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Can the Systemic Immune Inflammation Index Predict the Treatment of Ectopic Pregnancy?

Sevcan Sarikaya[1,*], Emre Uysal[2], Oğuzhan Günenç[1]

[1]Konya City Hospital, Department of Obstetric ve Gynecology, Konya, Turkey

[2]Yusufeli State Hospital, Department of Obstetric ve Gynecology, Artvin, Turkey

*Correspondence should be addressed to Sevcan Sarikaya, simsek_svcn_@hotmail.com

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Abstract

Objective: The aim of this study was to predict the selection of treatment for ectopic pregnancy (EP) using the values of platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR) and systemic immune inflammation index (SII) obtained from hematological parameters routinely used in clinical practice.

Design: Retrospective observational study.

Place & duration of study: This retrospective, cross-sectional study was conducted in the Department of Obstetrics and Gynecology of Konya City Hospital, between August 2020 and August 2022.

Methodology: The study included 140 patients who were diagnosed with EP in our hospital. The patients were separated as those who received medical treatment with methotrexate (MTX) (Group I) and those who underwent surgical procedures (Group II). The two groups were compared with respect to demographic characteristics and pre-treatment laboratory parameters.

Results: Of the 140 patients diagnosed with EP, 75 were in Group I, treated with MTX, and 65 were in Group II, treated with surgery. No significant difference was determined between the groups with respect to age, body mass index, and gravida-parity of the patients ($p>0.05$). The incidence of extrauterine mass, presence of yolk sac, and fetal heartbeat on ultrasonography was significantly higher in Group II than in Group I ($p<0.05$). NLR and MLR values in Group II were significantly lower than in Group I ($p<0.05$). The PLR value did not differ significantly between the groups ($p>0.05$). The SII value was significantly higher in Group II than in Group I ($p<0.05$).

Conclusion: NLR and MLR were found to be lower, and the SII was significantly higher in the patients who underwent surgery. Hematological parameters, especially SII, are potential markers that can be used in EP treatment selection.

Keywords: Ectopic pregnancy, Systemic immune inflammation index, Platelet/lymphocyte ratio, Neutrophil/lymphocyte ratio, Monocyte/lymphocyte ratio NLR, PLR, MLR, SII, Methotrexate, MTX

Introduction

Ectopic pregnancy (EP) refers to implantation of the embryo outside the uterine cavity. The incidence of EP has increased together with the currently increasing use of assisted reproductive technologies and now stands at 1.3-2% [1]. The most common localisation of EP is the tuba uterine (90%) [1,2], and the main causes of tubal EP are previous tubal surgery, history of EP, salpingitis, and *in vitro* fertilization [3]. In the process of a normal pregnancy, a secondary oocyte expelled from the ovary is captured by the tubal fimbriae and drawn into the tuba. The secondary oocyte matures into an ovum and is fertilized with sperm in the ampulla of the tuba, then, through the ciliary activity of the tuba, it enters the uterine cavity and implants. The disruption of any step in this pathway, or conditions of tubal ciliary activity disorder, or pelvic

inflammatory disease cause the embryo to be implanted in a place other than the uterine cavity [3].

Platelets also play a role in ensuring hemostasis in the body, together with coagulation factors, which interact with platelets, endothelial cells, and leukocytes. When platelets are stimulated due to this interaction, their shape changes, and the bioactive molecules stored in them are released [4]. In addition to functions in thrombosis and hemostasis, thrombocytes play an important role in wound healing, angiogenesis, remodelling, and the inflammatory process [5,6]. Various indices are calculated based on platelets, two of which are platelet distribution width and mean platelet volume (MPV). These parameters are biological markers of platelet activation [6].

A monocyte is an immune system cell with phagocytic ability secreted from the bone marrow. It can pass from the blood to the tissues, and is then known as macrophage in the tissue. Antibody-dependent cellular cytotoxicity in the body also plays an important role. Neutrophils, a crucial immune system element, are released from the bone marrow and are present in the blood and lymphatic system. Neutrophils are one of the first cells to reach an area of inflammation and in case of low expression, there is a susceptibility to infection. The amount of neutrophils increases in injuries, surgery, smoking, excessive stress, and bacterial infections [7]. Lymphocyte is one of the immune system cells manufactured in the bone marrow and is found in the blood and lymphatic system. The range in a healthy person is 1000-4800 mcl, and this increases in cases of inflammation [7].

In recent studies, some hematological parameters have been used to determine the prognosis of inflammatory diseases. These include the systemic immune-inflammatory index (SII) (platelet x neutrophil/lymphocyte), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), and neutrophil/lymphocyte ratio (NLR) [7]. Moreover, these rates can be easily calculated from a whole blood test, with no need for extra blood to be withdrawn from the patient. Previous studies in literature have shown that PLR, MLR, NLR, and SII are high in pregnancy complications (hyperemesis gravidarum, preeclampsia, gestational diabetes, intrahepatic cholestasis of pregnancy) and gynecological diseases (cancers, premature ovarian failure, endometriosis) [8]. Eskicioğlu et al. found low platelet distribution width and high monocyte values in tubal EP, and it was concluded that monocyte activation might have an effect on tubal motility and disrupt the microenvironment [9]. Some inflammatory cytokines are elevated in EP, both at the site of implantation and throughout the body's circulatory system [10]. There are studies reporting that leukocyte count and mean platelet volume (MPV) increase in EP [11]. According to Cekmez et al., MPV and NLR are accurate indicators of single-dose MTX therapeutic effectiveness [12]. In this study, beta-human chorionic gonadotropin (BhCG), and hematological indices (MLR, PLO, NLR, SII) calculated using routinely checked whole blood values (hemoglobin, hematocrit, leukocytes (WBC), platelets, neutrophils, monocytes) were compared between patients with EP who received MTX and those who underwent surgery. The aim of the study was to investigate the role of these parameters in determining the selection of EP treatment.

Materials and Methods

This retrospective, cross-sectional investigation wwas conducted in the Department of Obstetrics and Gynaecology of Konya City Hospital. Approval for the study was granted by the Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine (date: July 1, 2022; reference: 2022/3864).

The data of 152 patients diagnosed with EP between August 2020 and August 2022 were screened from the hospital information system. Exclusion criteria of acquired or congenital hematological disease, the use of any drug that may affect the hematological or anticoagulant system, and disease associated with systemic inflammation (systemic lupus erythematosus, diabetes mellitus, hypertension, vasculitis, rheumatoid arthritis, kidney and liver failure, etc.) were applied to 12 patients. Thus, a total of 140 patients were included in the research, of which 75 received MTX, and 65 underwent surgical treatment. A record was made of the demographic information and medical histories of the patients, such as age, blood type, pregnancy information (gravida, parity), number and type of surgery, pelvic infection, and EP history.

The whole blood values of the patients who were administered MTX treatment (Group I) and the patients who underwent surgical treatment (Group II) were obtained from the hospital information system. The BhCG values measured before treatment were recorded for both patient groups. For whole blood analysis, samples were taken into tubes with EDTA (ethylenediaminetetraacetate) and analyzed using a Premier Hb9210 device (Trinity Biotech, Ireland). From the whole blood values, hemoglobin (HB), hematocrit (HCT), leukocyte (WBC), platelet, neutrophil, monocytes and lymphocyte values and hematological indices (MLR, PLR, NLR, SII) obtained from these values were recorded. All these values were compared between the two groups of patients receiving medical or surgical treatment. The following formulas were used:

NLR = neutrophil count/lymphocyte count

PLR = platelet count/lymphocyte count

MLR= monocyte count/lymphocyte count

SII index = (platelet count × neutrophil count)/lymphocyte count

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn. 28.0 software. Descriptive statistics were stated as mean ± standard deviation (SD), median, minimum and maximum values for continuous data, and as number (n) and percentage (%) for categorical data. Conformity of the data to normal distribution was assessed using the Kolmogorov-Smirnov test. In the analyses of quantitative independent data, the Mann-Whitney U-test and the Independent Samples t-test were utilized. Dependent quantitative data were examined using the t-test, and qualitative independent data with the Chi-square test, and the Fischer test when the Chi-square test requirements were not met. A value of $p<0.05$ was accepted as the level of statistical significance.

Results

No significant difference was determined between the groups with respect to age, gravida-parity number, and body mass index of the patients ($p>0.05$). The BhCG value was determined to be substantially higher in Group II than in Group I ($p<0.05$). There were no significant differences between the groups in the frequencies of smoking, intrauterine devices, previous operations, or pelvic inflammatory illness ($p>0.05$). Extrauterine mass, yolk sac, and fetal heartbeat positive rates in Group II were all significantly greater than in Group I ($p<0.05$) (**Table 1**).

The HB and HCT values were significantly lower in Group II than in Group I ($p<0.05$). The WBC value was significantly higher in Group II than in Group I ($p<0.05$). No discernible difference was determined between the groups in respect of MPV values ($p>0.05$) (**Table 2**).

The neutrophil value in Group II was significantly higher than in Group I ($p<0.05$). Platelet and monocyte values were not significantly different between the groups ($p>0.05$). The lymphocyte value in Group II was significantly lower than in Group I ($p<0.05$). The NLR value in Group II was significantly lower than in Group I ($p<0.05$). The PLR value did not differ significantly between the groups ($p>0.05$). The MLR value in Group II was significantly lower than in Group I ($p<0.05$). The SII value in Group II was significantly higher than in Group I ($p<0.05$) (**Table 3**).

Table 1.

		MTX (n=75)			Surgery (n=65)			P	
		Mean ± sd/n-%		Median	Mean ± sd/n-%		Median		
Age (years)		31.6 ± 6.2		30.0	30.2 ± 6.1		31.0	0.196	t
Body mass index		25.8 ± 3.7		25.1	25.1 ± 3.3		24.4	0.142	m
Gravida		2.97 ± 1.55		3.00	3.46 ± 2.34		3.00	0.163	m
Parity		1.43 ± 1.38		1.00	1.78 ± 1.23		2.00	0.054	m
BhCG		2256.1 ± 3690.2		1166.0	9752.5 ± 15217.7		3025.0	***0.000***	m
Smoking	No	69	92.0%		61	93.8%		0.672	X^2
	Yes	6	8.0%		4	6.2%			
previous operation	No	45	60.0%		40	61.5%		0.853	X^2
	Yes	30	40.0%		25	38.5%			
pelvic inflammatory disease	No	66	88.0%		56	86.2%		0.745	X^2
	Yes	9	12.0%		9	13.8%			
Intrauterine device	No	69	92.0%		58	89.2%		0.573	X^2
	Yes	6	8.0%		7	10.8%			
Extrauterine mass	No	46	61.3%		4	6.2%		***0.000***	X^2
	Yes	29	38.7%		61	93.8%			
Yolk Sac	No	67	89.3%		35	53.8%		***0.000***	X^2
	Yes	8	10.7%		30	46.2%			
Fetal heartbeat	No	75	100.0%		52	80.0%		***0.000***	X^2
	Yes	0	0.0%		13	20.0%			

[t]Independent Ssamples t-test; [m]Mann-Whitney U-u test; X^2 Chi-square test (Fischer test)

Table 2.

	MTX (n=75)		Surgery (n=65)		P	
	Mean ± sd	Median	Mean ± sd	Median		
HB	12.1 ± 1.8	12.3	11.4 ± 1.8	11.7	***0.016***	m
HCT	38.0 ± 3.7	38.4	34.3 ± 5.3	35.1	***0.000***	m
WBC	8.3 ± 2.1	8.1	10.8 ± 4.0	10.5	***0.000***	m
MPV	10.47 ± 0.72	10.50	10.49 ± 0.97	10.40	0.763	m

[m]Mann-Whitney U-test; [w]Wilcoxon test; HB: Hemoglobin; HCT: Hematocrit; WBC: White Blood Cell; MPV: Mean Platelet Volume

Table 3.

	MTX (n=75)		Surgery (n=65)		p	
	Mean ± sd	Median	Mean ± sd	Median		
Neutrophil	5.10 ± 1.94	4.77	8.01 ± 4.47	6.84	***0.000***	m
Platelet	274.3 ± 55.4	265.0	272.5 ± 73.5	269.0	0.918	m
Monocytes	0.65 ± 0.62	0.55	0.61 ± 0.22	0.59	0.520	m
Lymphocyte	2.48 ± 0.76	2.46	2.17 ± 0.94	1.89	***0.026***	m
NLR	2.39 ± 2.09	1.87	4.98 ± 4.62	2.89	***0.000***	m
PLR	121.4 ± 46.3	107.7	151.3 ± 81.7	129.6	0.068	m
MLR	0.27 ± 0.25	0.24	0.32 ± 0.15	0.28	***0.002***	m
SII	640.4 ± 466.3	487.9	1373.6 ± 1373.4	859.6	***0.000***	m

[m]Mann-whitney U-test; [w]Wilcoxon test; NLR: Neutrophil/Lymphocyte Ratio; PLR: Platelet/Lymphocyte Ratio; MLR: Monocyte/Lymphocyte Ratio, SII: Systemic Immune-inflammation Index

Discussion

The rates of EP have increased as a result of the widespread use of assisted reproductive techniques and now have an important place among the causes of first trimester maternal death. Delayed diagnosis of ectopic pregnancies may cause adverse effects on fertility and maternal mortality [13]. In this study, comparisons were made of ectopic pregnancies between patient groups treated with methotrexate or surgery in terms of hematological inflammatory indices. This study is the first to have examined the use of SII in determining EP treatment preference.

MTX treatment is not appropriate in cases such as ruptured ectopic pregnancy, hemodynamically unstable patients, those who are unable to participate in follow-up, when embryonic cardiac activity is detected on transvaginal ultrasonography, a high initial hCG concentration, or ectopic pregnancy >4 cm in size on transvaginal ultrasonography imaging [14]. Previous studies have reported that the efficacy of MTX treatment is negatively impacted by a high BhCG value and the discovery of an extrauterine mass >30 mm during ultrasonography [15-17]. However, there are no biochemical markers that can help in determining the treatment choice or which will predict the success of the treatment. The results of the current study showed that the BhCG mean value and extrauterine mass detection rates were higher in the surgical group than in the MTX group.

Aktun et al. reported no difference in terms of HB, HCT and MPV values in ruptured ectopic pregnancies who underwent surgery compared to non-ruptured ectopic pregnancies [18]. In the current study, no significant difference was found between the groups in terms of changes in HB, HCT or MPV ($p>0.05$). It has been previously shown that monocyte activation may disrupt the microenvironment in ectopic pregnancies and thereby affect tubal motility [9]. Monocyte levels were found to be higher in the surgical group in the current study.

In another study that compared the MPV and WBC values of patients with unruptured tubal ectopic pregnancy and ruptured tubal ectopic pregnancy with healthy pregnancies, MPV was found to be high in ectopic pregnancies, and no difference was determined in the MPV values when ruptured and non-ruptured ectopic pregnancies were compared [11]. In the current study, there was no discernible difference between the groups in respect of the MPV value.

In a study by Doğru et al., ruptured ectopic pregnancies were compared with non-ruptured pregnancies. The results showed no difference between the groups in respect of PLR, while NLR was considerably higher in the ruptured group [19]. Ata et al. examined NLR and PLR in early pregnancy loss, and reported significantly higher values than in healthy pregnancies [8]. In another study, the change in NLR values on the 1st, 4th and 7th days of ectopic pregnancies treated with MTX was examined and it was found that NLR was sufficient to show the success of a single dose of MTX treatment. In the same study, PLR was not found to be significant in evaluating the success of MTX treatment [20]. The current study results showed no discernible difference between the surgical and MTX groups in respect of the change in PLR ($p>0.05$), while the NLR value was found to be statistically significantly lower in the surgical group ($p<0.05$). The SII value was significantly higher in the surgical treatment group than in the methotrexate group ($p<0.05$).

Although this study has emphasized the importance of evaluating new parameters to predict EP, there were some limitations to the study. Most patients undergoing surgical treatment are hemodynamically unstable and have hemoperitoneum as a result of rupture. Although inflammation markers are more likely to be high in these patients, hematological markers may be a guide in suspected cases. In addition, some confounding factors such as smoking, diet and body mass index can affect inflammation rates. Although there was no significant difference between the two groups in terms of these values in the current study, the effect on inflammatory markers could not be fully revealed. Nevertheless, the results of this study demonstrate that the NLR, PLR,MLR and SII values calculated from routinely checked complete blood count parameters, which do not require an invasive procedure, may be potential predictors of EP. Therefore ,this retrospective study can be considered of value.

Conclusions

The NLR, PLR, MLR, and SII can be easily calculated on hemogram analysis. It was concluded that these measures can be useful in deciding on the best course of treatment because NLR, MLR, and SII vary significantly between the groups. This study is the first to have shown that the SII can be used to determine treatment options for EP.

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