Significance of hemogram on diagnosis of acute appendicitis during pregnancy

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ABSTRACT

BACKGROUND: Acute appendicitis (AA) is the most common emergency surgical condition during pregnancy after obstetric and gynecological pathologies. Urgent and accurate diagnosis of AA in pregnant patients reduces maternal and fetal morbidity/mortality rates. This study evaluated the significance of hemogram to diagnose AA during pregnancy.

METHODS: Forty-seven pregnant patients operated for AA in the Ordu or Ondokuz Mayis University Medical School Hospitals between January 2007 and December 2017 were compared with 47 healthy pregnant women in terms of hemogram parameters, including the white blood cell (WBC) count, neutrophil count, lymphocyte count, platelet count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), and red cell distribution width (RDW) values. The operated group was evaluated based on post-operative pathologic results and subclassified into appendicitis positive (Group A) and appendicitis negative (Group B) groups. The subgroups were compared to the control group.

RESULTS: The WBC and neutrophil count and mean NLR and PLR values were significantly higher in Group A compared to Group B and the control group (p<0.001). The mean lymphocyte count was significantly lower in Group A compared to other groups (p<0.001). The MPV and RDW values and mean platelet count showed no significant difference between groups (p>0.05). When cutoff values for WBC, neutrophil count, NLR, PLR, and lymphocyte counts were set to >10300, >7950, >5.50, >155.2, and ≤1330, respectively, the sensitivity rates were 72.5%, 80%, 90%, 77.5% and 85%, whereas specificity rates were 72.3%, 79.7%, 89.4%, 74.5%, and 82.5%, respectively.

CONCLUSION: When comparing pregnant women diagnosed with AA to patients operated for suspected AA and healthy pregnant women, the WBC and neutrophil count and NLR and PLR values were found to be significantly higher, whereas lymphocyte counts were lower. In addition to medical history, physical examination and imaging techniques, hemogram parameters should be considered to diagnose AA in pregnant women.

Keywords: Appendicitis; diagnosis; hemogram; lymphocyte; neutrophil; pregnancy.

INTRODUCTION

Acute appendicitis (AA) is the most common surgical pathology diagnosed in patients admitted to emergency departments with abdominal pain. [1] AA is among the most common

indications for emergency surgery during pregnancy after obstetric and gynecological pathologies. The incidence of AA is I in 500–2000 pregnant women.^[2,3] AA occurs mostly during the second trimester, although it can be seen at any time during pregnancy.^[4] The urgent and accurate diagnosis

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of AA is essential for preventing potential complications for the mother and/or fetus. Symptoms including nausea, vomiting, and anorexia are usually seen in the early period of pregnancy and also in AA; therefore, the diagnosis of this condition is challenging for clinicians. Physiological increases in the leucocyte count and C-reactive protein (CRP) levels may be observed during pregnancy. Tomography is avoided in pregnant women to protect the fetus from ionized radiation. The preferred imaging techniques are ultrasonography and/or magnetic resonance imaging.^[5,6] Considering these factors, diagnosing AA during pregnancy can be challenging for physicians, and therefore, the diagnosis can be delayed.

Hemogram parameters including the white blood cell (WBC) count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) are inflammatory markers. The changing levels of these parameters are measured in several inflammatory pathologies.^[7]

It is extremely important to diagnose suspected AA early in pregnant women and to avoid unnecessary surgery. The aim of this study is to determine the hemogram parameters, which are readily available and are evaluated in emergency conditions as a diagnostic tool in diagnosis of AA during pregnancy.

MATERIALS AND METHODS

The study included 47 pregnant patients who were operated for suspected AA and 47 healthy pregnant women between January 2007 and December 2017 at Medical School Hospitals of the Ordu or Ondokuz Mayis University. The hemogram parameters including the WBC, neutrophil count, lymphocyte count, platelet count, NLR, PLR, MPV, and red cell distribution width (RDW) values were retrospectively examined from the medical records of the patients. The post-operative pathological results of appendix specimens were also investigated. All patients with a final pathological evaluation reported as acute focal appendicitis, acute suppurated appendicitis, acute perforated appendicitis, and acute gangrenous appendicitis were included in the AA group (Group A), whereas patients with a normal histopathology were included in the non-appendicitis group (Group B). Forty-seven healthy pregnant women who were under routine pregnancy followup during the same period at the obstetrics clinics of the same hospitals were included as the control group. Exclusion criteria were the presence of hematological diseases, chronic renal failure, chronic liver disease, chronic obstructive lung disease, asthma, autoimmune diseases, cancer, rheumatoid arthritis, bacterial, viral or parasitic infection, immune deficiency, alcohol or tobacco use, and missing records. The age, gestational age, time to diagnosis, length of hospitalization, type of surgical incision, WBC, neutrophil, lymphocyte, and platelet count, and the NLR, PLR, MPV, and RDW values for each patient were recorded. The study was approved by the Ethics Committee of the Ordu University.

All tests were performed on blood samples obtained via venous system and collected into ethylene diamine tetra acetic acid tubes. Hemograms that were taken within 24 hours prior to surgery were accepted for the AA group. The WBC, neutrophil, platelet, and lymphocyte counts, and the MPV and RDW values were analyzed via hemogram samples. The NLR and PLR values were calculated by dividing neutrophil and platelet counts to lymphocyte count. Hematological parameters were measured by an automated hematology analyzer (Abbott Cell-Dyn 3700 Hematology Analyzer, Abbott Diagnostics, USA). The upper limits of the reference intervals were as follows: leukocyte counts (WBC); 4600–10200 /µL, platelet; $142-424 \times 10^3/\mu$ L; neutrophil; $2-6.9 \times 10^3/\mu$ L; lymphocyte; $0.6-3.4 \times 10^3/\mu$ L, MPV; 0-99.9fL; and RDW; 0%-16.2%.

Statistical Analysis

Statistical analysis was performed using the SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk test was used to determine the compliance of data to a normal distribution, and the Levene test was used to determine the homogeneity of variances among the groups. The independent samples T test with bootstrap results was used to compare two independent groups, whereas the Mann-Whitney U test was used with the Monte Carlo simulation technique. One-way analysis of variance (robust test: Browne-Forsythe) was used together with bootstrap results to compare more than two groups with other groups. The Kruskal-Wallis H test, least significant differences, and Games-Howell tests were used for post-hoc analysis. The correlation between classification of the patient groups separated by cutoff values was calculated according to the variables, and real classification was expressed by examination of sensitivity and specificity using the receiver operating characteristic (ROC) curve analysis. Quantitative data are expressed as the mean±standard deviation, median-interquartile range, or median and range (maximum-minimum). Categorical data are expressed as n (number) or percentage (%) and analyzed by Fisher's exact test.

RESULTS

All the patients who underwent surgery were divided into two groups based on their pathology results; Group A consisted of 40 patients (85.1%) with AA and Group B with 7 (14.9%) patients without appendicitis. There was no significant difference between groups in terms of age, time period of admission to diagnosis, or the length of post-operative hospitalization (p>0.05). Of 40 patients in Group A, 16 (40%), 20 (50%), and 4 (10%) were in the 1st, 2nd, and 3rd trimester of pregnancy, respectively, whereas in Group B, 4 (57.1%) and 3 (42.9%) were in the 1st and 2nd trimester of pregnancy, respectively. The control group consisted of 15 (31.9%), 17 (36.1%), and 15 (31.9%) subjects in the 1st, 2nd, and 3rd trimester of pregnancy, respectively. No significant difference was found

between Group A and Group B for gestational age (p>0.05). Laparotomy was performed in all patients using McBurney's or right paramedian incisions. In pregnant women diagnosed with AA, McBurney's incision was mostly preferred (78.7%). Paramedian incision was preferred in patients with older gestational age. The mean post-operative length of hospitalization was 4.18±3.09 days in Group A and 3.57±1.39 days in Group B, and no significant difference was found between the groups in terms of length of hospitalization (p>0.05). A significantly higher WBC and neutrophil counts and the mean NLR and PLR values were detected in Group A compared to

Group B and the control group (p<0.001). The mean lymphocyte count was significantly lower in Group A compared to other groups (p<0.001). There was no significant difference between groups in terms of the mean MPV and RDW values and platelet count (p>0.05) (Table 1).

The ROC curve analysis was performed to evaluate the predictive ability of hemogram parameters to diagnose AA in pregnant women. Sensitivity, specificity, and accuracy rate values for hemogram parameters were estimated based on cutoff values determined by ROC analyses (Table 2).

Table 1. Comparison of groups for age, gestational age, time to diagnosis with symptoms, surgical incision, and hemogram parameters

	Group A (n=40)	Group B (n=7)	Control Group (n=47)	р
Age	27.0±5.55	25.14±5.08	29.74±6.13	0.36
Gestational age (weeks)	16.88±7.72	13.0±4.89	21.60±9.77	0.009
Time to diagnosis with symptoms (hours)	23.28±21.20	12.0±7.97	-	0.175
Surgical incision type				
Paramedian	20% (n=8)	28.57% (n=2)	_	0.630
McBurney	80% (n=32)	71.42 (n=5)	-	
Post-operative hospital stay (days)	4.18±3.09	3.57±1.39	-	0.617
White blood cells $(K/\mu L)^*$	12886±4785ª	13194±3520 ^a	9063±1869 ^ы	<0.001
Mean platelet volume* (fL)	8.03±1.22	7.56±1.27	7.51±0.90	0.07
Red cell distribution width* (%)	14.83±2.18	14.78±1.26	14.23±1.26	0.255
Neutrophil count (K/μL)*	11198±4624ª	10967±3550 ^a	6561±1616 ^b	<0.001
Lymphocyte count (K/μL)*	1093±442°	1415±413⁵	1845±641°	<0.001
Neutrophil-to-lymphocyte ratio**	12.10 (2.28-37.10) ^a	7.70 (3.40–13.60) ^b	3.57 (1.22–28.90) ^c	<0.001
Platelet-to-lymphocyte ratio**	218.91 (93.10-735.13) ^a	190.80 (93.10–289.60) ^{a,b}	130.30 (58.65—429.03) ^b	<0.001
Platelet count $(K/\mu L)^*$	229125±74976	261000±74446	238276±67148	0.528

 $^{^{\}mathrm{a,b,c}}$ Indicate inter-group differences within the row

Mann-Whitney U test (Monte Carlo)—one-way analysis of variance (Browne–Forsythe)—(Bootstrap)

Post-hoc test: least significant difference—Games-Howell

Kruskal-Wallis test

Post-hoc test (Monte Carlo): nonparametric post-hoc test (Miller, 1966)

*Mean±standard deviation; **Median; (range, maximum-minimum).

Table 2. Sensitivity and specificity rates for hemogram parameters based on cut-off values in pregnant women diagnosed with AA

	Hemogram parameters (cut-off values)	Sensitivity (%)	Specificity (%)	Accuracy rate (%)	AUC±SE
White blood cells (K/mL)	>10300	72.5	72.3	72.4	0.815±0.046
Mean platelet volume	>7.65	62.5	60.6	60.9	0.648±0.063
Red cell distribution width	>14.2	57.5	53.2	55.1	0.552±0.063
Neutrophil count (K/mL)	>7950	80.0	79.7	81.6	0.880±0.038
Lymphocyte count (K/mL)	<1330	85	82.5	85.0	0.864±0.042
Platelet count (K/mL)	>225000	57.4	47.5	50.5	0.536±0.063
Neutrophil-to-lymphocyte ratio	>5.50	90.0	89.4	90.8	0.920±0.034
Platelet-to-lymphocyte ratio	>155.20	77.5	74.5	75.8	0.795±0.050

ROC curve analysis (Youden index J—Honley and McNell). AA: Acute appendicitis; AUC: Area under the receiver operating characteristic curve, SE: Standard error.

To predict AA, the sensitivity and specificity values for various hemogram parameters at set cutoff values were as follows: for WBC; 72.5% sensitivity and 72.3% specificity at cutoff >10300 cells/mL, for neutrophil count; 80% sensitivity and 79.7% specificity at cutoff >7950 cells/ mL, for lymphocyte count; <1330 cells/mL had 85% sensitivity and 82.5% specificity, for NLR; 90% sensitivity and 89.4% specificity at cutoff >5.50, for PLR; 77.5% sensitivity and 74.5% specificity at cutoff >155.2, for platelet count; 57.4% sensitivity and 47.5% specificity at cutoff >225000 cells/mL; for RDW, 57.5% sensitivity and 53.2% specificity at cutoff >14.2; and for MPV; 62.5% sensitivity and 60.6% specificity at cutoff >7.65.

DISCUSSION

Diagnosis of AA in pregnant patients is more difficult compared to non-pregnant patients due to anatomical and physiological changes in pregnancy. Physiological features of pregnancy such as anorexia, nausea, and vomiting can mask AA symptoms. Uterus enlargement and reduced tonus of abdominal muscles causes uterus growing into the abdomen and the appendix displacement as well.[8] The utilization of radiological imaging techniques is limited in pregnant patients for the goal of fetus protection. Therefore, it is difficult to diagnose AA by history and physical examination. Delay in diagnosis increases the risk of appendix perforation. Perforation leads to peritonitis and sepsis, which causes increased mortality and morbidity rates for the mother and baby.[8-10] Babaknia et al.[11] have reported that the rate of fetal loss was 1.5% in non-perforated and 35.7% in perforated AA patients. The incidence of perforated appendicitis during pregnancy depends on the time between the onset of symptoms and surgical intervention, and the risk for perforation is increased by over 20 hours.[12] It is extremely important to confirm early diagnosis in pregnant patients with suspected AA. Although diagnosis should be confirmed urgently, negative appendectomy should be avoided as well. Negative appendectomy rates during pregnancy have been reported to range between 3% and 23%.[13,14] The rate of negative appendectomy was 14.9% in our study.

Hemogram is a readily available and valuable test, and it plays an essential role in diagnosis of AA. Among the hemogram parameters, the WBC, neutrophil, and lymphocyte counts and NLR, PLR, and MPV act as inflammatory markers. The predictive value of these markers for AA is currently becoming more promising.^[5,15,16] Leucocytosis is commonly observed in patients with AA. In our study, the WBC count of pregnant AA patients was found to be 12886±4785 mm³, and there was a significant difference compared to healthy pregnant women (p<0.001). Estimated sensitivity and specificity values for WBC with a cutoff value >10300 were 72.5% and 72.3%, respectively. Despite the mentioned sensitivity and specificity rates, the WBC count can increase up to 18.000–30.000 mm³ at a period closer to delivery.^[8] Therefore, the WBC count alone may be used as a specific predictor of AA during preg-

nancy. WBC should be used in combination with parameters such as the neutrophil and lymphocyte counts and NLR and PLR with higher sensitivity and specificity values.^[5]

In several inflammatory diseases, regular response of circulating leukocytes is an increased level of neutrophil and reduced level of lymphocyte counts.[17] AA is an inflammatory disease; therefore, a high neutrophil count and low lymphocyte count should be expected. Thus, in our study, the mean neutrophil count was higher and mean lymphocyte count was lower in the appendicitis group compared to other groups (p<0.001). Based on cutoff values, neutrophil and lymphocyte counts showed 80% and 85% sensitivity and 79.7% and 82.5% specificity, respectively. In the study by Yazar et al.,[5] high neutrophil and low lymphocyte values were found in pregnant patients with appendicitis. Recently, several studies suggested that an increased NLR or PLR could be better predictors of AA compared to CRP, WBC, or the neutrophil count alone. [5,18,19] A recent study by Yazar et al.[5] including 28 pregnant women with AA found 78.6% and 100% sensitivity and 80% and 42.9% specificity, based on cutoff values for NLR and PLR, respectively. Additionally, they have reported accurate diagnosis of AA with a 90.5% rate when NLR and PLR were combined with the WBC count, CRP level, and lymphocyte count. Similarly to previous studies, our study showed that NLR and PLR, based on cutoff values, have 90% and 77.5% sensitivity and 89.4% and 74.5% specificity, respectively. Among the hemogram parameters, a higher sensitivity and specificity were observed for NLR in terms of AA diagnosis in pregnant women.

MPV is the most common marker for the production and functional status of platelet, and it reflects inflammatory burden. There are several studies that indicate that MPV values are useful in diagnosing AA. Narci et al.[20] have suggested that high MPV values can be used for the diagnosis of AA. In another study, Albayrak et al.[21] found a significantly lower MPV level in patients with AA compared to the control group. Similarly, no difference was found between the groups in a study by Yazıcı et al., [5] which compared platelet counts in pregnant women. However, in our study, there was no significant difference in MPV values between pregnant women diagnosed with AA and the control group (p>0.05). The predictive value of RDW has been evaluated in several studies among patients with appendicitis; however these studies have concluded with controversial results.[22-24] To the best of our knowledge, ours is the first study to evaluate a predictive value of RDW levels to diagnose AA during pregnancy. We could not demonstrate a significant predictive value of RDW in our study.

Conclusion

In pregnant patients with suspected AA, a more urgent and accurate diagnosis can be achieved using the WBC, neutrophil, and lymphocyte counts and NLR and PLR values in combination with medical history, physical examination, and

imaging techniques. As a result, maternal and fetal morbidity/ mortality rates can be reduced and negative laparotomy rates can be minimized. Our results can contribute to the limited literature available on AA in pregnant women.

Limitation of the study: Retrospective design based on analyses of patient records and a relatively small sample size.

Conflict of interest: None declared.

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ORİJİNAL ÇALIŞMA - ÖZET

Gebelikte hemogramın akut apandisit tanısındaki önemi

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AMAÇ: Akut apandisit (AA) gebelik döneminde obstetrik ve jinekolojik patolojilerden sonra en sık acil cerrahi gerektiren durumdur. Gebe hastalarda AA tanısının hızlı ve doğru konulması maternal ve fetal morbite/mortalite oranlarını azaltır. Bu çalışma, hemogramın gebelik döneminde AA tanısı koymadaki önemini irdelemektedir.

GEREÇ VE YÖNTEM: Ordu veya Ondokuz Mayıs Üniversitesi Tıp Fakültesi Hastanesi'nde Ocak 2007–Aralık 2017 yılları arasında AA nedeniyle ameliyat edilen 47 gebe hasta ile 47 sağlıklı gebe hastanın hemogram parametrelerinden beyaz kan hücresi (WBC) sayısı, nötrofil sayısı, lenfosit sayısı, platelet sayısı, nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO), mean platelet volüm (MPV) ve kırmızı hücre dağıtım genişliği (RDW) değerleri kıyaslandı. Ameliyat edilen hastalar, patoloji sonucu apandisit olanlar Grup A normal olanlar ise Grup B olarak ikiye ayrıldı ve kontrol grubu ile kıyaslandı.

BULGULAR: Grup A hastalarının WBC sayısı, nötrofil sayısı, ortalama NLO ve PLO değerleri Grup B ve kontrol hastalarından anlamlı olarak yüksek tespit edildi (p<0.001). Lenfosit sayısı ortalamasının Grup A hastalarında diğer gruplardan anlamlı olarak düşük olduğu görüldü (p<0.001). MPV, RDW ve ortalama platelet sayısı açısından gruplar arasında anlamlı bir farklılık yoktu (p>0.05). WBC sayısı, nötrofil sayısı, NLO, PLO ve lenfosit sayısı için kestirim değerleri sırasıyla >10300, >7950, >5.50, >155.2 ve ≤1330 olarak alındığında sensivite oranları sırasıyla %72.5, %80, %90, %77.5 ve %85 olarak gözlenirken spesifite oranları ise sırasıyla %72.3, %79.7, %89.4, %74.5 ve %82.5 olarak tespit edildi.

TARTIŞMA: Akut apandisit tanısı olan gebe kadınlarda WBC sayısı, nötrofil sayısı, NLO ve PLO değerleri kontrol grubu ve apandisit şüphesi nedeniyle ameliyat edilen hastalardan istatistiksel olarak anlamlı olacak şekilde yüksek bulunurken lenfosit sayısı ise düşük bulunmuştur. Gebe kadınlarda AA tanısı koymak için anamnez, fizik muayene ve görüntüleme yöntemleri ile birlikte hemogram parametreleride göz önünde bulundurulmalıdır. Anahtar sözcükler: Apandisit; gebelik; hemogram; lenfosit; nötrofil; teşhis.

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