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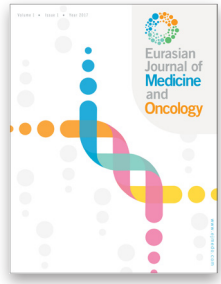

Research Article

Importance of Inflammatory Markers in Predicting the Rupture in Ectopic Pregnancies

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Abstract

Introduction: The aim is to examine the laboratory findings and inflammatory markers in the predicting the rupture in patients, who were admitted to our clinic with the complaints of ectopic pregnancy.

Objective: One-hundred and fifty-four tubal ectopic pregnancy patients, who were diagnosed with ectopic pregnancy and treated were retrospectively examined.

Results: When the neutrophil lymphocyte ratios (NLR) were compared between the two groups, the mean NLR values were 5.88±4.66 and 3.20±4.80 in the ruptured and unruptured groups, respectively, the results were statistically significant (p=0.001). Similarly, the mean platelet lymphocyte ratio (PLR) values were 148.14±75.59 and 118.79±54.08 in the ruptured and unruptured groups, respectively, the results were statistically significant (p=0.026). A statistically significant difference was found between the levels of b-hCG, WBC, PLR and NLR in accordance with the presence of rupture in the patients (p<0.05) and the results of ruptured ectopic patients were found to be higher The ratio of rupture risk was 4.5 times higher in patients with PLR of ≥166.6, and the ratio of rupture risk was 6.9 times higher in patients with NLR of ≥4.

Conclusion: We thought that the inflammatory markers of NLR and PLR could be used for the prediction of rupture.

Keywords: Ectopic pregnancy, rupture, inflammatory markers, neutrophil lymphocyte ratios, platelet lymphocyte ratio

Ectopic pregnancy, also known as tubal pregnancy, is defined as the growth of the gestational sac outside the uterine cavity. Ectopic pregnancy constitutes about 1-2% of all pregnancies with 98% occurring in the fallopian tubes.[1,2] It is the most significant cause of pregnancy-related maternal deaths in the first trimester, and accounts for 4-10% of pregnancy-related maternal deaths.[3]

The clinical symptoms are usually diagnosed at the 6th -8th weeks of the gestation and they are not observed in one-third of the cases, and it commonly presents with vaginal bleeding and abdominal pain.[4] In the ruptured ectopic pregnancies, hypovolemic symptoms, such as syncope and hemorrhagic shock, are associated with intra-abdominal hemorrhage.[5] The diagnosis and medical treatment of the unruptured ectopic pregnancy has various advantages, including less cost, less tubal damage and high potential of subsequent pregnancies.

In recent studies, neutrophil-lymphocyte ratio (NLR) is a commonly used marker of systemic inflammatory responses.[6] This ratio is determined with current hemogram parameters without additional costs, by dividing the total neutrophil count by the number of lymphocytes. It has been found that inflammatory cytokine levels are elevated both in the region of inflammation and systemic circulation during the

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ectopic pregnancies.[7] Platelet-lymphocyte ratio (PLR) and mean platelet volume (MPV) have been useful as predictive and prognostic markers in various systemic inflammatory diseases, cardiovascular diseases and malignancies.[8-10]

In the present study, the aim is to examine the laboratory findings and inflammatory markers in the predicting the rupture in patients, who were admitted to our clinic with the complaints of ectopic pregnancy.

Methods

One-hundred and fifty-four tubal ectopic pregnancy patients, who were diagnosed with ectopic pregnancy and treated between June 2012 and March 2017 in our clinic, were retrospectively examined. The age, number of pregnancies and births, initial complaints and examination findings, contraception method, previous ectopic surgery, history of previous tubal surgery and sterilization, ultrasonographic findings, b-HCG values, hemogram parameters and treatment approaches were examined. Patients history of smoking, patients with use of anticoagulant drugs and any drug that may interfere with hematologic parameters are excluded. Also, patients having chronic inflammatory diseases, such as systemic lupus erythematosus, chronic hypertension, diabetes mellitus, hepatic and renal failure, previous myocardial infarction, history of thrombosis and malignancy were excluded from the study.

Blood samples were obtained for hemogram and b-hCG counts at the first admission of all patients. NLR and PLR were calculated by using these hemogram values. Patients who were hemodynamically stable, patients with intact gestational sac, patients without fetal cardiac activity, patients with no known allergy to methotrexate, and those with normal hepatic and renal function were evaluated as unruptured ectopic pregnancy, and methotrexate therapy was administered to these patients (50 mg/m^2). At the first administration, 4th and 7th days, b-hCG was measured again and dose was repeated in case of a reduction less than 15%. Patients developing rupture following methotrexate therapy were evaluated as a failure in the treatment, and they were not included in the ruptured ectopic pregnancy group. Surgical therapy was performed in patients who were hemodynamically unstable, patients without intact gestational sac, patients having intra-abdominal free fluid and acute abdominal examination findings, and those with contraindication to methotrexate. Patients who were hemodynamically unstable, without intact gestational sac, having intra-abdominal free fluid and acute abdominal examination findings were accepted as ruptured ectopic pregnants. Also, diagnosis was confirmed with surgical findings. Laparoscopy, both laparotomy and salpingostomy, or salpingectomy was performed.

The study was approved by the Ethics and Clinical Investigation Committee. Statistical data was evaluated by using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program. Study data were evaluated by using descriptive statistics (mean, standard deviation, median, frequency, ratio, minimum, maximum); for the comparison of qualitative data, Student-t test was used to compare two groups of normally distributed variations and Mann Whitney U was used to compare two groups of not normally distributed variations. Pearson Chi-Square test and Fisher's Exact test were used for the comparison of quantitative data. The p values less than <0.05 was accepted as significant.

Results

A total of 154 patients were analyzed. The mean age of the patients was 31.31±5.73 years, and the gravida was 2.71±1.61. Eleven patients had the history of ectopic pregnancy (7.15%) and nine had the history of RIA (5.85%). Totally, 44 and 16 patients had surgical treatment due to ruptured ectopic pregnancy and not matching the methotrexate criteria, respectively. In patients receiving surgical treatment, laparoscopy and laparotomy were performed to 31 and 27 patients, respectively. Ninety-four patients received methotrexate therapy. Of the 88 patients, 74 were treated with single dose and 14 were treated with double dose, the success

Table 1. Cases had methotrexate treatment

		MTX Treatment		p
		Successful (n=88)	Unsuccessful (n=6)	
BHCG	Mean±SD	2249.72±6762.58	9796.25±9938.28	[a]0.014*
Ectopic mass diameter	Mean±SD	21.09±8.56	18.84±6.50	[a]0.787
NLR	Min-Max (Median)	0.87-48.32 (2.14)	1.55-4.28 (2.51)	Z:-1.103
	Mean±SD	3.09±5.25	2.74±0.93	[a]0.270
PLR	Min-Max (Median)	46.22-342.86 (102.61)	48.51-178.4 (101.02)	Z:-0.448
	Mean±SD	119.13±52.40	105.36±45.21	[a]0.654

[a]Mann Whitney U Test; [b]Fisher's Exact Test; *p<0.05.

rate was 93.6%. Rupture was developed in 6 patients after single-dose methotrexate therapy and surgical treatment was performed in these patients. The rate of unsuccessful methotrexate therapy was detected as 6.4% in our clinic.

The association between the level of b-hCG, the diameter of ectopic foci, NLR and PLR in patients with successful or unsuccessful methotrexate therapy results were presented in Table 1. While a significant difference was detected between the two groups in terms of b-hCG levels, there was no significant difference between the groups in terms of NLR, PLR and the diameter of ectopic foci. The levels of b-hCG, the diameter of gestational sac, MPV, NLR and PLR in ruptured and unruptured patients at the diagnosis were presented in Table 2. There was no significant difference between the two groups in terms of MPV. The mean values of b-hCG were 9976.75±14724 mIU/ml and 3590.38±7607 mIU/ml in the ruptured and unruptured groups, respectively, and the results were statistically significant (p=0.001). The mean diameter of ectopic foci was 32.24±11.86 mm and 21.86±8.99 mm in the ruptured and unruptured groups, respectively, the results were statistically significant (p=0.001). When the NLRs were compared between the two groups, the mean NLR values were 5.88±4.66 and 3.20±4.80 in the ruptured and unruptured groups, respectively, the results were statistically significant (p=0.001). Similarly, the mean PLR values were 148.14±75.59 and 118.79±54.08 in the ruptured and unruptured groups, respectively, the results were statistically significant (p=0.026). A statistically significant difference was found between the levels of b-hCG, WBC, PLR and NLR in accordance with the presence of rupture in the patients (p<0.05) and the results of ruptured ectopic patients were found to be higher (Table 2).

The cut-off points for the b-hCG of ≥919.1 was statistically significant in the ruptured ectopic pregnant patients (p=0.001). When the cut-off value of b-hCG was taken as 919.1, the sensitivity was 88.37% and specificity was 47.22%. The ratio of rupture was 6.8 times higher in patients with b-hCG of ≥919.1 than those with b-hCG of <919.1. The odds ratio for b-hCG was 6.8 (95% CI: 2.48-18.59) (Table 3).

Table 2. Comparision of ruptured and unruptured cases

		Ruptured (n=44)	Unruptured (n=110)	p
BHCG	Mean±SD	9976.75±14724.30	3590.38±7607.52	[a]0.001**
Ektopic mass diameter	Min-Max (Median)	15-70 (30.0)	8-50 (20.0)	Z:-4.549
	Mean±SD	32.24±11.86	21.86±8.99	[a]0.001**
WBC				
	Mean±SD	11.18±4.55	9.10±3.10	[a]0.004**
MPV	Min-Max (Median)	5.9-12.4 (7.6)	5.3-20.4 (7.9)	Z:-0.995
	Mean±SD	8.10±1.47	8.33±1.81	[a]0.320
HB				
	Mean±SD	10.44±1.54	11.78±1.60	[c]0.001**
HTC				
	Mean±SD	31.44±4.50	35.44±4.50	[c]0.001**
NLR	Min-Max (Median)	0.1-19.5 (4.4)	0.87-48.3 (2.21)	Z:-3.905
	Mean±SD	5.88±4.66	3.20±4.81	[a]0.001**
PLR	Min-Max (Median)	53.4-352.7 (122.9)	46.22-342.8 (102.6)	Z:-2.222
	Mean±SD	148.14±75.59	118.79±54.08	[a]0.026*

[a]Mann-Whitney U Test; [c]Student t Test; *p<0.05; **p<0.01 .

Table 3. Screening Test and ROC Curve results for BHCG, WBC, PLR and NLR

	Diagnostic Scan					ROC Curve		p
	Cut off	Sensitivite	Spesifisite	Positive Predictive Value	Negative Predictive Value	Area	95% Confidence Interval	
BHCG	≥919.1	88.37	47.22	40.00	91.07	0.706	0.615-0.797	0.001**
WBC	≥10.9	50.00	79.44	50.00	79.44	0.649	0.547-0.751	0.004**
PLR	≥166.6	34.09	89.72	57.69	76.80	0.615	0.512-0.719	0.026*
NLR	≥4	56.82	84.11	59.52	82.57	0.703	0.602-0.803	0.001**

The cut off points for PLR of ≥166.6 was found to be statistically significant (p=0.001). When the cut-off value of PLR was taken as 166.6, the sensitivity was 34.09% and specificity was 89.72%. The ratio of rupture was 4.51 times higher in patients with PLR of ≥166.6 than those with PLR of <166.6. The odds ratio for PLR was 4.51 (95% CI: 1.86-10.9) (Table 3).

The cut off points for NLR of ≥4 was found to be statistically significant (p=0.001). When the cut-off value of PLR was taken as 4, the sensitivity was 56.82% and specificity was 84.11%. The ratio of rupture was 6.96 times higher in patients with NLR of ≥4 than those with NLR of <4. The odds ratio for NLR was 6.96 (95% CI: 3.16-15.35) (Table 3).

All patients were treated either a medical or a surgical approach, and complication was not found in any of the patients.

Discussion

Ectopic pregnancy is a leading cause of pregnancy-related maternal mortality in the first trimester, and accounts for 4-10% of all pregnancy-related maternal deaths.[3] Tubal ectopic pregnancy is the implantation of the fertilized ovum in the tubas, instead of endometrium, due to a defect or variations in the tubal lumen during the tubal transport of fertilized ovum before reaching to the endometrial cavity, and the increased levels of inflammatory cytokines have been detected both in the region of inflammation and systemic circulation in these patients.[7]

Medical treatment might be considered in hemodynamically stable and unruptured ectopic pregnancy patients and the most common method is the single-dose methotrexate therapy.[11,12] The success rate of methotrexate therapy is between 90% and 94.2% in favorable patients.[12,13] In our study, the success rate of methotrexate therapy is compatible with the literature. There are various studies investigating the factors that affect the success rate of methotrexate therapy in the ectopic pregnancy. The most prominent factor is the initial serum level of β-hCG. As the initial serum level of β-hCG increases, the success rate is decreased.[14,15]

Spira et al. defined four factors that enhance the rupture risk while diagnosing ectopic pregnancy; never having used contraception, history of infertility and tubal damage, induction of ovulation and high level of b-hCG (at least 10,000 IU/L). The ratio of tubal rupture was reported as 18%.[16]

There is no a consensus on the initial value of b-hCG level that predicts success in the treatment. According to the studies of Corsan et al.[16], Nazac et al.[15] and Ragiv et al.[17], the initial b-hCG levels of ≥1500 mIU/ml, ≥1000 mIU/ml and ≥2000 mIU/ml decrease the success rate of methotrexate therapy, respectively.

In the study of Ugurlucan et al., the initial b-hCG level was not found significant in terms of rupture in patients who received methotrexate therapy. Besides, they detected that the success rate decreased when the size of ectopic foci was above 30 mm.[18] In the current study, MTX treatment successful group of ectopic mass diameter is lower than unsuccessful group.

In the recent studies, it has been found that the values of NLR, PLR and MPV have been useful as predictive and prognostic markers associated with various systemic inflammatory disease, cardiovascular disease and malignancies.[8,10] The ratios of leukocytes in the circulation changes during the inflammatory response. The response of leukocytes to the stress causes an increase in the neutrophil count and decrease in the lymphocyte count, and thus, the ratio of neutrophil and lymphocyte counts has been used as inflammation marker in intensive care practices.[19] However, in the recent studies, NLR has been shown to be a prognostic factor on the overall survival in colorectal and over malignancies.[20,21] Dogru et al. reported elevated NLR levels in patients with ruptured ectopic pregnancy in comparison to those with unruptured ectopic pregnancy.[22] In the same study, PLR value was found to be statistically insignificant between the two groups. In our study, both parameters were detected in patients with ruptured ectopic pregnancy. We are of opinion that NLR and PLR can be used together for the prediction of rupture in patients with ectopic pregnancy.

In our study, the inflammatory markers of NLR and PLR levels were significantly high in patients with ruptured ectopic pregnancy, while MPV levels were found to similar between the groups. There was no difference between successfully treated and unsuccessfully treated patients in terms of NLR and PLR in the patients treated with methotrexate.

Platelets have a role in endothelial damage, angiogenesis and hypoxia that are seen in the pathogenesis of ectopic pregnancy. MPV, as an indicator of platelet function, is a hematological parameter that is examined in all pregnant women.[23] In the study of Artunc et al., MPV value was found to be lower in patients with ectopic pregnancy compared to the control group, and it was lower in ruptured cases than the unruptured ectopic pregnancy cases.[24]

Besides, on the contrary, Abdulkadir et al. reported that MPV was significantly higher in ectopic pregnancies but they found no difference for the prediction of rupture.[25] Similarly, in our study, we detected that MPV level was insignificant between the ruptured and unruptured ectopic pregnancy cases.

Conclusion

In conclusion, the ratio of rupture risk was 4.5 times higher in patients with PLR of ≥166.6, and the ratio of rupture risk was

6.9 times higher in patients with NLR of ≥4. We thought that the inflammatory markers of NLR and PLR could be used for the prediction of rupture. The data about this topic in the literature is quite limited. Because the current study had small number of patient and was retrospectively designed, studies involving more patients are required for the prediction of rupture.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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