



## Tubal Ektopik Gebeliklerde Metotreksat Tedavi Başarısını Öngörmede Nötrofil-lenfosit Oranı ve Platelet-lenfosit Oranı

### Neutrophil-lymphocyte Ratio and Platelet-lymphocyte Ratio on the Prediction of Methotrexate Treatment Success in Tubal Ectopic Pregnancy

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#### ÖZET

**Giriş:** Ektopik gebelik tüm gebeliklerin %2'sini oluşturmaktadır, aynı zamanda vakaların %95'ten fazlası fallop tüplerinde lokalizedir. Bu çalışmada; tubal gebeliklerde metotreksat tedavi başarısını değerlendirmek, ve nötrofil-lenfosit oranı, trombosit-lenfosit oranı ve tubal ektopik gebelik rüptürü arasındaki ilişkiyi incelemek amaçlanmıştır.

**Gereç ve Yöntem:** Bu retrospektif çalışma, Gaziosmanpaşa Üniversitesi, Kadın Hastalıkları ve Doğum Anabilim Dalı'nda 2012 ve 2014 yılları arasında yapılmıştır. Veriler Statistical Package for Social Sciences (SPSS) yazılım versiyonu 20.0 (SPSS Inc., Chicago, IL) ile analiz edildi. Tüm karşılaştırmalarda çift taraflı p değeri < 0.05 olarak kabul edildi.

**Bulgular:** Nötrofil-lenfosit oranı rüptüre olup cerrahi tedavi geçirmiş hastalarda rüptüre olmayıp metotreksat tedavisi alan hastalara göre yüksek saptandı (p = 0.009). Beraberinde, nötrofil-lenfosit oranı metotreksat tedavisine yanıt veren hastalarda yanıt vermeyenlere göre yüksek bulundu (p = 0.027).

**Sonuç:** Ektopik gebelik kese çapı ve B-HCG değeri yanında, nötrofil-lenfosit oranı ve platelet-lenfosit oranı metotreksat tedavisinin başarısını öngörmede yararlı belirteçler olabilirler.

**Anahtar Kelimeler:** Gebelik, Ektopik, Metotreksat, Nötrofil, Lenfosit, Plateletler

#### ABSTRACT

**Objective:** A %2 of all pregnancies composed of ectopic pregnancy, further more than 95% of cases localized on the fallopian tubes. The aim of this study is to assess the success of methotrexate treatment on tubal pregnancy, and the relation between the neutrophil-lymphocyte ratio and thrombocyte-lymphocyte ratio, and tubal ectopic pregnancy rupture.

**Materials and Methods:** This retrospective study was conducted in Gaziosmanpaşa University, Department of Obstetrics and Gynecology between 2012 and 2014. Patients with a diagnosis of tubal ectopic pregnancy whose admitted to the Department of Obstetrics and Gynecology were enrolled in the study. The data was analyzed using the Statistical Package for Social Sciences (SPSS) software version 20 (SPSS Inc., Chicago, IL). A two-tailed p value <0.05 was regarded as statistically significant for all comparisons.

**Results:** The neurophil-lymphocyte ratio was significantly higher in ruptured surgical treated patients compared to unruptured-methotrexate treated patients (p = 0.009). Additionally, the neurophil-lymphocyte ratio was significantly higher in methotrexate responsive patients than in non-responsive ones (p = 0.027).

**Conclusion:** Beside B-HCG level and ectopic pregnancy sac diameter, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio may be useful tools to predict the success of the methotrexate therapy.

**Keywords:** Pregnancy, Ectopic, Methotrexate, Neutrophils, Lymphocytes, Blood Platelets

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## INTRODUCTION

The implantation of fertilized ovum to another place except uterine cavity is defined as ectopic pregnancy [1-3]. Currently, %2 of all pregnancies composed of ectopic pregnancy, further more than 95% of cases localized on the fallopian tubes. Despite advances in diagnosis and treatment, it has been an important cause of maternal death associated with pregnancy in the first trimester [4]. The main risk factors of ectopic pregnancy are tubal damage, previous ectopic pregnancies and adjuvant fertility technics [3]. The pathogenesis depends on changes occurred in micro environment of fallopian tubes leading early implantation of fertilized ovum and ciliary dysfunction [5]. Clinically, one-third of patients show no symptoms. In addition, a positive pregnancy test with syncope or hemorrhagic shock may be the findings of a ruptured ectopic pregnancy [6,7]. Medical treatment with methotrexate in unruptured cases is an effective and safe alternative method to surgery [8,9].

A current study have emphasized the role of platelets and platelet derived agents in thrombosis, angiogenesis, inflammation and immunity [10]. In ectopic pregnancy, inflammatory cytokine levels increase in both inflammation site and systemic circulation [5]. Similarly with the activation of signaling pathways, such leukocytes guided by cytokines, chemokines and integrins to the inflammatory site, the embryo is directed to the implantation field [11].

Furthermore, hemogram parameters including immune system items have an important role in the diagnosis of several disorders. Lymphocytes, leucocytes and thrombocytes, hold significant roles in controlling of inflammation [12-14]. Recently, the ratio of neutrophil to lymphocyte count and platelet to lymphocyte have been used as a biomarker of systemic inflammation, and evaluated in various malignancy studies [15-17].

The aim of this study is to assess the success of MTX treatment on tubal pregnancy, and the relation between the neutrophil-lymphocyte ratio and thrombocyte-lymphocyte ratio, and tubal ectopic pregnancy rupture.

## MATERIALS AND METHODS

This retrospective study was conducted in Gaziosmanpasa University, Department of Obstetrics and Gynecology between 2012 and 2014. Patients with a diagnosis of tubal ectopic pregnancy whose admitted to the Department of Obstetrics and Gynecology were enrolled in the study. The following parameters were the exclusion criteria: connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, chronic inflammatory diseases such as vasculitis, renal or hepatic failure, chronic hypertensive disease, diabetes mellitus, a previous history of myocardial infarction and thrombosis.

The condition of tubal ectopic pregnancy either ruptured or treated with methotrexate, maternal age,  $\beta$ -HCG level, ectopic pregnancy sac diameter, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio were obtained from the patient records. The hemogram parameters after admission were used to calculate the neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio. The success of methotrexate treatment was defined as the decrease in  $\beta$ -HCG level more than 15% between the 4<sup>th</sup> and 7<sup>th</sup> days. In addition, failure in treatment was described as the requirement of an additional methotrexate dose or an operation.

Qualitative data was presented as number and percentage, since qualitative data as mean and standard deviation. Mann Whitney U test was used to compare for all groups. The data was analyzed using the Statistical Package for Social Sciences (SPSS) software version 20 (SPSS Inc., Chicago, IL). A two-tailed p value <0.05 was regarded as statistically significant for all comparisons.

## RESULTS

A total of 39 patient records were included. The mean age was  $31,48 \pm 4,49$ . The median value of gravida was 3 (minimum = 1, maximum = 5), and parity was 1 (minimum = 1, maximum = 5). Since 16 patients were operated due to ruptured tubal ectopic pregnancy, a sum of 23 cases with unruptured tubal ectopic pregnancy

were treated with methotrexate. In nine cases the methotrexate treatment was successful, while in 14 cases was not.

The  $\beta$  HCG levels, the mean diameters of ectopic pregnancy sac, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio of ruptured and unruptured ectopic pregnancy cases were presented in Table 1. The neurophil-lymphocyte ratio was significantly higher in ruptured surgical treated patients compared to unruptured-methotrexate treated patients ( $p = 0.009$ ).

**Table 1.** Characteristics of ruptured and unruptured patients

	UR-MTP	R-STP	p
	Mean $\pm$ SD	Mean $\pm$ SD	
$\beta$ -HCG	1071,08 $\pm$ 763,56	3368,12 $\pm$ 3121,93	<b>0,003*</b>
Sac Diameter (cm)	2,06 $\pm$ 0,74	2,41 $\pm$ 1,10	0,373
PLR	125,28 $\pm$ 43,64	143,76 $\pm$ 90,31	> 0,05
NLR	2,79 $\pm$ 1,98	5,43 $\pm$ 3,40	<b>0,009*</b>

\* $p < 0.05$

PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; UR-MTP, unruptured-methotrexate treated patients; R-STP, ruptured surgical treated patients

The  $\beta$ -HCG levels, the mean diameters of ectopic pregnancy sac, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio of success and failed methotrexate treated ectopic pregnancy cases were presented in Table 2. The neurophil-lymphocyte ratio was significantly higher in methotrexate responsive patients than in non-responsive ones ( $p = 0.027$ ).

**Table 2.** Methotrexate treated patients.

	Responsive	Non-responsive	p
	Mean $\pm$ SD	Mean $\pm$ SD	
$\beta$ -HCG	1299,71 $\pm$ 824,15	715,44 $\pm$ 515,58	0,101
Sac Diameter (cm)	2,26 $\pm$ 0,80	1,76 $\pm$ 0,53	0,216
PLR	123,02 $\pm$ 49,82	128,80 $\pm$ 34,37	0,488
NLR	3,30 $\pm$ 2,35	2,00 $\pm$ 0,83	<b>0,027*</b>

\* $p < 0.05$

PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio.

## DISCUSSION

The present study revealed that the NLR was higher in ruptured tubal ectopic pregnancy than methotrexate treated patients. In addition, the NLR was higher in failure of methotrexate treated patients compared to successfully treated with methotrexate.

Ectopic pregnancy is a combination of tubal micro environmental changes including impaired tubal transportation of fertilized ovum and early implantation to the fallopian tube [5]. Inflammation in fallopian tube due to infection or smoking leads to ectopic pregnancy by effecting the smooth muscle activity and ciliary movement [8,9].

Hemogram parameters including immune system elements has a significant role on the assessment and diagnosis of a variety of diseases [12-14]. Recently, neutrophil-lymphocyte ratio shows a remarkable factor as an inflammatory marker, which has been currently used as a prognostic tool for cardiovascular diseases, cancer and several inflammatory disorders [18-21]. Neutrophils are the most prominent leukocytes those leading to inflammation and tissue injury in patients with ulcerative colitis [22]. In histopathological evaluation, it is shown that neutrophil accumulation and abcess formation are ocured in the intestinal crypts at the apical epithelial surface in patients with ulcerative colitis [23]. In contrast, the lymphocyte functions shows abnormalities on both peripheral blood and mucosal level in patients with inflammatory bowel disease. According to these outcomes, Torun et al. reported that NLR were significantly rises in active ulcerative colitis [24].

In relation, Celikbilek et al. demonstrated that NLR has a close relationship with active ulcerative colitis [25]. The present study revealed that the NLR is increased during an impairment in clinical condition or responsiveness to medical treatment. This result suggested that NLR can predict the rupture risk of ectopic pregnancy and responsiveness to medical therapy.

Furthermore, the clinical use of methotrexate treatment is first established by Tanaka et al. in 1980 [26]. A study conducted by Menon et al. on

503 patients showed that B-HCG level over 5000 mIU/ml may associated with a lower success rate of treatment [27]. A recent study by Sagiv et al. on 238 patients treated with methotrexate demonstrated that a B-HCG level of > 2000 mIU/ml had a 4.5 fold failure risk in treatment with treatment [28]. In the present study, the B-HCG level was higher in patients with ruptured tubal ectopic pregnancy compared to metotrexate treated cases.

Moreover, there has been controversy on the adequate sac diameter of ectopic pregnancy for medical treatment. Many investigators reported a higher success in a sac diameter up to 3,5 cm, where the others indicated larger than 3,5 cm [29-31].

In addition, Feras et al. revealed that no association was existed between response to methotrexate treatment and ectopic pregnancy sac diameter [32]. Similar with the latter study, the current study showed no relation between response to medical treatment and ectopic pregnancy sac diameter.

Platelets are the natural sources of tissue regeneration, angiogenesis and growth factors those are crucial in inflammation [33]. Whether ruptured or not, various platelet indexes such as MPV and PDW can be altered associated with

the inflammation and tubal micro environmental changes [34]. In this context, Artunc et al. reported that MPV values were lower in tubal pregnancy than in intrauterine pregnancies as well as in ruptured tubal pregnancies [35]. The PLR values were similar between methotrexate treated patients and ruptured ectopic pregnancy patients in the current study. Further, the PLR values showed no difference between the methotrexate responsive and non-responsive patients.

In conclusion, late diagnosis of ectopic pregnancy resulting of tubal inflammation is a life threatening condition. Medical treatment can be an alternative therapy to surgery. The present study revealed that beside B-HCG level and ectopic pregnancy sac diameter, NLR and PLR may be useful tools to predict the success of the methotrexate therapy. However, further studies including larger populations are required to elucidate the effectiveness.

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#### COMPETING INTERESTS

None declared.

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