GENERAL SURGERY

Royal Australasian College of Surgeons

Significance of laboratory parameters in diagnosing acute appendicitis during pregnancy

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Key words
acute appendicitis, diagnosis, laboratory parameters, pregnancy.

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This article's abstract section presented as oral presentation by 'Ist Turkish International Colorectal surgery Congress and XVIIIth Turkish Colon and Rectal Surgery Congress'

Accepted for publication 17 December 2021.

doi: 10.1111/ans.17443

Abstract

Background: Acute appendicitis (AA) is the most frequently seen surgical emergency in pregnant women and the most frequently encountered cause of non-obstetric acute abdomen. Due to the physiological and anatomical changes that occur during pregnancy and the limited use of radiological methods, it is difficult to diagnose AA during pregnancy. These conditions increase the risk of morbidity and mortality; therefore, it is crucial to identify ideal laboratory markers that can be utilized to diagnose disease.
Methods: One hundred and ten pregnancies that fulfilled the inclusion criteria for AA diagnosis were retrospectively analysed between 2010 and 2021. Markers with high diagnostic values were discussed.
Results: The patients were divided into three groups as follows; Group I: negative appendectomy ($n = 19$); Group IIa: uncomplicated appendicitis ($n = 59$); Group IIb: complicated appendicitis ($n = 32$). There was no statistically significant difference in mean age or gestational week ($P > 0.05$). Group IIb had a higher rate of complications and a longer length of hospital stay ($P < 0.05$). There were significant differences between the groups in terms of white blood cell (WBC), neutrophil, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein, lymphocyte-to- C-reactive protein ratio, total, direct, and indirect bilirubin values ($P < 0.05$). While platelet and lactate dehydrogenase (LDH) values did not differ substantially between groups, both were found to have a high diagnostic value.
Conclusion: It was concluded that WBC, neutrophil, NLR, PLR, total, direct and indirect bilirubin levels could be utilized to diagnose AA. Moreover, levels of WBC, neutrophil, NLR, platelet, PLR, LDH, total, direct and indirect bilirubin can be utilized to diagnose complicated appendicitis.

Introduction

Acute appendicitis (AA) is the leading cause of non-obstetric surgery during pregnancy, with an incidence similar to non-pregnant women.[1] Diagnostic criteria for AA include the patient's anamnesis, physical exam findings and results of laboratory tests. Diagnosing AA in pregnant women is more difficult than in non-pregnant patients due to anatomical and physiological changes related to pregnancy.[2] History and physical examination findings in pregnancy do not have a consistently predictive role in diagnosing the disease.[3] Although white blood cell (WBC) and C-reactive protein (CRP) values are the most often utilized blood values, their levels increase during the physiological process of pregnancy. Thus, there is no precise laboratory parameter for diagnosing AA.[4,5] While ultrasonography (USG) is the most often utilized imaging technique in the diagnosis of AA, it falls short of expectations due to the anatomic changes that occur during pregnancy. The use of Magnetic Resonance (MR) utilization, on the other hand, is limited due to its high cost, the difficulty of access, and lengthy examination time. Besides, the use of computed tomography (CT) is not recommended due to the ionizing radiation effect.[6] Rapid and accurate diagnosis and treatment are critical to minimizing disease complications for both mother and foetus. While misdiagnosis leads to negative appendectomy, delay

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in treatment causes perforation of the appendix. Both conditions increase the risk of foetal and maternal morbidity and mortality.[7,8]

Due to changes that occur during pregnancy and the limited use of radiological methods, there is no ideal diagnostic tool for AA. Therefore, it is vital to identify optimal laboratory markers that can be utilized in the diagnosis of the disease.

The present study aimed to emphasize the importance of laboratory parameters that are readily accessible in various medical centres can be analysed swiftly, and are cost-effective in diagnosing AA in patients and determining its severity.

Methods

This study was approved by the Ethics Committee of Erzurum Atatürk University Faculty of Medicine. The data of 130 pregnant women aged 16 to 42 who were observed and operated on with a preliminary diagnosis of AA were retrospectively analyzed between January 2010 and June 2021. Patients whose laboratory parameters were unavailable, those with a known haematological disease, allergic disease, malignant or inflammatory disease, chronic disease, or taking medicines that could impact laboratory parameters were also excluded from the study.[9,10]

Twenty patients with basic laboratory values influenced by factors other than AA were excluded from the study. A total of 110 patients who met the inclusion criteria were included in the study. The data were collected from the patients' files and the hospital's electronic software system. Patients' demographic characteristics, type of appendix, comorbidities, type of surgery (laparoscopic, open), length of stay, and complications were recorded. Besides, preoperative hemogram and biochemistry values were examined (WBC, neutrophil, neutrophil-to-lymphocyte ratio (NLR), lymphocyte (LYM), haematocrit, MCV, MCH, MCHC, RDW, platelet, PLR (Platelet-lymphocyte ratio, MPV, Platelet distribution width (PDW), urea, creatinine, ALT, AST, total bilirubin, indirect bilirubin, direct bilirubin, albumin, lactate dehydrogenase (LDH), phosphorus, CRP, lymphocyte-to- C-reactive protein ratio (LCR), CRP/Albumin). Markers with high diagnostic value (high AUC (Area under the curve) value, high sensitivity, and specificity) were discussed.

The patients were divided into three groups according to postoperative histopathologic results.

Group I (normal appendix, obliterative appendix, lymphoid hyperplasia) was evaluated as normal. (Negative appendectomy).

Group IIa (suppurative appendicitis, phlegmonous appendicitis, catarrhal appendicitis) was evaluated as uncomplicated appendicitis.

Group IIb (gangrenous appendicitis, plastron appendicitis, perforated appendicitis) was evaluated as complicated appendicitis.

Statistical analysis

Descriptive data were expressed as mean and *SD* for the numerical variables and as numbers and percentages for the categorical variables. The distribution of the data was examined with histogram graphics. One way ANOVA, Kruskal Wallis Test, Tamhane test and Tukey from Post hoc tests were used in data analysis. In order to measure the ability of laboratory values to distinguish pathological positivity, receiver operating characteristic (ROC) curves were generated. The area under the curve (AUC) and a cut-off value of each measurement were determined. Sensitivity, specificity and positive likely-hood ratio (LR+) cut-off values were calculated and evaluated together. ROC analyses were carried out for patients diagnosed with acute appendicitis and those with normal appendix (Table 2, Fig. 1). Moreover, separate ROC analyses were performed for complicated and uncomplicated patients (Table 3, Fig. 2). Data were analyzed at a 95% confidence interval, and a *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 23 software.

Results

Throughout the 11-year study period, 130 consecutive patients were operated on for prediagnosis of acute appendicitis. Twenty patients (15.38%) were excluded from this study since their blood parameters were affected by a factor other than acute appendicitis (six

Table 1 Demographic features and laboratory values of the patients

	Appendix type			*P*-value*
	Normal appendix ($n = 19$)	Uncomplicated AA ($n = 59$)	Complicated AA ($n = 32$)	
Age	27.57 ± 6.11	28.03 ± 6.34	26.96 ± 6.43	0.745
Gestational week	19.53 ± 6.66	16.35 ± 7.33	19.86 ± 9.77	0.192
Length of stay/day	3.42 ± 1.57	2.72 ± 0.81	4.53 ± 2.72	<0.001
Postoperative complication rate %	5.26	3.38	12.5	<0.05
WBC	12.74 ± 2.91	13.56 ± 3.69	15.84 ± 3.99	0.005
Neutrophil	9.59 ± 2.3	11.09 ± 3.6	13.66 ± 3.95	<0.001
NLR	4.5 ± 1.38	10.72 ± 12.73	12.68 ± 6.81	<0.001
Platelet	264.6 ± 87.8	233.2 ± 64.7	257.6 ± 77.7	0.151
PLR	127.1 ± 56.5	168.03 ± 81.6	233.2 ± 112.3	<0.001
Total bilirubin	0.35 ± 0.12	0.52 ± 0.3	0.56 ± 0.13	0.002
Indirect bilirubin	0.27 ± 0.099	0.40 ± 0.27	0.48 ± 0.25	0.019
Direct bilirubin	0.08 ± 0.04	0.12 ± 0.077	0.14 ± 0.073	0.002
LDH	222.2 ± 53.2	218.2 ± 65	239.5 ± 55.7	0.125

LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; WBC, white blood cell.

*One Way ANOVA, Kruskal Wallis Test.

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patients whose blood parameters could not be identified, two patients with malignant pathology, two patients with multiple comorbid diseases, four patients who underwent appendectomy during childbirth, four patients with other surgical pathologies, and two patients with non-surgical pathologies). After excluding these patients, the study enrolled a total of 110 patients. The patients were divided into three groups as Group I: normal appendix (negative appendectomy) ($n = 19$, 17.27%); Group IIa: uncomplicated appendicitis ($n = 59$, 53.63%); Group IIb: complicated appendicitis ($n = 32$, 29.09%) (Table 1). All patients were female, with a mean age of 27.65 ± 6.29 years (range: 16–42 years). There was no significant difference among the groups related to mean age ($P = 0.745$) and gestational week ($P = 0.192$). The mean gestational week was 18.01 ± 8.03 weeks, 35 (31.81%) patients were in the first trimester, 61 (55.45%) patients were in the second trimester and 14 (12.72%) patients were in the third trimester (Table 1).

Twenty-six laboratory parameters were evaluated. However, only the parameters with high diagnostic values were discussed. While there was a significant difference in LYM and PDW values between the groups, they were not addressed due to their low AUC values. Since sufficient CRP values could not be reached, CRP and other CRP-related values were not analyzed.

There were significant differences between the groups regarding WBC, neutrophil, NLR, PLR, CRP, LCR, total, direct, and indirect bilirubin values ($P < 0.05$). Although the differences between the groups were not statistically significant, platelet and LDH levels were found to have a high diagnostic value ($P > 0.05$) (Table 1).

The WBC, neutrophil, NLR, PLR, total bilirubin, direct bilirubin and indirect bilirubin were found to be biomarkers for acute appendicitis diagnosis (Table 2, Fig. 1). WBC, neutrophil, NLR, Platelet, PLR, total bilirubin, direct bilirubin, indirect bilirubin and LDH

Table 2 Evaluation of patients with and without AA*

Parameters	Cut-off value	AUC(p)	Sensitivity (%)	Specificity (%)	LR+
WBC	11.52	0.605 (0.246)	84	38	1.37
NEU	10.90	0.681 (0.045)	60	61	1.57
NLR	5.21	0.848 (<0.001)	78	77	3.39
PLR	121.20	0.733 (0.010)	78	69	2.54
Total bilirubin	0.30	0.773 (0.003)	82	61	2.14
Direct Bilirubin	0.08	0.788 (0.001)	64	84	4.2
Indirect bilirubin	0.24	0.754 (0.005)	82	61	2.14

AUC, area under the curve; +LR, positive likelihood ratio; WBC, white blood cell; NEU, neutrophil; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

*ROC curve test.

Fig 1. ROC curve analyses of significant parameters for the diagnosis of acute appendicitis.

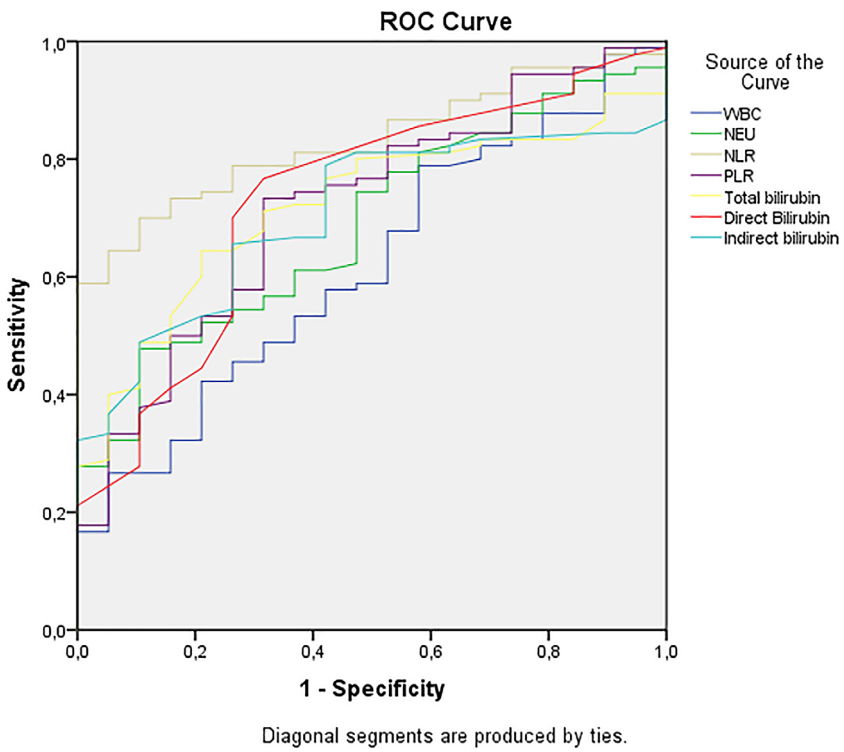

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Table 3 Comparison of complicated and uncomplicated appendicitis groups*

Parameters	Cut-off value	AUC(p)	Sensitivity (%)	Specificity (%)	LR+
WBC	13.66	0.714 (0.001)	74	64	2.06
NEU	11.98	0.724 (0.001)	67	70	2.24
NLR	10.86	0.684 (<0.005)	58	71	2.05
Platelet	241.00	0.602 (0.122)	58	54	1.28
PLR	186.01	0.689 (0.004)	61	70	2.03
Total bilirubin	0.54	0.611 (0.090)	54	60	1.38
Direct bilirubin	0.12	0.620 (0.67)	58	68	1.81
Indirect bilirubin	0.35	0.597 (0.141)	64	43	1.13
LDH	210	0.617 (0.076)	74	52	1.57

AUC, area under the curve; LDH, lactate dehydrogenase; +LR, positive likelihood ratio; NEU, neutrophil; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; WBC, white blood cell.

*ROC curve test.

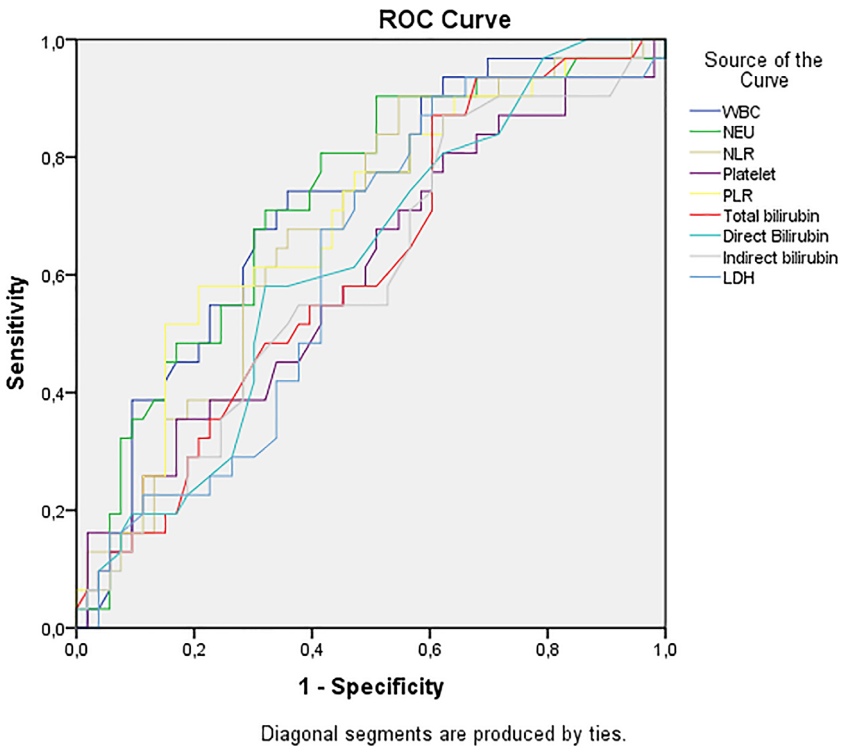

Fig 2. ROC curve analyses of significant parameters for complicated and uncomplicated appendicitis.

values were found to be biomarkers for predicting the severity of acute appendicitis (Table 3, Fig. 2).

In terms of advanced imaging techniques, 94.5% of the patients were examined by USG and 41.8% by MR imaging.

Of the patients, 88.2% were operated under general anaesthesia and 11.8% under spinal anaesthesia; 108 of the operations (98.18%) were open (11.81% McBurney, 84.56% right paramedian, 1.81% midline) and 2 (1.82%) were laparoscopic.

The average length of hospital stay was 3.42 ± 1,57 days in Group I, 2.73 ± 0.81 days in Group IIa, and 4.53 ± 2,72 days in group IIb, with a significant difference between the groups ($P < 0.001$) (Table 1).

Postoperative complications were compared between the groups using the Clavien–Dindo classification (CDC).[11] According to the CDC, seven patients were classified as Grade 2. While the postoperative complication rate was 6.36%, complication rates were 5.26% in Group I, 3.38% in Group IIa and 12.5% in Group IIb, with significant differences ($P < 0.05$).

Discussion

AA is one of the most often seen surgical emergencies in pregnant women, accounting for the majority of non-obstetric acute abdomens.[9,12] AA is more common during the second trimester of pregnancy.[13,14] 55.45% of the patients were in the second trimester in our study.

Unlike non-pregnant women, pregnant women with a prediagnosis of AA usually apply to obstetrics and gynaecology clinics, and pregnancy-related causes are the first to come to mind. The anamnesis and physical examination differ with the size of the

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foetus during pregnancy, and hormonal changes complicate disease diagnosis. Radiologic methods with high diagnostic value, such as CT used in other patients, cannot be used in pregnant women, emphasizing the importance of utilizing laboratory parameters.[9,12,15]

Because WBC is commonly accessible and very inexpensive, it is the most often used laboratory parameter in the diagnosis of AA. Although leukocytosis is not a pathognomonic finding in patients with AA, it is utilized as an auxiliary criterion.[9] WBC and CRP values are the most frequently used laboratory parameters in the diagnosis of AA during pregnancy. On the other hand, physiological leukocytosis can occur during pregnancy, which should be considered when evaluating the patient's status. According to previous studies, the WBC value was significantly higher in patients who underwent AA operation compared with healthy pregnant women and pregnant women with a prediagnosis of AA.[4,9] Moreover, WBC level was found to be higher in pregnant patients with AA diagnosis than in non-pregnant women with AA diagnosis.[16,17] Previous studies have reported that WBC in AA diagnosis has a sensitivity range of 57.1–72.5%, a specificity range of 52.0–82.9%, and an AUC value of 0.661.[4,18] WBC value is significantly higher in complicated appendicitis than in uncomplicated appendicitis.[19] The WBC value, which was found to have the highest sensitivity in both groups when group comparisons were performed, was identified in our study as a laboratory parameter with a high diagnostic value that can be used to diagnose acute appendicitis and determine the condition of the appendix becoming complicated. This marker could not be discussed because a sufficient CRP value could not be obtained for statistical analysis in our study. Therefore, prospective studies on this subject, in particular, will be beneficial.

The neutrophil value, a WBC component, is a good diagnostic marker used in the diagnosis of AA.[20] Neutrophils are very important cells in the immune defence system and play an active role in inflammatory conditions; they are potent regulators of epithelial cells, mast cells and macrophages.[21] Neutrophil percentage and count should be considered in the diagnostic evaluation of AA to guide treatment and resource utilization better.[13] In many studies, the diagnostic value of neutrophils was found to be higher than the leukocyte value17, while in our study, the neutrophil value was a laboratory parameter with a high diagnostic value that can be used both in diagnosing acute appendicitis and determining the condition of the appendix becoming complicated. Furthermore, it was found to be the marker with the highest AUC (0.724) value in determining the condition of the appendix becoming complicated in patients with AA.

NLR (neutrophil to lymphocyte ratio) values may be more sensitive than leukocyte counts; changes in the NLR can be an early indicator of viral and bacterial infections. The increase in the difference between neutrophils and lymphocytes reflects the severity of the inflammatory response. Therefore, the NLR has been employed as a biomarker for various pathologic events for many years, including chronic inflammatory diseases, malignancies, and postoperative complications.[22–24] Moreover, NLR has statistically higher diagnostic sensitivity than WBC and CRP for AA.[25] A systematic review and meta-analysis study showed that while NLR was significantly higher in patients with AA than without appendicitis, it was significantly higher in complicated appendicitis than uncomplicated appendicitis. This study suggests that NLR >4.7 independently predicts AA, and NLR > 8.8 independently predicts complicated appendicitis with acceptable diagnostic values.[26] In the current study, a 5.21 cut-off value of the NLR was found to have 78% sensitivity and 77% specificity in the differentiation of acute appendicitis from the normal appendix (AUC:0.848, $P < 0{,}001$), and a 10.86 cut-off value of NLR could be predictive in the differentiation of complicated appendicitis from acute appendicitis with the sensitivity of 58% and specificity of 71% (AUC:0.684, $P < 0{,}005$). Based on these findings, NLR's diagnostic values are higher than other parameters. Its utilization is strongly suggested for both diagnosing appendicitis and determining its severity.

Platelets are helper cells in the modulation of various inflammatory events; PLR has been recently proposed to be a predictor of inflammatory conditions.[27] PLR might also be useful for the diagnosis of AA during pregnancy.[4,28]Pehlivanli *et al.* showed that the PLR value could diagnose AA and differentiate perforated appendicitis from acute appendicitis.[22] The study of Yazar *et al.* reported that when the cut-off value of PLR was taken as 121.78, it had 100% sensitivity and 42.9% specificity on pregnant appendicitis patients. Again in the same study, PLR was found to be more significant than the platelet value.[4] However, in the current study, a 121.2 cut-off value of the PLR was found to have 78% sensitivity and 69% specificity in the differentiation of acute appendicitis from the normal appendix. PLR value was an important laboratory value in diagnosing AA and determining the severity of appendicitis, while the platelet value is only a marker that determines the condition of the complicated appendix (Table 2, Table 3). Platelet value is expected to be lower in patients with acute appendicitis.[29] Although it was low in acute appendicitis patients, our study revealed that the platelet value was significantly higher in the complicated appendicitis group than in the uncomplicated appendicitis group, contrary to expectations. Due to conflicting results, further studies are needed on this subject.

It has been shown that bilirubin levels increase in inflammatory diseases in the abdomen, indicating a relation between bacteria and serum bilirubin levels.[30] In recent years, the importance of serum bilirubin value in the diagnosis of AA has been emphasized in various studies.[31,32] Bilirubin values can be used as an additional biomarker in diagnosing acute appendicitis and detecting perforation. In a meta-analysis study, when the cut-off value was 1 mg/dL, sensitivity was shown as 49%, specificity as 82%, AUC value as 0.73, and positive likelihood ratio as 2.51 in determining appendix perforation.[33] However, in our study, the cut-off value was 0.54 mg/dL, the AUC value was 0.611, the sensitivity was 54%, the specificity was 60% and the positive likelihood ratio was 1.38 in determining the complicated appendicitis condition. Total, direct and indirect bilirubin values draw attention as blood values with high diagnostic value both in the diagnosis of AA and in determining the condition of the complicated appendix. In addition, direct bilirubin value has the highest specificity (84%) in diagnosing AA. To the best of our knowledge, this is the first study showing that bilirubin levels are a parameter that can be used in the diagnosis of AA and in determining the complication of appendix in pregnancy.

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The number of studies on the link between LDH levels and AA is limited; however, LDH levels have increased in inflammatory diseases. Tumour cells and infections damage tissues and increase serum LDH levels.[34,35] Kukreja *et al.* discovered a correlation between AA levels and LDH levels in their study. In this study, the sensitivity for LDH level in the diagnosis of AA was 77.5%, and the specificity was 80%.[36] Currently, there is no study investigating the relationship between serum LDH level and AA in pregnancy. In our study, LDH level was found to be high in the complicated patient group; and it is the marker with the highest specificity in the differentiation of complicated-uncomplicated appendix (AUC:0.617, sensitivity 74%, specificity 52%).

Our study is important in terms of being the first study to show that total, direct, indirect bilirubin and LDH values can be used to diagnose acute appendicitis during pregnancy.

The risky results of AA in pregnant women compared with non-pregnant women cause these patients to be treated more aggressively, which causes negative appendectomy rates to be higher.[7,8] The negative appendectomy rate has been reported to be between 13.3%–36% during pregnancy.[12,37,38] Due to the disease being diagnosed late in pregnancy, the likelihood of developing complicated appendix increases.

Appendix perforation rate has been reported to be between 14% and 42.9% in pregnant patients.[13,28] In two large studies involving pregnant patients, the negative appendectomy rate ranged between 23 and 28.9%, whereas the rate of the complicated appendix was 15.6–25%.[7,37] In our study, the negative appendectomy rate was 17.27%, and the rate of complicated appendectomy was 29.09%. Like the literature, almost half of the patients are operated on either unnecessarily or late, which demonstrates the critical nature of disease markers in diagnosing the disease or determining the severity.

The risk of maternal and foetal morbidity and mortality increases in unnecessary surgeries or delayed diagnosis of the disease.[37] In the studies performed, the postoperative complications rate has been reported as 5.74–6.8%,[7,38] while in our study, the postoperative complications rate was 6.36%, which was mostly seen in the complicated appendicitis patient group, as expected. This situation also prolonged the hospital stay. Since our study aimed to emphasize the importance of laboratory values, foetal complications of the disease were not investigated.

The most limitation of our study is that it is a retrospective study. Another limitation is that the CRP value, which is the most used in the diagnosis of the disease after leukocyte count in pregnant women, could not be evaluated in our study due to the insufficient number. The other limitations are the inability to create a decisional algorithm based on blood values and the efficacy of other diagnostic tests such as anamnesis, physical examination, and imaging tests cannot be discussed together with blood values.

Conclusion

Due to the some changes that occur during pregnancy, it is difficult to diagnose AA during pregnancy. In pregnant women, approximately half of the patients are either misdiagnosed as AA or diagnosed late. These results increase the length of hospital stay and the rate of postoperative complications. Although there is no standard test to predict AA and its severity, basic laboratory parameters can be used this aim. Preoperative WBC, neutrophil, PLR, NLR, MPV, total, direct and indirect bilirubin levels can be used in the diagnosis of AA in pregnancy patients. Again, WBC, neutrophil, NLR, platelet, PLR, LDH, total, direct and indirect bilirubin levels can be used to determine complicated appendicitis. Although these blood values have high diagnostic value, it would be more valuable to use them in combination with other diagnostic tests. Prospective studies with large patient volumes are needed on this subject.

Conflict of interest

None declared.

Author contributions

Rıfat Peksöz: Conceptualization; data curation; formal analysis; investigation; methodology; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Esra Dişçi:** Conceptualization; data curation; investigation; methodology; validation; writing – review and editing. **Abdulkadir Kaya:** Data curation; formal analysis; investigation; methodology; software; supervision; writing – review and editing. **Enes Ağırman:** Data curation; investigation; methodology; resources; validation; writing – original draft; writing – review and editing. **Ercan Korkut:** Data curation; investigation; methodology; software; validation; writing – review and editing. **Nurhak Aksungur:** Conceptualization; investigation; methodology; supervision; validation; visualization; writing – original draft. **Necip Altundaş:** Formal analysis; investigation; methodology; supervision; writing – review and editing. **Salih Kara:** Conceptualization; resources; supervision; writing – review and editing. **Sabri Selçuk Atamanalp:** Conceptualization; data curation; investigation; methodology; supervision; validation; visualization; writing – review and editing.

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