



## ASSESSMENT OF METHOTREXATE EFFICACY IN THE TREATMENT OF ECTOPIC PREGNANCY

### Ektopik Gebelik Olgularında Methotrexatın Tedavi Etkinliğinin Değerlendirilmesi

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#### Abstract

**Aim:** Our aim in this study was to assess efficacy of single-dose methotrexate (MTX) as medical treatment for ectopic pregnancy (EP) by evaluating the results of patients given this treatment.

**Materials and Methods:** Between September 2016 and August 2017, the treatment outcomes of EP cases treated with MTX at Gazi Yaşargil Training and Research Hospital of Health Sciences University were evaluated retrospectively.

**Results:** In total, 126 cases treated for EP were evaluated and 65 cases were included in the study. In cases administered a single dose of MTX, the success rate was 80%, the failure rate was 13.8%, and the emergency surgery rate was 6.2%. The overall success rate of the medical treatment was 90.7% for a second dose of MTX. An unsuccessful result was considered as less than a 15% reduction in the beta-human chorionic gonadotropin ( $\beta$ -hCG) level between 4 and 7 days after single dose MTX administration. In all cases, the rate of emergency surgery after treatment was 9.3%.

**Conclusions:** In our study, success rates in patients with EP treated with MTX were 80% after a single dose and as high as 90.7% when a second dose was added.

**Key words:** ectopic pregnancy, medical treatment, methotrexate efficacy, success rate.

#### Öz

**Amaç:** Bu çalışmadaki amacımız ektopik gebelik' te (EP) medikal tedavi olarak tek doz methotrexat (MTX) tedavisi verilen olguların sonuçlarının değerlendirilmesidir.

**Materyal ve Metot:** Eylül 2016 ile Ağustos 2017 arasında Sağlık Bilimleri Üniversitesi Gazi Yaşargil Eğitim ve Araştırma Hastanesinde tedavi edilen EP olgularında MTX tedavisi uygulanmış olanların tedavi sonuçları retrospektif olarak değerlendirildi.

**Bulgular:** Çalışmanın yapıldığı tarihler arasında EP nedeniyle tedavi edilen 126 olgu çalışmaya dahil edildi. Tek doz MTX tedavisi başlanan olgularda başarı oranı %80, başarısızlık %13.8 ve acil cerrahi oranı %6.2 olarak gerçekleşti. Tek doz MTX uygulaması sonrasında 4 ve 7 günler arasında beta-human chorionic gonadotropin ( $\beta$ -hCG) seviyesinin %15 ten az düşmesi sonucunda başarısız olarak kabul edilen olgularda yapılan 2. doz MTX sonucunda, medikal tedavinin toplam başarı oranı %90.7 olarak gerçekleşirken, bu olguların tümünde tedavi sonrası acil cerrahi oranı %9.3 olarak gerçekleşti.

**Sonuç:** Çalışmamızda uygun endikasyonla MTX tedavisi uygulanan EP olgularında medikal tedavinin başarı oranı %90.7 gibi oldukça yüksek bir oranda gerçekleşmiş olup olguların sadece %9.3 de MTX tedavisi sonrasında acil cerrahi tedavi gerekmiştir.

**Anahtar kelimeler:** başarı oranı, ektopik gebelik, medikal tedavi, methotrexat etkinliği.

## INTRODUCTION

EP is described as the placement of the fertilized ovum anywhere outer the uterine cavity, and occurs with a frequency between 1–2% among all pregnancies<sup>1-3</sup>. EP is most commonly located in the fallopian tubes and particularly in the ampulla part of the tubes<sup>4-5</sup>. Clinically, approximately 50% of patients the existing with non-specific symptoms, such as abdominal pain, amenorrhea, and irregular vaginal bleeding, whereas the remaining patients may present with

hemodynamic instability due to nonspecific clinical symptoms or with intraabdominal bleeding resulting in tubal rupture<sup>6</sup>. However, in women with delayed menstruation, serial beta-human chorionic gonadotropin ( $\beta$ -hCG) measurements, progesterone measurements, and transvaginal ultrasonography (TV-USG) can allow early diagnosis and medical treatment<sup>7-9</sup>.

Single or multiple doses of methotrexate (MTX) are a common treatment worldwide, although single-dose MTX administration is more widely

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used<sup>9</sup>. The success rates following single-dose treatment are between 52 and 94%<sup>10</sup>. If a decrease in  $\beta$ -hCG of less than 15% is noted between 4 and 7 days following a single-dose MTX treatment, a second dose is administered, and the literature shows a success rate of approximately 20% for these cases<sup>10-11</sup>. EP can be treated surgically or non-surgically and generally if treated with surgically and if not contraindicate, laparoscopic approach is preferred because of minimally invasive surgical technic. During surgery, ectopic pregnancy can be treated with salpingectomy, salpingostomy, salpingotomy, or milking<sup>12-14</sup>. There are some situations which contraindicate for medical treatment such as tubal rupture, hypotension, anemia, ectopic pregnancy mass size of 4 cm or more, persistent abdominal pain for 24 hours, or contraindications for metabolic evaluation (blood count, liver and kidney functions, etc.)<sup>12-15</sup>.

The aim of our study was to assess the outcome of patients treated with a single dose of MTX as a medical treatment for EP.

## MATERIALS AND METHODS

The included cases were 65 patients with tubal EP who were principally treatment with MTX at the Department of Gynecology and Obstetrics of Diyarbakir Gazi Yaşargil Training and Research Hospital of Health Sciences University between September 2016 and August 2017. Patient data were collected from the hospital information system in the form of inpatient protocols, progress notes, ultrasound reports, laboratory-analyzed reports, and, if applicable, surgery protocols and reviewed retrospectively. Institutional review board approval was provided from the Ethical Commission of Diyarbakir Gazi Yaşargil Training and Research Hospital. This

study was conducted according to the 2008 Declaration of Helsinki principles.

The EP was evaluated and diagnosed using standard clinical, TV-USG, and serial  $\beta$ -hCG measurements<sup>15-16</sup>. The inclusion criteria were EP patients receiving a single dose MTX protocol (single dose MTX intramuscular injections) or those receiving a second dose of MTX in EP patients who did not show a decline in serum  $\beta$ -hCG of 15% between days 4 and 7 after the single MTX application. The indications for the initiation of single-dose MTX (50 mg/m<sup>2</sup>) therapy in the diagnosed cases were hemodynamic stabilization, no intraabdominal hemorrhage, observation of a transvaginal ultrasound extrauterine EP focus, an extrauterine EP focus of 3.5 cm or less, no fetal cardiac activity, no the detection of trophoblastic tissue by endometrial sampling of the transvaginal ultrasound, absences an intrauterine gestational sac, despite the presence of a normal  $\beta$ -hCG value in the range of 1500-2000 mIU/mL . EP can be treated surgically with laparoscopic or laparotomy approaches in cases with tubal rupture, hypotension, anemia, an ectopic pregnancy mass 4 cm or more in size, persistent abdominal pain for 24 hours, or contraindications for metabolic evaluation (blood count, liver and kidney functions, etc.)<sup>14-15</sup>. The achievement of single dose MTX treatment was defined as a reduction in  $\beta$ -hCG  $\geq$ 15% between 4 and 7 days and no surgery or no second MTX dose required until the  $\beta$ -hCG value attained <5 mIU/mL in the weekly follow-ups. If the decrease in serum  $\beta$ -hCG level between day 4 and 7 was inadequate, a second dose of MTX (50 mg/m<sup>2</sup>) was administered. Surgery was planned in cases showing hemodynamic instability due to the failure of medical treatment with MTX or intraabdominal

bleeding resulting in tubal rupture during follow-up after treatment.

All cases were compared with the literature in terms of age, gravida, parity, previous surgical history (gynecologic, obstetric, or other abdominal surgeons), initial  $\beta$ -hCG level, and Douglas free fluid on TV-USG. Patients who were not followed up after treatment or who had incomplete records were excluded.

Statistical analysis was conducted using IBM SPSS 18.0 (IBM, Chicago) for Windows. The measured variables were stated as mean  $\pm$  standard deviation, and categorical variables were stated as values and percentages. A p-value of under 0.05 was accepted as statistically significant.

**RESULTS**

During the study period, a single dose of MTX was administered to 65 of 126 patients with EP. The distribution of the characteristics of all cases is summarized in Table-1. The median ages of the patients was  $29.4 \pm 5.6$ , gravidity was  $3.7 \pm 2.0$ , parity was  $1.7 \pm 1.5$ , and the day-0  $\beta$ -hCG level was  $2431 \pm 3542$  (Table 1).

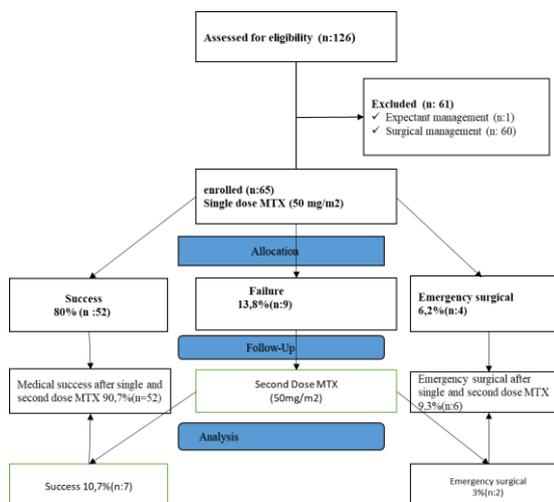
**Table 1.** Distribution of characteristics of ectopic pregnancies

Age (year), [median $\pm$ SD]	29.4 $\pm$ 5.6
Gravida, [median $\pm$ SD]	3.7 $\pm$ 2.0
Parity, [median $\pm$ SD]	1.7 $\pm$ 1.5
Previous surgery, n (%)	18 (27%)
Free fluid on TV-USG, n (%)	17 (26%)
Fetal cardiac activity (+), n (%0)	0 (%0)
Day 0 $\beta$ -hCG level, [median $\pm$ SD], (mIU/mL)	2431 $\pm$ 3542
Blood transfusion, n (%)	2 (%3)
MTX side effects	0 (%)

$\beta$ -hCG: beta-human chorionic gonadotropin, TV-USG: transvaginal ultrasonography, SD: standard deviation, MTX: methotrexate.

The distribution of treatments and outcomes for EP are summarized in the figure-1. In total, 65 patients (51.5%) were treated with a single dose of MTX, 60 (47.7%) patients underwent surgery,

and 1 expectant patient (0.8%) was followed (figure-1).



**Figure 1.** Distribution of treatments and results due to ectopic pregnancy

Of the 65 patients treated with a single dose of MTX, 52 (80%) were effectively treated, a second dose of MTX was required in 9 (13.8%), and 4 (6.2%) underwent emergency salpingectomy surgery (6.2%). Of the 9 patients who accepted a second dose of MTX, treatment was successful in 7 cases, and the other 2 underwent emergency salpingectomy surgery. Medical treatment with single and second dose MTX was successful in 52 cases (90.7%), and in these cases, a surgical need emerged in 6 cases (9.3%). (Figure-1).

In 17 patients evaluated with TV-USG, Douglas free fluid was detected and 14 of these cases were effectively treated with a single dose of MTX. Unilateral salpingectomy was performed in the 3 patients in which the single-dose MTX treatment failed. No fetal heart activity was detected in any case (Table-2). Eighteen patients had a surgical history: 4 patients had past gynecologic surgery, 8 patients had past cesarean section, 2 patients had past abdominal surgery, and 4 patients had past EP surgery. All patients who had previously undergone gynecological surgery (myomectomy, etc.) were

effectively treated with single-dose MTX therapy. The single dose MTX treatment was also successful in 5 of the patients with cesarean section history (2 patients received second doses of MTX treatment), and the 3 patients whose treatment failed underwent salpingectomy. Single-dose MTX treatment was successful in 1 patient with a history of other abdominal surgery, and salpingectomy was performed in 1 patient in which single-dose MTX treatment failed. Single dose MTX treatment was successful in 3 patients with a previous EP surgical history, but it failed in 1 patient, who subsequently underwent salpingectomy. Two (3%) patients required a blood transfusion due to tubal rupture following medical treatment (Table-2).

**Table 2.** Comparison of the characteristics of the unsuccessful EP group with the successful EP group given a single-dose MTX treatment

	Success Group (n=52)	Failure Group (n=9)	P value
Age (year), [median (IQR)]	28 (24–33)	30.5 (25–35.3)	0.609
Gravida, [median (IQR)]	3 (2–5)	4 (2.8–5)	0.509
Parity, [median (IQR)]	2 (0–2)	2 (1–2.3)	0.267
Previous operations, n (%)			
Gynecologic surgery	4 (7.7)	0	0.459
Caesarean section	5 (9.6)	3 (21.4)	
Other abdominal surgery	1 (1.9)	1 (7.7)	
EP surgery	3 (5.8)	1 (7.7)	
Free fluid on TV-USG, n (%)	14 (26.9)	3 (21.4)	0.676
EP mass on TV-USG, mm, [mean±SD]	10 (9.3–11)	10.5 (9–11.3)	0.760
Day 4 β-hCG level, [median (IQR)], (mIU/mL)	696 (304–2115)	4390 (627–8514)	0.011
Day 7 β-hCG level, [median (IQR)], (mIU/mL)	461 (172–1636)	3898 (518–8449)	0.001
Decreasing β-hCG level on day 4, n (%)	34 (65.4)	4 (28.6)	0.013

## DISCUSSION

The success rates for MTX treatment with appropriate indications in EP cases in the present study were 80% after a single dose and 90.7% when a second dose was added. A comprehensive meta-analysis by Barnhart et al reported similar rates of 88% and 93%, respectively<sup>9</sup>. This high rate of success can only be achieved with medical treatment if EP is

diagnosed early and if the appropriate indications are available. MTX has its effect by competitively inhibiting the folate-dependent step in the synthesis of nucleic acids, effectively killing the ectopic trophoblasts, which divide rapidly<sup>17</sup>. However, this competitive inhibition of nucleic acid synthesis can inhibit bone marrow production and lead to impaired liver and renal function tests, although these side effects are more common with multi-dose treatment regimens<sup>9</sup>. In our study, 80% of the cases were effectively treated with a single dose, with only the other 13.8% requiring a second dose, and no MTX-related side effects were observed.

Kusgoz et al. reported a treatment rate of 18.7% for a second dose of MTX following a single-dose MTX treatment due to observation of a <15% reduction of β-hCG between 4 and 7 days<sup>18</sup>. Other studies in the literature report this ratio in the range of 14–20%<sup>14,19</sup>. Our ratio of 13.8% is lower in than that reported by Kusgoz et al.<sup>18</sup>, however our result agrees with the other rates reported in the literature<sup>14,19</sup>.

Kusgoz et al. also reported that tubal rupture end-stage surgery was needed in 6.2% of their patients following MTX treatment, while Aybat et al. reported a rate of 18.7%<sup>18,20</sup>. Our rate of 9.3% was somewhat high, but lower than the rate reported by Aybat et al.

Past surgical history in the etiology of ectopic pregnancy is one of the most important risk factors leading to intra-abdominal adhesions, and this effect is believed to lead to degradation and deterioration of tubal patency, thereby affecting the migration of the fertilized ovum<sup>21-24</sup>. The available literature indicates an average rate of surgical history in patients with EP of 16.5%<sup>21-23</sup>, but some studies show a much higher rate of

50%<sup>24</sup>. In our study, the rate of surgical history for previous episodes of EP was 24%, similar to the rate of increase reported in other studies in the literature.

This study had several limitations, including its retrospective, single-center nature and its relatively small number of cases. However, in all our cases treated with MTX, the treatment planning was in accordance with the indications mentioned in the literature, and the success rates were consistent with the extensive meta-analyses in the literature.

Our study indicated a success rate of 80% in EP cases with appropriate indications when treated with single-dose MTX. Conversely, a second-dose MTX treatment in patients showing a reduction of  $\beta$ -hCG <15% between 4 and 7 days of treatment had a success rate of 90.7%, and only 9.3% of the cases required urgent surgical treatment after MTX treatment.

In conclusion, in our study, success rates in patients with EP treated with MTX were 80% after a single dose and as high as 90.7% when a second dose was added. As we have demonstrated in our study, if EP is diagnosed at an early stage and if the appropriate indications are present, a high rate of success can be achieved.

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