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Retrospective Evaluation of the Relationship Between Serum Inflammatory Markers and the Efficacy of Methotrexate in the Treatment of Ectopic Pregnancy

Serum Enflamasyon Belirteçleri ile Ektopik Gebelik Tedavisinde Kullanılan Metotreksat'ın Etkinlik İlişkisinin Retrospektif Olarak Değerlendirilmesi

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ABSTRACT

Objective: Inflammatory processes play a significant role in the pathogenesis of ectopic pregnancy. Therefore, certain serum inflammatory markers are considered to have potential value in predicting the treatment outcome. The objective of this study is to investigate the relationship between methotrexate (MTX) efficacy in the management of ectopic pregnancy and serum inflammatory markers.

Methods: The study was conducted retrospectively at Dokuz Eylül University Hospital. Women aged 18 years or older who were diagnosed with an ectopic pregnancy and underwent treatment between 2015 and 2025 were included. The study population was initially stratified into two groups according to the success or failure of MTX treatment. Patients with successful treatment were further subdivided into single-dose and double-dose MTX cohorts. The groups were compared with respect to characteristic features and ultrasonographic, laboratory, and surgical findings.

Results: No significant differences were found in systemic inflammation markers between the groups (p=0.96, p=0.58, p=0.47, p=0.80). When groups with successful and unsuccessful MTX treatment were compared with respect to baseline, fourth-day, and seventh-day β-hCG levels and changes between these measurements, a significant difference was found (p<0.001). β-hCG was an effective predictor of treatment success (p=0.001, p=0.001, p=0.006).

Conclusion: No significant correlation was found between serum inflammatory markers and the success of MTX treatment. β HCG levels and their rates of change are thought to be more powerful predictors of MTX treatment success.

Keywords: Ectopic pregnancy, serum inflammatory markers, methotrexate

ÖZ

Amaç: Ektopik gebelik patogenezinde enflamatuar süreçlerin önemli bir etkisi bulunmaktadır. Bu nedenle, bazı serum enflamasyon belirteçlerinin tedavi sürecinin öngörüsünde etkin olabileceği düşünülmektedir. Amacımız, ektopik gebelik tedavisinde kullanılan metotreksatın etkinliği ile serum enflamasyon belirteçlerinin ilişkisini araştırmaktır.

Yöntem: Çalışma, Dokuz Eylül Üniversitesi Hastanesi' nde retrospektif olarak gerçekleştirilmiştir. 2015-2025 yılları arasında, ektopik gebelik tanısı alarak tedavi edilen 18 yaş ve üzeri kadın olgular çalışmaya dahil edilmiştir. Olgular, öncelikle metotreksat tedavisinin başarılı olup olmamasına göre iki gruba ayrılmıştır. Metotreksat tedavisi başarılı olan olgular kendi içerisinde tek doz ve çift doz tedavi uygulanan olgular olarak ayrıca iki gruba ayrılmıştır. Gruplar, karakteristik özellikleri, ultrason, laboratuvar ve cerrahi bulguları açısından karşılaştırılmıştır.

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Bulgular: Çalışmamızın sonucunda, metotreksat tedavisinin başarılı olduğu grupla başarısız olduğu grup arasında, sistemik enflamasyon belirteçleri açısından anlamlı fark saptanmamıştır (p=0,96, p=0,58, p=0,47, p=0,80). Metotreksat tedavisinin başarılı ve başarısız olduğu gruplar, başlangıç, 4. ve 7. gün β HCG düzeyleri ve aralarındaki değişim açısından karşılaştırıldığında anlamlı fark saptanmıştır (p<0,001). β HCG'' nin tedavi başarısını öngörmede etkin bir belirteç olduğu saptanmıştır (p=0,001, p=0,001, p=0,006).

Sonuç: Sonuç olarak, serum enflamasyon belirteçleriyle metotreksat tedavisinin başarısı arasında anlamlı bir ilişki saptanmamıştır. β HCG düzeyi ve β HCG değişim oranlarının metotreksat tedavisinin başarısını öngörmede daha güçlü bir belirteç olduğu düşünülmektedir.

Anahtar Kelimeler: Ektopik gebelik, serum enflamasyon belirteçleri, metotreksat

INTRODUCTION

Ectopic pregnancies account for approximately 1% of all pregnancies and for about 4.7% of patients who present to the emergency department in early pregnancy.[1,2] Despite declining mortality rates from ectopic pregnancy owing to advances in diagnosis and surgical interventions, the financial burden of numerous diagnostic and follow-up procedures remains substantial, and the psychological impact on patients is considerable.[3]

In ectopic pregnancies, implantation most frequently occurs in the ampullary portion of the fallopian tube. Recognized risk factors include a previous ectopic pregnancy, tubal injury resulting from infection or surgical procedures, smoking, and use of assisted reproductive techniques.[4] Certain serum inflammatory mediators and cytokines are implicated in the pathogenesis of ectopic pregnancy by contributing to impaired embryo transport to the uterus and to premature implantation.[5] Given that ectopic pregnancy is a prominent cause of maternal mortality during the first trimester, prompt diagnosis and appropriate management are essential.[6]

There is no single definitive treatment for ectopic pregnancy. Management varies depending on the site of implantation and the clinical status of the patient. Treatment options include both pharmacological and surgical approaches. In addition, given the possibility of spontaneous resorption in a considerable proportion of cases, expectant management with serial β-hCG monitoring may also be applied. As a pharmacological option, single-dose or multidose methotrexate (MTX) regimens are used.[7] The most commonly employed protocol involves monitoring serum β-hCG levels on days 4 and 7 after MTX administration. If β-hCG decreases by more than 15%, weekly β-hCG monitoring is continued, whereas a decrease of less than 15% warrants a second MTX dose.[8] Reports indicate that approximately 20% of patients require an additional dose of MTX.[6,9]

With increasing evidence demonstrating the important role of inflammatory processes in the pathogenesis of ectopic pregnancy, several studies have suggested that certain serum inflammatory markers may also serve as predictors of treatment outcomes.[5,10-13] While some studies have reported that an increased neutrophil-to-lymphocyte ratio (NLR) is associated with a higher risk of ectopic pregnancy rupture and with reduced MTX treatment success, other studies have found no significant association.[11,12,14] This inconsistency in the literature prompted us to investigate whether systemic inflammatory markers could reliably predict MTX treatment outcomes in patients with ectopic pregnancy. Our aim, in light of the current literature, is to evaluate the predictive value of serum inflammatory markers for the effectiveness of MTX treatment, a pharmacological treatment option for ectopic pregnancy, and to protect these patients from the risks of prolonged hospitalization, MTX side effects, and delayed surgical intervention.

METHODS

This research was conducted retrospectively in the Department of Obstetrics and Gynecology. This study was approved by the Dokuz Eylül University Non-interventional Research Ethics Committee (decision number: 2025/14-08, date: 30.04.2025). The research was performed following the ethical guidelines outlined in the 2008 Declaration of Helsinki. Women aged 18 years and older who were admitted to our gynecology inpatient clinic or outpatient department between January 2015 and April 2025 and who were diagnosed with ectopic pregnancy and subsequently treated were included in the study. Women with systemic inflammatory diseases or concomitant malignancies were excluded. Informed consent was collected from every patient before treatment initiation. Data retrieved retrospectively from medical records included: body surface area (BSA), age, body mass index (BMI), gravida, parity, ultrasonographic (USG) findings at admission (presence of gestational sac, gestational sac diameter, and location of ectopic pregnancy), history of pelvic surgery, history of ectopic pregnancy, history of assisted reproductive treatment, gestational age (weeks), pre-treatment and post-MTX β-hCG levels, pre-treatment complete blood count parameters [hemoglobin (Hb), hematocrit, platelet (Plt) count, white blood cell (WBC) count, red cell distribution width (RDW), mean platelet volume (MPV), NLR, monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), pan-immun inflamation value (PIV), systemic immune-inflammation index (SII), systemic immune-inflammation response index (SIRI)] and type of surgery performed (salpingectomy, salpingostomy, diagnostic laparoscopy).

The hematological parameters included in the analysis were collected in a standardized manner as part of routine clinical care and were consistently measured at the time of hospital admission and prior to MTX administration for all patients. Serum β-hCG samples were collected on the day of MTX initiation and on days 4 and 7 thereafter. In patients requiring additional MTX doses, serum β-hCG measurements were repeated. USG findings were recorded during the initial gynecological examination on admission. BSA was calculated as: [height (cm) × weight (kg)] / 3600)$^{1/2}$. BMI was calculated as weight (kg) / height (m)^2. NLR was calculated as neutrophil count (×10³/μL) / lymphocyte count (×10³/μL). PLR was calculated as the Plt count (×10³/μL) divided by the lymphocyte count (×10³/μL). MLR was calculated as the ratio of monocyte count (×10³/μL) to lymphocyte count (×10³/μL). SII was calculated as (Plt count × neutrophil count) / lymphocyte count. SIRI was calculated as [neutrophil count (×10³/μL) x monocyte count (×10³/μL)] / lymphocyte count (×10³/μL) and PIV was calculated as [neutrophil count (×10³/μL) x monocyte count (×10³/μL) x Plt count (×10³/μL)] / lymphocyte count (×10³/μL).

Initially, patients were categorized into two groups based on the outcome of MTX therapy. Group I: patients with successful MTX treatment, and Group II: patients with unsuccessful MTX treatment. Patients in Group I were further subdivided into those who received a single dose of MTX and those who required two doses of MTX; these subgroups were then compared. Patients who underwent surgery during follow-up due to hemodynamic instability or rupture of the ectopic pregnancy, and those who required surgery after two MTX doses because of an insufficient decline in β-hCG levels, were classified as treatment failures. Patients with ectopic pregnancies who demonstrated positive fetal cardiac activity at initial presentation and were scheduled for primary surgery; patients who required emergency surgery due to rupture at admission; patients with extra-tubal or extra-ovarian ectopic pregnancies; and patients with missing data were excluded from the study. The groups were compared with respect to characteristic features, clinical, surgical, and laboratory findings. The study flowchart is summarized in Figure 1.

Statistical Analysis

SPSS v. 26 was used to perform statistical analyses. Comparisons of clinical and demographic characteristics between groups were performed using an independent t-test for parametric distributions and a Mann-Whitney U test for non-parametric distributions. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess normality. Numeric variables were expressed as mean and standard deviation for normally distributed data, and as median (minimum-maximum) for skewed distributions. Categorical data were analyzed using chi-square test or the two-sided Fisher's exact test, as appropriate. The odds ratio was calculated where applicable. To determine the

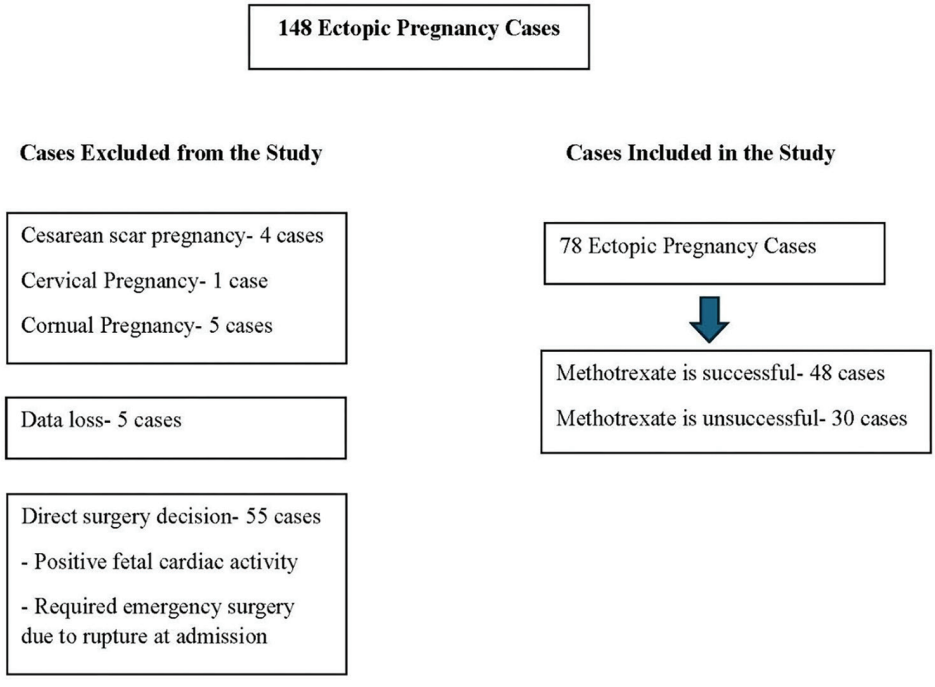

Figure 1. Study flow chart

predictive values of significant variables, logistic regression analyses were performed. In the statistical analysis, the mean values for normally distributed data and the median values for non-normally distributed data are presented in the table. Data with normal and non-normal distributions are indicated in footnotes below the table. p≤0.05 was considered significant.

RESULTS

When the groups with successful and unsuccessful MTX treatment were compared in terms of characteristics, no significant differences were observed in age (31.4 vs. 31.47 years, p=0.95) or in other characteristics. Evaluation of laboratory findings revealed no significant differences among groups in NLR, PLR, MLR, SII, PIV, or SIRI values (p=0.96, p=0.58, p=0.47, p=0.80, p=0.99, p=0.80) (Table 1).

Among patients with successful MTX treatment, a subgroup analysis comparing single-dose and double-dose MTX revealed no statistically significant differences in characteristics. Laboratory evaluation showed that only Hb levels were significantly higher in patients who received a single MTX dose than in those who received two doses (12.45 vs. 11.55 g/dL; p=0.02). No significant differences were found among the groups with respect to NLR, PLR, MLR, SII, PIV, or SIRI (NLR: p=0.24; PLR: p=0.95; MLR: p=0.93; SII: p=0.40; PIV: p=0.717; SIRI: p=0.785) (Table 2).

When patients with unsuccessful versus successful MTX treatment were compared regarding changes in β-hCG levels following MTX administration, the successful treatment group showed a significant decline in β-hCG on days 4 and 7 relative to baseline, whereas the unsuccessful group showed minimal change or an increase. These differences were significant (p<0.001 for all comparisons). Furthermore, a comparison of mean β-hCG levels on the day of MTX initiation, day 4, and day 7 revealed that levels were significantly lower in the MTX-successful group (1469 vs. 3254.5, p<0.001; 1052.4 vs. 5711.5, p<0.001; 619.26 vs. 4062, p<0.001) (Table 3).

A total of 59 patients received a single dose of MTX. Treatment was successful in 34 patients, whereas 25 required surgical intervention due to treatment failure. Evaluation of these patients to assess the predictive role of β-hCG levels for treatment success demonstrated that greater reductions in β-hCG were associated with an increased likelihood of successful treatment; this relationship was significant (p=0.001, p=0.001, p=0.006) (Table 4).

Nineteen patients received a double-dose MTX regimen. Treatment was successful in 14 patients, whereas 5 experienced treatment failure and required surgical intervention. Evaluation of the predictive role of β-hCG levels on the day of the first MTX dose, on day 7, and of the change between these values for the success of the second MTX dose revealed that neither baseline nor day-7 β-hCG levels were predictive of second-dose treatment success. The change in β-hCG levels between baseline and day 7 appeared to be associated with second-dose treatment outcomes. However, these relationships were not statistically significant (p=0.089, p=0.066, and p=0.09) (Table 5).

Table 1. Comparison of groups in terms of characteristic features and laboratory findings

	Group I (n=48)	Group II (n=30)	p
Age	31.4±4.95	31.47±4.33	0.95
BMI (kg/m²)*	23.30 (18-35.20)	22.65 (18.50-33.20)	0.17
BSA (m²)	1.68±0.16	1.65±0.11	0.37
Gravida*	2 (1-6)	2 (1-5)	0.52
Parity*	0.50 (0-3)	1 (0-3)	0.55
Ultrasound findings **Presence of gestational sac** **Gestational sac diameter** **Localization** **Right** **Left**	 22 19.64±5.74 18 30	 17 18.3±6.61 13 17	 0.485 0.35 0.641
History of previous ectopic pregnancy	4	2	1
History of previous pelvic surgery	27	10	0.064
Assisted reproductive therapy **Yes** **No**	 3 45	 2 28	1
Gestational age (weeks)	6.21±1.43	6.50±1.24	0.36
Table 1. Continued			

	Group I (n=48)	Group II (n=30)	p
Serum parameters			
Hb	12.0±1.25	12.09±1.12	0.75
Hct	35.98±3.35	36.28±3.31	0.70
WBC	8.40±2.28	8.45±2.96	0.94
Plt	268.05±68.95	267.67±79.15	0.98
MPV	8.72±1	8.52±1.02	0.41
RDW	14.25±1.61	13.80±1.02	0.18
NLR*	2.79 (1.05-12)	2.85 (0.72-15.11)	0.96
PLR*	131.77 (73.64-590)	137.02 (42.63-300)	0.58
MLR	0.3±0.13	0.28±0.09	0.47
SII*	649.32 (156-3540)	713.17 (93.79-3264)	0.80
MCV	83.57±6.71	86.12±5.08	0.08
MCH	27.88±2.65	28.59±1.97	0.21
MCHC	33.31±0.93	33.24±0.60	0.73
RBC	4.31±0.34	4.22±0.42	0.29
Neutrophil	5.56±1.83	5.56±2.42	1.0
Eosinophil*	0.1 (0-0.50)	0.1 (0-1)	0.14
Monocyte*	0.50 (0.10-1.5)	0.50 (0.30-1.70)	0.36
Lymphocyte	2.10±0.73	2.16±1.39	0.81
PCT	0.23±0.05	0.22±0.06	0.56
PIV*	376.2 (15.6-1705.6)	380.1 (28.1-979.2)	0.99
SIRI*	1.4 (0.31-5.59)	1.5 (0.35-4.5)	0.80

BMI: Body mass index (kg/cm^2)

BSA: Body surface area (m^2)

*: Data with non-normal distribution

MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RBC: Red blood cell, PCT: Plateletcrit, Hb: Hemoglobin, Plt: Platelet, MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune-inflammation index, PIV: Pan-immun inflamation value, SIRI: Systemic immune-inflammation response index

Table 2. Comparison of single- and double-dose methotrexate regimens in the successful treatment group in terms of characteristics features and laboratory findings

	Single-dose MTX (n=34)	Double-dose MTX (n=14)	p
Age	32±5.20	29.93±4.08	0.19
BMI (kg/m^2)	25.18±4.87	24.08±3.6	0.45
BSA (m^2)	1.68±0.17	1.68±0.12	0.91
Gravida*	2 (1-6)	2 (1-4)	0.14
Parity*	0.50 (0-3)	0.50 (0-3)	0.9
Ultrasound findings **Presence of gestational sac** **Gestational sac diameter** **Localization** **Right** **Left**	 14 18.96±5.26 10 24	 8 21.29±6.68 8 6	 0.35 0.20 0.103
History of previous ectopic pregnancy	3	1	1
History of previous pelvic surgery	20	7	0.75
Assisted reproductive therapy **Yes** **No**	 2 32	 1 13	1

Table 2. Continued			
	Single-dose MTX (n=34)	**Double-dose MTX (n=14)**	**p**
Gestational age (weeks)	6.41±1.26	5.71±1.73	0.13
Serum parameters			
Hb*	12.45 (7-13.9)	11.55 (10.1-13.3)	0.02**
Hct	36.55±3.46	34.58±2.67	0.063
WBC	8.52±2.42	8.12±1.96	0.59
Plt	269.76±78.48	263.86±39.07	0.73
MPV	8.67±1.15	8.84±0.53	0.60
RDW	14.12±1.62	14.55±1.63	0.41
NLR*	2.90 (1.05-12)	2.37 (1.23-7.36)	0.24
PLR*	130.19 (73.64-590)	133.55 (79.67-278.90)	0.95
MLR	0.3±0.15	0.3±0.10	0.93
SII*	660.92 (156-3540)	554.54 (294.77-1957)	0.40
MCV	84.3±6.16	81.78±7.86	0.24
MCH	28.14±2.41	27.21±3.16	0.27
MCHC	33.34±0.94	33.22±0.94	0.69
RBC	4.34±0.28	4.26±0.46	0.50
Neutrophil	5.65±1.75	5.32±2.06	0.57
Eosinophil*	0.1 (0-0.50)	0.1 (0-0.20)	0.43
Monocyte*	0.50 (0.10-1.50)	0.6 (0.4-0.8)	0.51
Lymphocyte	2.11±0.80	2.08±0.53	0.88
PCT*	0.23 (0.04-0.35)	0.22 (0.18-0.30)	0.89
PIV*	392.6 (15.6-1705.6)	311 (160-978.5)	0.717
SIRI*	1.48 (0.31-5.6)	1.35 (0.55-3.68)	0.785

MTX: Methotrexate

BMI: Body mass index (kg/cm^2)

BSA:Body surface area (m^2)

*: Data with non-normal distribution

**: p<0.05

MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RBC: Red blood cell, PCT: Plateletcrit, Hb: Hemoglobin, Plt: Platelet, MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune-inflammation index, PIV: Pan-immun inflamation value, SIRI: Systemic immune-inflammation response index

Table 3. Comparison of changes in β hCG levels following the first dose of methotrexate between the groups			
	MTX successful group (n=48)	**MTX unsuccessful group (n=30)**	**p**
β hCG levels on the MTX day	1469 (36.71-17.641)	3254.50 (478.77-8060)	<0.001*
β hCG levels on 4th day after MTX	1052.40 (27.91-13586)	5711.5 (527-14819)	<0.001*
β hCG levels on 7th day after MTX	619.26 (3.58-7875)	4062 (519-14454)	<0.001*
β hCG change between MTX day and 4th day	-12.36% (-85.22-66%)	45.01% (-6.1-501.51%)	<0.001*
β hCG change between MTX day and 7th Day	-54.5% (-97.29-59.85%)	42% (-14.68-298.33%)	<0.001*
β hCG change between 4th day and 7th day	-38.19% (-88.93-38.27%)	0.04% (-31.42-164.85%)	<0.001*

MTX: Methotrexate

*: p<0.05

Table 4. Predictive role of β hCG levels in treatment success among cases receiving single-dose methotrexate			
	Odds ratio	**95% confidence interval**	**p**
β hCG change between MTX day and 4th day	0.87	0.80-0.95	0.001*
β hCG change between MTX day and 7th Day	0.96	0.94-0.98	0.001*
β hCG change between 4th day and 7th day	0.85	0.76-0.96	0.006*
MTX: Methotrexate *: p<0.05			

Table 5. Predictive value of β hCG changes between methotrexate day and day 7 for second-dose methotrexate treatment success			
	Odds ratio	**95% confidence interval**	**p**
MTX day β hCG levels	1	1-1.001	0.089
β hCG level on the 7th day after MTX	1.001	1-1.001	0.066
β hCG change between MTX day and 7th Day	0.964	0.923-1.006	0.093
MTX: Methotrexate			

DISCUSSION

Ectopic pregnancy is one of the common causes of maternal morbidity during the first trimester. With the increasing use of assisted reproductive treatments and the rise in cesarean deliveries, it is considered a frequent cause of maternal mortality.[4,15] Delays in the diagnosis and treatment of ectopic pregnancy may result in damage to the fallopian tubes that is sufficient to adversely affect future fertility, as well as in hemorrhage and mortality associated with rupture.[16] MTX is a safe option for the treatment of ectopic pregnancy; however, in some cases, it may result in tubal rupture. Factors such as gestational age, size of the ectopic pregnancy, and pre-treatment β-hCG levels can influence the success of MTX therapy.[17-20] In current practice, β-hCG remains the only biomarker used in ectopic pregnancy, and baseline β-hCG levels are considered the best prognostic indicator of follow-up response and of the success of single-dose MTX treatment.[21]

In the recent study, the predictive value of serum inflammatory markers for the success of MTX treatment in ectopic pregnancy was evaluated; no significant relationship was found between these markers and treatment outcome. Dereli et al.[22] reported that when comparing ectopic pregnancy patients treated with MTX versus surgery, lower NLR and SII levels were observed in the group with successful MTX treatment. Furthermore, patients with prior abdominal surgery or repeated cesarean sections were found to have higher rates of MTX treatment failure, which have been attributed to intra-abdominal adhesions, increased scar tissue, and repeated transverse uterine incisions, all of which lead to compromised adnexal vascularization and reduced MTX delivery to the target tissue. However, in our study, we did not find a relationship between prior abdominal surgery and MTX treatment success (p=0.064). Therefore, our findings are not consistent with the existing literature in this regard. This discrepancy may be attributable to the relatively small sample size of our study, which may not have provided sufficient statistical power to detect this association. In another study evaluating patients treated with MTX for ectopic pregnancy, the decline in NLR from treatment initiation to day 4 was assessed; patients with a decrease of more than 23% in NLR had a greater likelihood of successful MTX treatment.[12] Another study reported higher baseline NLR, MPV, and RDW values in the MTX-treated group, with the underlying mechanism attributed to increased inflammation.[13] A study investigating the association between NLR and PLR and ectopic pregnancy rupture found that ruptured cases exhibited higher NLR and PLR, and that NLR and PLR positively correlated with β-hCG levels and tubal lumen diameter.[14] In our study, no significant association was found between USG findings and treatment modality. Another study indicated that elevated levels of NLR and PDW could serve as markers for tubal rupture, and the association between high NLR and MTX treatment failure was hypothesized to result from neutrophil-mediated suppression of cytotoxic T cells via cytokines and chemokines during inflammatory processes. Accordingly, increased NLR is an indirect measure of the host immune response, and in that study, NLR was higher in the ruptured group.[23] Reis et al.[24] also reported higher WBC levels in the non-ruptured ectopic pregnancy group, suggesting that WBC may play a role in suppressing the maternal immune response against the fetus and in limiting trophoblast invasion. In our study, however, no relationship was observed between MTX treatment success and WBC levels.

Several studies have reported that systemic inflammatory markers may be associated with embryo implantation and the course of ectopic pregnancies.[25-27] The rationale for considering inflammatory processes in these cases is that fetal growth within the fallopian tube can irritate the tube and surrounding structures, such as the peritoneum, leading to inflammation. This process may trigger the release of inflammatory cytokines, and assessing their levels could serve as a useful diagnostic tool for tubal ectopic pregnancy.[27] Supporting this notion, Rajendiran et al.[27] reported increased interleukin-6 levels and decreased interleukin-8 levels in patients with tubal ectopic pregnancy. NLR serves as a strong indicator of systemic immune inflammation and has been identified as an independent predictor of mortality in cardiovascular disease, and as a prognostic marker in patients with primary central nervous system lymphoma undergoing high-dose MTX-based therapy.[28-31] The mechanism linking NLR and MTX treatment is not fully understood, but is thought to be related to the immune response. An elevation in NLR serves as an indirect indicator of immune activity. Neutrophils, as components of the innate immune system, can suppress the maternal immune response toward the fetus and limit trophoblast invasion.[12,23,24,32]

In our study, to add to the existing literature, we evaluated PIV and SIRI -recently highlighted as promising markers for certain cancer types and chronic diseases- with respect to their potential impact on the prognosis of MTX treatment. Previous studies have suggested that PIV may serve as a non-invasive marker for prognosis and remission assessment in some malignancies.[33] Similarly, PIV and SIRI have been reported to be important inflammatory indicators in conditions such as preeclampsia, rheumatoid arthritis, and psoriasis.[34-36] Since these markers are derived from serum measurements and reflect chronic systemic inflammation, it was hypothesized that they might serve as effective predictors of prognosis in ectopic pregnancy. For this purpose, PIV and SIRI values were compared between patients with successful and unsuccessful MTX treatment outcomes. However, no significant associations were identified between MTX treatment success and either PIV or SIRI (p=0.99 and p=0.80, respectively).

Reviewing the literature, Soykan Sert and Bertizlioğlu,[11] similarly to our study, reported no significant relationship between systemic inflammatory markers and ectopic pregnancy treatment outcomes, highlighting β-hCG as a more reliable marker. Tubal ectopic pregnancy can lead to elevated serum inflammatory markers. Soykan Sert and Bertizlioğlu[11] suggested that in cases of ruptured ectopic pregnancy, higher levels of these markers may obscure the relationship with MTX treatment outcomes. MTX exerts an antimetabolic effect, inhibiting cell proliferation; its efficacy is greater at lower β-hCG levels. Soykan Sert and Bertizlioğlu[11] proposed that this could overshadow the association with serum inflammatory markers, emphasizing β-hCG as a stronger prognostic indicator. The findings of our study are consistent with the observations reported by Soykan Sert and Bertizlioğlu.[11]

In our study, evaluation of changes in β-hCG levels after the first MTX dose revealed a significantly greater decrease in the MTX-successful group than in the unsuccessful group. Furthermore, in patients treated with single-dose MTX, β-hCG was a strong predictor of treatment outcome. Consistent with our findings, previous studies have reported that changes in β-hCG levels on days 1 and 4 significantly influence the success of MTX therapy.[11,37,38] Another study demonstrated that both lower baseline β-hCG levels and the rate of decline during the first four days serve as predictors of treatment success.[39] In a study evaluating ruptured and resolved ectopic pregnancies after MTX treatment, cases that ruptured despite therapy were more frequently associated with vaginal spotting and smaller changes in β-hCG levels.[40] In addition to previous studies, our study specifically investigated the predictive role of baseline and day-7 β-hCG levels, as well as the change between these two values, for the success of second-dose MTX treatment. While baseline and day 7 β-hCG levels were not associated with second-dose treatment outcomes, the change in β-hCG levels between baseline and day 7 appeared to reduce the risk of treatment failure. However, this relationship was not statistically significant, which may be attributable to the small sample size. This small sample size (19 cases) represents a major limitation of our study, potentially restricting the ability to detect clinically meaningful differences. Therefore, studies with larger sample sizes may better clarify the nature of this association.

In our study, a comparison of baseline Hb levels between patients with successful and unsuccessful MTX treatment revealed no significant difference. However, within the successful MTX group, a comparison of single- vs. double-dose treatment showed that patients requiring a second MTX dose had significantly lower Hb levels than those treated with a single dose (p=0.02). Nonetheless, this finding does not have a clinical implications.

CONCLUSION

The literature presents conflicting evidence regarding the relationship between serum inflammatory markers and MTX treatment success in ectopic pregnancy. In our study, no significant relationship was found between serum inflammatory markers and MTX treatment outcomes. In our study, as an original contribution to the literature, chronic inflammation markers, including PIV and SIRI, were

evaluated. However, no significant association was found between these markers and MTX treatment outcomes. Based on current literature, β-hCG levels and the rate of β-hCG change are considered the most reliable indicators of MTX treatment success in ectopic pregnancy, a conclusion supported by our findings. As previously noted, one of the major limitations of our study is the relatively small sample size. Therefore, we believe that prospective randomized studies with larger cohorts are needed to better elucidate the relationship between these markers and treatment outcomes.

Ethics

Ethics Committee Approval: This study was approved by the Dokuz Eylül University Non-interventional Research Ethics Committee (decision number: 2025/14-08, date: 30.04.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.A., O.Y., A.M., E.A.K., E.Ç., Concept: S A.A., Design: A.A., Data Collection or Processing: A.A., O.Y., A.M., E.A.K., Analysis or Interpretation: A.A., O.Y., E.A.K., E.Ç., Literature Search: A.A., A.M., E.Ç., Writing: A.A., O.Y., E.Ç.

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