

Comparison of the Effects of Different Treatment Methods on Subsequent Reproductive Results in Tubal Ectopic Pregnancy Treatment

Tubal Ektopik Gebelik Tedavisinde Farklı Tedavi Yöntemlerinin Sonraki Üreme Sonuçları Üzerine Etkisinin Karşılaştırılması

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ABSTRACT

Objective: Ideal management of ectopic pregnancy is still debated and effect of initial treatments on future reproductive outcome is a major concern for clinicians' dealing with reproductive endocrinology. In this study, we aimed to compare the subsequent fertility outcome of patients who were treated for tubal ectopic pregnancy either medically or surgically. **Material and Methods:** We retrospectively reviewed records of 287 ectopic pregnancy patients who were treated in a tertiary care centre between January 2014 and December 2016. Subsequent reproductive outcomes of patients learned by phone interview. 153 patients accompanied follow-up protocol fully, and gave consent for study in phone interview. **Results:** Mean age of patients was 31.98. Radical surgery (salpingectomy) was performed in 75 (45%) women, conservative surgery (salpingostomy) was performed in 24 (15%) women, and medical therapy was chosen for 54 (35.2%) women. Nine patients were operated due to failure in medical therapy. Among 153 women who treated for EP, 79 (52%) of them try to conceive. Among the 79 women who attempted to conceive, 40 (51%) became pregnant spontaneously and 19 (24%) got pregnant with assisted reproductive technology. Treatment modalities did not differ between patients who could achieve pregnant and who could not. **Conclusion:** Results of our study show that; it seems preferable, whenever it is possible, choosing a conservative treatment method to potentiate subsequent fertility outcome while not increasing the risk of recurrence.

Keywords: Ectopic pregnancy; methotrexate; salpingectomy, salpingostomy

ÖZET

Amaç: Ektopik gebeliğin ideal yönetimi hala tartışılmaktadır ve ilk tedavilerin gelecekteki üreme sonuçları üzerindeki etkisi, üreme endokrinolojisi ile ilgilenen klinisyenler için önemli bir endişe kaynağıdır. Bu çalışmada, tubal ektopik gebelik nedeniyle medikal veya cerrahi olarak tedavi edilen hastaların sonraki fertilitate sonuçlarını karşılaştırmayı amaçladık. **Gereç ve Yöntemler:** Ocak 2014 ve Aralık 2016 tarihleri arasında üçüncü basamak bir merkezde tedavi edilen 287 ektopik gebelik hastasının kayıtları retrospektif olarak incelendi. Hastaların sonraki reproduktif sonuçları telefon görüşmesi ile öğrenildi. 153 hasta takip protokolünü tam olarak takip etti ve telefon görüşmesinde çalışma için onay verdi. **Bulgular:** Hastaların yaş ortalaması 31.98 idi. Radikal cerrahi (salpinjektomi) 75 (%45) kadma, konservatif cerrahi (salpingostomi) 24 (%15) kadına uygulandı ve 54 (%35,2) kadın için medikal tedavi seçildi. Dokuz hasta medikal tedavideki başarısızlık nedeniyle ameliyat edildi. EP tedavisi gören 153 kadından 79'u (%52) gebe kalmayı denedi. Gebe kalmayı deneyen 79 kadından 40'ı (%51) kendiliğinden, 19'u (%24) ise yardımcı üreme teknolojisi ile gebe kalmıştır. Tedavi modaliteleri gebe kalabilen ve kalamayan hastalar arasında farklılık göstermemiştir. **Sonuç:** Çalışmamızın sonuçları, mümkün olduğunda, nüks riskini artırmadan sonraki fertilitate sonuçlarını güçlendirmek için konservatif bir tedavi yöntemi seçmenin tercih edilebilir olduğunu göstermektedir.

Anahtar Kelimeler: Ektopik gebelik; metotreksat; salpinjektomi; salpingostomi

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Ectopic pregnancy (EP), an extrauterine pregnancy, responsible for 1-2% of all pregnancies and 3-4% of all maternal deaths.^{1,2} While most of EPs occur in the fallopian tubes, nontubal sites include cervical, interstitial, ovarian, scar, and abdominal pregnancies. The most common clinical scenario on EP is first-trimester vaginal bleeding and abdominal pain with no signs of intrauterine pregnancy.³ No signs of intrauterine pregnancy on transvaginal ultrasonography and an insufficient beta human chorionic gonadotrophin (hCG) rise are diagnostic of EP. Recently, guidelines have become more conservative about rising hCG levels. A slower increase is expected when initial hCG levels are high. While the expected increase of hCG is approximately 49% in early pregnancies when the hCG level is <1.500 mIU/ml and 33% when it is >3.000 mIU/ml, low serum progesterone levels are no longer useful to predict EP.^{1,4,5}

Various treatment methods are available for tubal EP. These are surgery (e.g., salpingectomy or salpingostomy, either with laparoscopy or laparotomy), methotrexate (MTX) treatment, and expectant management.⁶ MTX is a folate antagonist that inhibits DNA synthesis and repair by interrupting the synthesis of purine nucleotides. A single-dose MTX regimen administered 50 mg/m² intramuscularly was defined in 1991 by Stowall et al. and is considered to be the easiest among the three MTX regimens. Nevertheless, it is worth noting that in around 25% of patients, an extra dosage may be necessary to achieve complete remission.^{1,7} Surgical treatment is preferred to medical therapy when hCG levels >5.000 mIU/ml or there is fetal cardiac activity.⁸ Laparoscopic surgery is preferable to open surgery in hemodynamically stable patients. Salpingectomy is recommended if the other tube is healthy, but salpingostomy should be performed on women who have risk factors for reduced fertility, such as a previous ectopic pregnancy, damage to the other tube, a history of abdominal surgery, or a history of pelvic inflammatory disease.⁵ However, there is still a debate on pregnancy outcomes after salpingostomy and salpingectomy. Recently published systematic reviews and meta-analyses have stated that subsequent intrauterine pregnancy rates were higher after salp-

ingostomy. On the other hand, there is no difference in recurrent EP rates between salpingectomy and salpingostomy.⁹ Similarly, a cohort study found that salpingostomy is associated with a higher rate of subsequent intrauterine pregnancy compared with salpingectomy. The authors also mentioned that recurrent EP risk is higher after salpingostomy.¹⁰ In contrast, randomized controlled trials (RCTs) found no significant differences in subsequent intrauterine pregnancy or recurrent EP rates between salpingectomy and salpingostomy groups.¹⁰

In the present study, we evaluated subsequent pregnancy outcomes after medical and surgical treatment for EP.

MATERIAL AND METHODS

This study involved a retrospective cohort analysis of medical records involving women who received treatment for ectopic pregnancy (EP) at the inpatient gynecology clinic of a university hospital. The data collection period ranged from January 2014 to December 2016. It was aimed to evaluate reproductive outcomes in the five years following treatment. The Institutional Review Board approved the study protocol and the study complied with the Declaration of Helsinki. The inclusion criteria for this study consisted of tubal EP that was verified by ultrasound imaging, as well as an inadequate increase in human chorionic gonadotropin (hCG) levels between two measures taken 48 hours apart. The exclusion criteria were nontubal EP, pregnancy in an unknown location, abnormal results on liver or renal function tests, and requirement of multiple doses of the MTX regimen. We obtained the subsequent reproductive history of patients in five years after EP treatment by phone interview. One hundred and fifty-three patients who responded to the phone interview and gave their consent were involved in the study. In accordance with our medical practice, women presenting with symptoms of pelvic discomfort and unusual vaginal bleeding subsequent to an atypical menstrual pattern are subjected to an evaluation for EP. The patient's condition was determined to be tubal EP based on the observation of an inadequate increase in hCG levels (<66%) during a 48-hour period, as well as the pres-

ence of a complex or solid adnexal mass during ultrasound examination, in the absence of an intrauterine gestational sac. A single-dose MTX regimen was applied for asymptomatic patients with no evidence of tubal rupture, hemodynamic instability, or fetal cardiac activity. The dosage of methotrexate is determined based on the individual patient's body surface area, with a standard calculation of 50 mg/m². Patients who were hemodynamically unstable, had contraindications to MTX treatment, or had persistent hCG rise or plateau after a 2-dose MTX injection were treated surgically. The decision on which surgical procedure to apply was made based on an individualized approach according to the characteristics of the patient and the attending surgeon's discretion.

STATISTICAL ANALYSES

Data analyzes were performed using SPSS Version 20.0 (IBM Corporation, Armonk, NYC, USA). Samples were tested with Shapiro-Wilk to determine the normality of distributions. According to the distribution of the data, continuous variables were compared with the student t test or Mann-Whitney U test. Categorical variables were compared with the chi-square

test or Fisher's exact test, where appropriate. In addition, one-way ANOVA and Kruskal-Wallis methods were used as post-hoc analyzes for multiple comparisons. A P value of <0.05 was considered statistically significant.

RESULTS

During the study period, 287 women were followed up and treated for EP in our clinic. A total of 153 individuals who received treatment for EP were successfully contacted and agreed to participate in the study through telephone interviews. The mean age of the patients was 31.98. Medical treatment was applied to 54 out of 153 patients (35.2%). The remaining patients (99/153) underwent surgical procedures. Salpingostomy was performed in 24 patients (15.6%), and salpingectomy was preferred in 75 patients (84.4%). Nine patients (5.8%) were operated on due to failure of medical treatment. A comparison of demographics between EP treatment groups is shown in [Table 1](#).

Subsequent reproductive outcomes are shown in [Table 2](#). Recurrent EP rates were 13% in the MTX group, 16% in the salpingostomy group, and 11% in

TABLE 1: Comparison of demographics between EP treatment groups.

	MTX (n=54)	Salpingostomy (n=24)	Salpingectomy (n=75)	P value
Patient Characteristics				
Age, years, mean±SD	32.8±5.1	31.3±6.2	32.0±4.4	0.213
Body mass index, kg/m ² , mean±SD	28.6±8.1	29.2±7.4	27.9±6.4	0.811
Parity, median, (min-max)	1 (0-4)	0 (0-1)	2 (0-3)	0.907
Smokers, n (%)	6 (11)	4 (17)	10 (13)	0.356
Presence of intrauterin device, n (%)	2 (4)	1 (4)	0 (0)	0.696
Using oral contraceptive drugs, n (%)	1 (2)	0 (0)	0 (0)	0.370
Previous ectopic pregnancy, n (%)	3 (6)	2 (8)	2 (3)	0.617
History of ART, n (%)	3 (6)	1 (4)	4 (5)	0.793
Surgical History				
Ceasarean section, n (%)	12 (22)	3 (13)	15 (20)	0.255
History of tubal surgery, n (%)	5 (9)	4 (17)	10 (13)	0.403
Other abdominal surgery, n (%)	6 (11)	3 (13)	11 (15)	0.871
Patients symptoms				
Abdominal pain, n (%)	19 (35)	10 (47)	40 (58)	N/A
Vaginal bleeding, n (%)	15 (27)	5 (23)	19 (84)	N/A
Asymptomatic, n (%)	20 (37)	6 (28)	10 (14)	N/A

ART: Assisted reproduction technology, MTX: Methotrexate.

TABLE 2: Pregnancy outcomes of patients who applied different treatment approach.

	MTX (n=54)	Salpingostomy (n=24)	Salpingectomy (n=75)	P value
Recurrent ectopic pregnancy n (%)	7 (13)	4 (17)	9 (12)	0.593
Spontaneous pregnancy, n (%)	13 (24)	5 (21)	22 (29)	0.758
ART, n (%)	5 (9)	3 (13)	11 (15)	0.471
Time period until pregnancy, months, mean±SD	17.09±3.07	15.29±3.11	15.66±2.20	0.340

ART: Assisted reproduction technology, MTX: Methotrexate.

the salpingectomy group, respectively. Additionally, spontaneous pregnancy rates were comparable between the groups. In all treatment methods, the mean time to achieve a new pregnancy was more than 12 months, with no significant difference between treatment modalities.

DISCUSSION

The present study aimed to evaluate the effect of various EP therapy procedures on subsequent reproductive outcomes. Intrauterine pregnancy and recurrent EP rates were found to be similar across all procedures, with no significant delay in the time to achieve a new pregnancy after EP.

Routine EP treatment algorithms guide the treatment decisions of clinicians. However, there is an ongoing debate regarding the effects of treatments on future fertility potential and candidates for surgical procedures. In a systematic review and meta-analysis published in 2023, six publications involving 1591 patients were analyzed to compare reproductive outcomes after salpingostomy and salpingectomy procedures. The study found that the rates of subsequent intrauterine pregnancy were higher in patients who underwent salpingostomy rather than salpingectomy (OR=1.61, 95% CI: 1.29 to 2.01, $P < 0.001$), without a significant difference in the rates of recurrent ectopic pregnancy between the two groups (OR=1.21, 95% CI: 0.62 to 2.37, $P=0.58$).⁹ Similarly, a recently published systematic review and meta-analysis compared the therapeutic effects of salpingostomy and salpingectomy and included 24 RCTs. The results of the meta-analysis indicated that intrauterine pregnancy rates were higher in the salpingostomy group (OR=2.49; 95% CI, 1.61-3.86; $p < 0.0001$). However, no significant difference in recurrent EP rates was

found between the two groups (OR=1.15; 95% CI, 0.64–2.07; $p = 0.64$).¹¹ Furthermore, the results of cohort studies incorporated in a systematic review and meta-analysis conducted by Cheng et al. in 2016 demonstrate that salpingostomy is linked to a greater likelihood of future intrauterine pregnancy (relative risk [RR], 1.24; 95% confidence interval [CI], 1.08-1.42). However, it is also associated with a greater likelihood of recurrent ectopic pregnancy (10% versus 4%; RR, 2.27; 95% CI, 1.12-4.58) when compared to salpingectomy. On the other hand, when examining the treatment of ectopic pregnancy, randomized controlled trials have shown that there is no statistically significant distinction between salpingectomy and salpingostomy in terms of subsequent intrauterine pregnancy rates (relative risk [RR]: 1.04; 95% confidence interval [CI]: 0.899-1.21) or recurrent ectopic pregnancy rates (RR: 1.30; 95% CI: 0.72-2.38).¹⁰ On the other hand, Hao et al. reported significantly higher rates of intrauterine pregnancy in the MTX group compared with surgical treatment (OR=1.52, 95% CI: 1.20 to 1.92, $P < 0.001$). However, there was no significant difference in recurrent ectopic pregnancy rates between the surgical treatment and MTX groups (OR=1.12, 95% CI: 0.84 to 1.51, $P=0.43$). While no significant difference was found in the rates of intrauterine pregnancy between the MTX and salpingostomy groups (OR=1.04, 95% CI: 0.79 to 1.38, $P=0.78$), the rates of intrauterine pregnancy were higher in the MTX group compared to patients with salpingectomy (OR=2.11, 95% CI: 1.52 to 2.93, $P < 0.001$).⁹

Similarly, in a retrospective study published in 2023, the authors compared subsequent pregnancy outcomes between patients who were treated with MTX and salpingectomy for EP in their previous

pregnancy. The study found that spontaneous pregnancy rates were higher in patients who received MTX for EP.¹² Nevertheless, in a multicenter randomized trial (the DEMETER Trial) published in 2013 by Fernandez et al., patients with ectopic pregnancy were divided into two groups. Within a particular cohort, individuals were assigned at random to receive either conservative surgical intervention (salpingostomy) or medical treatment. In the other group, patients were randomly allocated to receive either conservative or radical surgery (salpingectomy). However, the authors stated that they also applied MTX to patients who underwent conservative surgery. The study found that there was no significant difference in subsequent fertility after 2 years between MTX and conservative surgery or between conservative surgery and radical surgery.¹³ Moreover, in another recently published study, fertility outcomes were investigated following the medical and surgical management of ectopic pregnancy. The authors concluded that there were no significant differences between patients treated with surgical and medical management in terms of intrauterine pregnancy rates, the time interval to a new pregnancy, or pregnancy outcomes.¹⁴

The American College of Obstetricians and Gynecologists (ACOG) suggests that salpingectomy should be preferred in cases where there is a healthy contralateral fallopian tube or significant tubal damage. However, salpingostomy is recommended when patients have a desire for fertility but do not have a healthy contralateral tube.¹ As a result of this study, we found no significant differences in pregnancy outcomes between therapy procedures. By the way, this study has a few limitations. The major limitations of the study were its retrospective design and the heterogeneous distribution of patients. However, the heterogeneity observed was primarily due to variations in the status of the fallopian tubes, the surgeon's ex-

perience, and the patient's preferences regarding fertility. On the other hand, the comprehensive evaluation of all therapy procedures was a strength of our study. Moreover, we included only tubal EPs diagnosed by transvaginal ultrasonography and serial hCG measurements.

CONCLUSION

There is an ongoing debate in the literature regarding the effects of treatment protocols for EP on future fertility. In our study, subsequent reproductive outcomes after EP treatment were similar between different therapy procedures. Our results suggest that neither medical nor surgical treatment is superior to the other in terms of subsequent reproductive outcomes.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Bulut Varlı, Göksel Kanmaz; **Design:** Bulut Varlı, Kaan Baydemir, Göksel Kanmaz; **Control/Supervision:** Çağatayhan Öztürk, Meltem Sönmezer; **Data Collection and/or Processing:** Kaan Baydemir, Çağatayhan Öztürk; **Analysis and/or Interpretation:** Bulut Varlı, Kaan Baydemir, Meltem Sönmezer, Göksel Kanmaz; **Literature Review:** Kaan Baydemir, Çağatayhan Öztürk; **Writing the Article:** Bulut Varlı, Kaan Baydemir, Meltem Sönmezer; **Critical Review:** Çağatayhan Öztürk, Göksel Kanmaz.

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