. observed lower MPV values in patients with EP, particularly in ruptured cases, although the differences were not statistically significant; they suggested that this pattern might be related to the intense inflammatory response associated with tubal rupture.^[12] The absence of a significant difference in platelet-based markers in our study may be explained by the fact that our cohort largely consisted of early-stage, non-ruptured cases. Indeed, Dinc et al. found no significant differences in hemoglobin, platelet count, MPV, RDW, NLR, or PLR according to the depth of tubal wall invasion. More advanced trophoblastic invasion was associated with higher leukocyte counts and systemic immune-inflammation index values.^[19] The absence of a difference between groups in hemoglobin and hematocrit values in our study is consistent with our cohort being hemodynamically stable and predominantly comprising non-ruptured cases, as lower hemoglobin and hematocrit levels have been associated with ruptured EP.^[20]

The other inflammatory indices that showed no significant difference in our study also reflect the conflicting picture in the literature. No significant differences were found between our groups in terms of PLR and LMR. Ata et al. investigated the value of NLR and PLR in predicting threatened miscarriage and early pregnancy loss and reported that the diagnostic contribution of these indices may be limited.^[21] Similarly, Bas et al. observed decreased PLR and MPV values but increased neutrophil, lymphocyte, and NLR levels in spontaneous abortion.^[22] Taken together, these findings suggest that the direction and magnitude of inflammation-based markers may vary according to the underlying pregnancy pathology and gestational age. Regarding LMR, no significant difference was observed between the groups. Eriç Horasanlı et al. found LMR to be higher in EP compared with the control group and interpreted this finding as a potentially useful inflammatory

marker for early diagnosis,^[14] whereas Feng et al. suggested that higher LMR levels might play a protective role in threatened miscarriage.^[23] Our finding that lymphocyte count did not differ between the groups also contrasts with the results of Eriç Horasanlı et al., who reported significantly higher lymphocyte counts in both EP and threatened miscarriage compared with the control group.^[14] These discrepancies may reflect differences in the underlying pregnancy pathology, gestational age, study populations, and laboratory timing. From a clinical perspective, these markers are inexpensive, rapidly available, and widely accessible; nevertheless, the moderate discriminative performance observed in our study suggests that they may serve as supportive rather than definitive diagnostic markers.

Our study has several strengths. The comparison was not limited to a single inflammatory index. Hemoglobin, hematocrit, leukocyte, platelet, neutrophil, lymphocyte, monocyte, PDW, and RDW values, together with the NLR, PLR, and LMR indices, were evaluated simultaneously. In addition, ROC analysis was performed to determine cutoff values for the parameters that showed significant differences. However, our study also has several limitations. First, its retrospective, single-center design and relatively limited sample size restrict the generalizability of the results. Second, the significant difference in gestational age between the ectopic pregnancy and control groups is an important confounding factor that complicates the interpretation of parameters such as neutrophil count and NLR, which may change physiologically with gestational age. In addition, owing to the retrospective design, subclinical or asymptomatic infections, including asymptomatic urinary tract infections, could not be systematically excluded in all participants, which represents another potential confounding factor. Third, the fact that our cohort predominantly consisted of early-stage and largely non-ruptured cases means that the findings obtained cannot be directly generalized to ruptured ectopic pregnancy. Finally, cases were not stratified by rupture status, and the relationship between hematological parameters and β -hCG levels was not examined.

CONCLUSION

Among the complete blood count parameters evaluated, only neutrophil count and the neutrophil-to-lymphocyte ratio were significantly lower in women with EP than in those with normal intrauterine pregnancy and demonstrated modest discriminative performance with relatively high specificity. Although these inexpensive and readily accessible hematological parameters may serve as supportive markers during the initial evaluation of suspected EP, they should not be considered standalone diagnostic markers. Larger prospective studies with gestational age-matched populations and stratification according to rupture status are warranted to validate these findings and further clarify their clinical utility.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Aksaray University Faculty of Medicine Ethics Committee (Decision No: 2022/13-02).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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