



FERTILITY OUTCOMES AFTER MEDICAL AND SURGICAL MANAGEMENT OF TUBAL ECTOPIC PREGNANCY

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SUMMARY – The objective was to investigate whether the method of treatment (surgical or medical) affects achieving a new pregnancy, as well as the time to and prognosis of the new pregnancy, in women with ectopic pregnancy (EP). Information on patients treated in our hospital between 2013 and 2014 for EP was retrieved from the computerized patient records. Data on whether these patients achieved pregnancy after EP treatment, time from treatment to new pregnancy, and prognosis of pregnancy were collected by phone interviews. A total of 101 women were analyzed. In addition to descriptive analysis, the χ^2 -test and Kruskal Wallis test were used to compare the groups. A new pregnancy was present in 84 (83.2%) of the women after EP treatment. There was no significant difference among the women having undergone medical treatment (methotrexate), surgical treatment, medical treatment followed by surgical treatment, or observational management approach in terms of achieving a new pregnancy after treatment and time to and prognosis of the new pregnancy. The study could not determine which treatment method would be superior in women with EP and in planning future pregnancy, but concluded that close clinical and laboratory monitoring is appropriate before deciding on aggressive interventions.

Key words: *Ectopic pregnancy; Fertility outcome; Treatment method*

Introduction

Ectopic pregnancy (EP) is a problem seen in 2% of all pregnancies, which unfavorably influences the woman's health and future fertility¹. It can occur in the uterine tube, cervix or ovary, or in both cavity and tube, which is then called heterotopic pregnancy². About 95.5% of EP cases occur in fallopian tubes, while other implantation sites include ovaries (3.2%) and abdomen (1.3%)³. The primary goal of treating EP is to prevent tubal injury, minimize the risk of recurrence, and preserve patient's fertility. There are two treatment op-

tions for EP, surgical and medical therapy¹. Nevertheless, observational management approach is another option before deciding on surgical or medical treatment. Since early EPs have the risk of resulting in spontaneous abortion and reabsorption, the patient may be given some time by close clinical and laboratory monitoring before starting aggressive treatment⁴. In surgical treatment of tubal EPs, salpingotomy, partial salpingectomy followed by laparoscopic anastomosis, or fimbrial milking is performed to preserve tubal functions. In case the patient does not plan any further pregnancies or the tubes are seriously damaged or ruptured, salpingectomy is performed⁴. As a noninvasive treatment option, methotrexate (MTX) is the primary agent used in medical treatment. The experience of the team and the reproductive desire of the patient, as well as the factors such as beta-hCG level, size of the mass, and presence of blood in the peritoneal cavity are ef-

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fective in deciding on medical treatment and in the success of treatment⁵.

History of previous EP and previous tubal surgery has an important place among the risk factors for EP⁴. Therefore, further intrauterine pregnancies, either spontaneous or by assisted reproductive technologies (ART), pose a challenge in those treated for EP. The present study aimed to investigate whether the method of treatment (surgical or medical) affects achieving pregnancy, as well as the time to and prognosis of the new pregnancy in those treated for EP.

Materials and Methods

Computerized medical records of patients having been treated for EP between 2013 and 2014 in our hospital, which is a tertiary hospital, were retrospectively reviewed and treatment-related data were retrieved. After two years of treatment, patients were called by phone. A telephone interview was conducted and the patients were asked whether they used any contraceptive method after EP treatment, as well as on pregnancy achieved after EP treatment, within which time the new pregnancy occurred, and how that pregnancy ended up. The patients who had used any contraceptive methods after EP treatment were not included in the study. The study was approved by the Ethics Committee of our hospital. Verbal informed consent was obtained from the patients during phone interviews.

Statistical analysis was performed by use of SPSS version 21.0 package program. Descriptive statistics were presented as numbers and percentages for cate-

gorical variables, and as median, minimum and maximum for numerical variables. Independent categorical variables were compared using χ^2 -test, whereas multi-group comparison of numerical variables was done using Kruskal-Wallis test. The level of statistical significance was defined as $p < 0.05$.

In power analysis, when $\alpha = 0.05$ and $1 - \beta$ (power) = 0.80, it was estimated that at least 27 subjects were needed to be taken from each treatment group (medical and surgical) to yield a mean change of 1.3 months in the time to new pregnancy.

Results

A total of 101 subjects (age range 18-45 years) treated for EP were included in the analysis. Eighty-four (83.2%) of 101 subjects achieved a new pregnancy after treatment. Women who did and did not achieve a new pregnancy were evaluated in terms of MTX use for the treatment of previous EPs. While the percentage of pregnancy was 81.8% in those who had been treated with MTX ($n = 55$), it was 84.8% in those who had not received MTX ($n = 46$). There was no difference in terms of achieving pregnancy and time to and prognosis of the new pregnancy between those who received different doses of MTX and those who did not receive MTX (Table 1).

Women who did and did not achieve a new pregnancy were evaluated in terms of surgical treatment for their previous EPs. The rate of achieving a new pregnancy was 84.9% in the patients having undergone surgical treatment ($n = 53$) and 81.3% in those patients who had not undergone surgical treatment ($n = 48$;

Table 1. Presence of a new pregnancy in patients treated with methotrexate for ectopic pregnancy

	n	Methotrexate use				P
		No	Single dose	2 doses	Multiple doses	
New pregnancy after EP treatment						
Yes	84	39 (84.8)	38 (86.4)	7 (70)	0 (0.0)	0.086
No	17	7 (15.2)	6 (13.6)	3 (30)	1 (100.0)	
Interval to new pregnancy (months)	83	5 (2-23)	5.5 (2-17)	5 (3-11)	-	0.843
Prognosis of the new pregnancy						
Term delivery	64	33 (82.5)	27 (77.1)	4 (66.7)	-	0.632
Other ^a	17	7 (17.5)	8 (22.9)	2 (33.3)	-	

EP = ectopic pregnancy; data are presented as number (%) or median (minimum-maximum), where appropriate; ^apreterm delivery, extra-uterine pregnancy, abortion or medical abortion due to an anomaly

Table 2. Presence of a new pregnancy in patients having undergone surgical treatment for ectopic pregnancy

	n	Surgery			p
		None	Salpingectomy/ salpingostomy	Other ^a	
New pregnancy after EP treatment					
Yes	84	39 (81.3)	36 (83.7)	9 (90.0)	0.791
No	17	9 (18.8)	7 (16.3)	1 (10.0)	
Interval to new pregnancy (months)	84	6 (2-23)	5 (2-16)	5 (2-8)	0.602
Prognosis of the new pregnancy					
Term delivery	64	28 (73.7)	29 (82.9)	7 (87.5)	0.519
Other ^b	17	10 (26.3)	6 (17.1)	1 (12.5)	

EP = ectopic pregnancy; data are presented as number (%) or median (minimum-maximum), where appropriate; ^amilking + oophorectomy + other; ^bpreterm delivery, extrauterine pregnancy, abortion or medical abortion due to an anomaly

Table 3. Presence of a new pregnancy according to treatment method used for ectopic pregnancy

	Treatment method used for EP				p
	Observational method	Medical	Surgical	Medical followed by surgical	
New pregnancy after EP treatment					
Yes	3 (60.0)	35 (83.3)	35 (87.5)	10 (76.9)	0.425
No	2 (40.0)	7 (16.7)	5 (12.5)	3 (23.1)	
Interval to new pregnancy (months)	7 (3-8)	6 (2-17)	5 (2-16)	4 (2-9)	0.675
Prognosis of the new pregnancy					
Term delivery	3 (75.0)	24 (72.7)	29 (82.9)	7 (87.5)	0.690
Other ^a	1 (25.0)	9 (27.3)	6 (17.1)	1 (12.5)	

EP = ectopic pregnancy; data are presented as number (%) or median (minimum-maximum), where appropriate; ^apreterm delivery, extrauterine pregnancy, abortion or medical abortion due to an anomaly

p=0.624). There was no significant difference in terms of achieving pregnancy and time to and prognosis of the new pregnancy between the patients having undergone salpingectomy/salpingostomy or other surgical methods and those who did not undergo any surgical treatment (Table 2). The other 17 patients who did not achieve pregnancy after EP treatment did not undergo ART treatment until telephone interview.

When patients were grouped according to the method of treatment for EP as medical treatment (MTX), surgical treatment, medical treatment followed by surgical treatment, and observational method, no significant difference was determined among the four groups in terms of achieving new pregnancy after treatment, or time to and prognosis of the new pregnancy (Table 3).

Discussion

Ectopic pregnancy is an important health problem associated with morbidity and mortality in women. History of previous EP is a risk factor for the development of a future EP. ART is another risk factor reported for EP^{6,7}. The increasing use of ART would enhance the incidence of EP. Success of the method preferred for the treatment of EP and its effects on future pregnancies are important issues that need to be investigated.

Today, advanced laboratory and imaging methods allow for early diagnosis and medical treatment with MTX in the cases with EP⁸. MTX is successfully used for the treatment of unruptured EPs as an effective, safe and noninvasive method with minimal or no side effects⁹. In the treatment of EP, MTX use has been

reported to have no unfavorable effect on the subsequent ovarian reserve, ovarian responsiveness, or success of *in vitro* fertilization¹⁰⁻¹². In a study investigating future fertility status of 158 women who received MTX for tubal EP, the cumulative intrauterine pregnancy and EP rates were 57.5% and 66.9%, and 15.4% and 23.7% after 1 and 2 years, respectively. In Cox regression analysis, after adjustment for factors associated with fertility, only previous history of infertility was associated with poor reproductive performance. The authors suggest that fertility is associated with the previous medical history of the patient rather than the treatment for EP¹³. In a systematic review and meta-analysis study including data on 329 patients from seven observational studies, Ohannessian *et al.*¹⁴ report that the mean number of oocytes retrieved during the cycles, baseline plasma follicle-stimulating hormone level, duration of stimulation, total gonadotropin dose used for stimulation, and estradiol level on the day ovulation was triggered, were similar before and after MTX treatment for EP in patients having undergone ART. There was no statistically significant difference in terms of treatment success between the patients having received single or multi-dose MTX for unruptured EP. Nevertheless, single-dose strategy is cost-effective and is associated with better fertility outcome than using multi-dose MTX¹⁵. Dhar *et al.*¹⁶ report on a success rate of 65% in 60 cases that received a single dose of systemic MTX for EP. Success rate of fertility has been reported to be 30% in the first year and 13.3% in the second year, whereas the secondary fertility rate was 11.6%. Smorgick *et al.*¹⁷ evaluated success rate and future fertility in 31 cases with unruptured EP that received combined local or systemic MTX, and the success of combination therapy was 73.9% for EP located in the fallopian tubes (n=23). The researchers questioned pregnancy status of 28 women by telephone interviews and learned that 24 women had tried to become pregnant, 18 of them had been successful, and 15 women had given birth to a living baby. In the present study, the rate of achieving a new pregnancy was 81.8% in the cases that received MTX for EP. There were no differences between those who had received different doses of MTX and those that had not received MTX in terms of achieving a new pregnancy, and time to and prognosis of the new pregnancy.

Owing to its advantages such as short hospital stay, low cost and less adhesion formation, laparoscopic ap-

proach is preferred to laparotomy for EPs in which surgery is indicated, and salpingostomy is preferred to salpingectomy in women with unruptured tubal pregnancy who desire to preserve their fertility⁸. In a multicenter study, women that would undergo surgery for EP were randomized to salpingotomy (n=215) or salpingectomy (n=231) group, and were followed for achieving a new pregnancy. The cumulative pregnancy rates were 60.7% and 56.2% after salpingotomy and salpingectomy, respectively. The rates of repeat EP were 8% and 5% in women who had undergone salpingotomy and salpingectomy, respectively. Based on these results, the researchers conclude that salpingostomy does not significantly improve success of fertility as compared to salpingectomy in women with tubal pregnancy and a healthy contralateral tube¹⁸. A retrospective study found that 70.2% (n=618) of the cases with tubal EP underwent salpingectomy, 18.1% underwent salpingostomy, and 11.7% underwent tubal anastomosis. The crude intrauterine pregnancy rates within 24 months of surgery were 55.5% for salpingectomy, 50.9% for salpingostomy, and 40.3% for tubal anastomosis¹⁹. In the present study, the rate of achieving a new pregnancy was 84.9% in the patients that underwent surgery for EP. There was no difference between the patients who underwent salpingectomy/salpingostomy or other surgical methods and those who did not undergo any surgical intervention in terms of achieving a new pregnancy, and time to and prognosis of the new pregnancy.

Some studies compared outcomes of surgical and medical treatments. In a population-based observational study, the future fertility status of 1064 women who underwent laparoscopic surgery or medical treatment for tubal EP was investigated. The 24-month cumulative rates of intrauterine pregnancy (IUP) were 76%, 76% and 67% in the patients who received conservative medical (11%), conservative laparoscopic (salpingostomy) (61%), or radical laparoscopic (salpingectomy) treatment (28%), respectively. Although the rate of achieving pregnancy was lower after radical treatment, multivariate analysis yielded no significant difference among the three methods of treatment. In that study, the outcome of future pregnancies was found to be independent of the method of treatment²⁰. Ultrasound-confirmed EP cases were analyzed in a randomized, controlled, multi-center study. Two hundred and seven women with less active EP in Arm 1

underwent conservative surgery and systemic intramuscular (IM) MTX within 24 hours of surgery or medical treatment with IM MTX alone. One hundred and ninety-nine women with active EP in Arm 2 underwent radical surgery alone or conservative surgery with postoperative MTX treatment. The 2-year IUP rates were 67% after medical treatment and 71% after conservative surgery in Arm 1, whereas 2-year IUP rates were 70% after conservative surgery and 64% after radical surgery in Arm 2. No significant difference in subsequent 2-year fertility was found between those having undergone medical treatment and conservative surgery in patients with less active EP, or between those having undergone conservative and radical surgery in patients with most active EP²¹. A retrospective study found no difference in terms of post-treatment change in the ovarian reserve and oocyte yield between patients who underwent ART and were treated with MTX (n=153) and surgery (n=36). It was determined that the dose of MTX had no effect on ovarian reserve. No between-group difference was found in future live births either, so it was concluded that EP treatment had no unfavorable effect on future fertility²². In a study with a long (maximum 10 years) follow-up period, 106 women with EP were randomized to two groups of medical (MTX, n=53) and surgical (laparoscopic salpingotomy, n=53) treatment. During the follow-up period, spontaneous intrauterine pregnancy rates were 73% and 62% after surgery and MTX treatment, respectively, and the EP rate was 9.6% in patients treated with MTX, while the corresponding rate was 17.3% in patients having undergone surgical treatment. It was concluded that medical treatment with a single dose of MTX and laparoscopic surgery yielded similar outcomes in hemodynamically stable women with EP who wish to preserve their future fertility²³. There was no difference in the rate of achieving pregnancy between the patients having received medical treatment with MTX and those having undergone salpingectomy or salpingostomy for tubal EP (69%, 65% and 60%, respectively)²⁴. In their review, Varma and Gupta²⁵ assessed relevant reviews, randomized-controlled studies and observational studies to investigate which method of treatment would have a prognosis-improving effect in women with unruptured tubal EP. They failed to obtain clear evidence showing the superiority of any of the methods for women that desire pregnancy in the future.

Jamard *et al.*²⁶ compared the effect of salpingostomy and salpingectomy on fertility and recurrence of EP and concluded that there was no statistically significant difference between the two surgery methods. Correlatively, Chen *et al.*²⁷ report no difference regarding fertility outcomes between the laparoscopic salpingostomy and salpingectomy methods. According to a retrospective study from Italy, reproductive outcomes after laparoscopic salpingectomy were found to be similar to salpingostomy. Nevertheless, they report on the 2-year recurrent EP rates of 5.3% and 18.7% and the persistent trophoblastic disease rates of 1.8% and 12% for salpingectomy and salpingostomy, respectively²⁸.

In the present study, we found no difference in terms of achieving new pregnancy and time to and prognosis of the new pregnancy among the patients having received medical treatment (MTX), surgical treatment, medical treatment followed by surgical treatment, or observational management approach either. In conclusion, based on these findings and the above-mentioned literature information, observational management approach and medical treatment should be preferred in women who present with EP unless there is an obligatory indication, and surgery should be considered when these methods fail.

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Sažetak

NOVA TRUDNOĆA NAKON MEDIKAMENTNOG I KIRURŠKOG LIJEČENJA
EKTOPIČNE TRUDNOĆE*S. Arda Düz*

Cilj je bio ispitati utječe li metoda liječenja (kirurška ili medikamentna) na postizanje nove trudnoće, kao i na vrijeme i prognozu nove trudnoće u žena s ektopičnom trudnoćom (EP). Podaci o bolesnicama liječenim u našoj bolnici između 2013. i 2014. godine zbog EP-a preuzeti su iz računalne evidencije bolesnika. Podaci o tome jesu li te bolesnice postigle trudnoću nakon liječenja EP-om, o vremenu proteklom od liječenja do nove trudnoće i o prognozi trudnoće prikupljeni su telefonskim razgovorima. Analizirana je ukupno 101 žena. Uz deskriptivnu analizu, za usporedbu skupina primijenjeni su χ^2 -test i Kruskal-Wallisov test. Nova trudnoća bila je prisutna u 84 (83,2%) žene nakon liječenja EP-a. Nije utvrđena značajna razlika između žena koje su bile podvrgnute medikamentnom liječenju (metotreksat), kirurškom liječenju, medikamentnom liječenju praćenom kirurškim liječenjem ili pristupu promatranja u pogledu postizanja nove trudnoće nakon liječenja te u vremenu proteklom do nove trudnoće i prognozi nove trudnoće. Nije utvrđeno koja je metoda liječenja uspješnija kod žena s EP i u planiranju buduće trudnoće, ali je zaključeno da je potrebno pažljivo kliničko i laboratorijsko praćenje prije nego se odlučimo za agresivne intervencije.

Ključne riječi: *Ektopična trudnoća; Nova trudnoća; Metoda liječenja*