FERTILITY OUTCOMES AFTER MEDICAL AND SURGICAL MANAGEMENT OF TUBAL ECTOPIC PREGNANCY

Senem Arda Düz

Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, İnönü University Faculty of Medicine, Malatya, Turkey

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 χ²-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 fertility. It can occur in the uterine tube, cervix or ovary, or in both cavity and tube, which is then called heterotopic pregnancy. About 95.5% of eP cases occur in fallopian tubes, while other implantation sites include ovaries (3.2%) and abdomen (1.3%). 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 options for eP, surgical and medical therapy. 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 treatment. 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 performed. 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-
fective in deciding on medical treatment and in the success of treatment’.

History of previous EP and previous tubal surgery has an important place among the risk factors for EP. 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 categorical variables, and as median, minimum and maximum for numerical variables. Independent categorical variables were compared using χ²-test, whereas multigroup 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 α=0.05 and 1-β (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;...
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).

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

| New pregnancy after eP treatment | None | Salpingectomy/salpingostomy | Othera | p |
|---------------------------------|------|----------------------------|--------|---|
| Yes                             | 39 (81.3) | 36 (83.7) | 9 (90.0) | 0.791 |
| No                              | 9 (18.8)  | 7 (16.3)  | 1 (10.0)  |       |
| Interval to new pregnancy (months) | 6 (2-23)  | 5 (2-16)  | 5 (2-8)   | 0.602 |

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

| Treatment method used for eP | Observational method | Medical | Surgical | Medical followed by surgical | p |
|------------------------------|---------------------|---------|----------|------------------------------|---|
| 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 |

### 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 eP.8 MTX is successfully used for the treatment of unruptured ePs as an effective, safe and noninvasive method with minimal or no side effects.9 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 fertilization. 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 EP. In a systematic review and meta-analysis study including data on 329 patients from seven observational studies, Ohannessian et al. 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 of 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 MTX. Dhar et al. 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. 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 approach 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 fertility. In a multicenter study, women that would undergo surgery for EP were randomized to salpingectomy (n=215) or salpingostomy (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 salpingectomy does not significantly improve success of fertility as compared to salpingectomy in women with tubal pregnancy and a healthy contralateral tube. 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 anastomosis. 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 treatment. 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 EP. 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 fertility. 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 salpingostomy, 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 fertility. 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). In their review, Varma and Gupta 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. 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. 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, respectively.

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.

References

1. Juneau C, Bates GW. Reproductive outcomes after medical and surgical management of ectopic pregnancy. Clin Obstet Gynecol 2012;55(2):455-60. doi: 10.1097/GOF.0b013e3182510a88
2. Ivkošić IE, Bauman R, Ujević B, Vasilj O, Kojić IP, Ivkošić A, et al. Spontaneous heterotopic, ectopic cervical and ectopic tubal pregnancy – ever present diagnostic difficulty: three case reports. Acta Clin Croat. 2015 Sep;54(3):367-70. PMID: 26661110
3. Rana P, Kazmi I, Singh R, Afzal M, Al-Abbasi FA, Aseerī A, et al. Ectopic pregnancy: a review. Arch Gynecol Obstet 2013; 288(4):747-57. doi: 10.1007/s00404-013-2929-2
4. Alkatout I, Honemeyer U, Strauss A, Tinelli A, Malvasi A, Jonat W, et al. Clinical diagnosis and treatment of ectopic pregnancy. Obstet Gynecol Surv. 2013;68(8):571-81. doi: 10.1097/OGX.0b013e3182929cdebb
5. Cecchino GN, Araujo Júnior E, Elito Júnior J. Methotrexate for ectopic pregnancy: when and how. Arch Gynecol Obstet. 2014;290(3):417-23. doi: 10.1007/s00404-014-3266-9
6. Refaat B, Dalton E, Ledger WL. Ectopic pregnancy secondary to in vitro fertilisation-embryo transfer: pathogenic mechanisms and management strategies. Reprod Biol Endocrinol. 2015;13:30. doi: 10.1186/s12958-015-0025-0
7. Li C, Zhao WH, Zhu Q, Cao SJ, Ping H, Xi X, et al. Risk factors for ectopic pregnancy: a multi-center case-control study. BMJ Pregnancy Childbirth. 2015;15:187. doi: 10.1186/s12884-015-0613-1
8. Al-Sunaidi M, Tulandi T. Surgical treatment of ectopic pregnancy. Best Pract Res Clin Obstet Gynaecol. 2009;23(4):519-27. doi: 10.1016/j.bpobgyn.2009.07.005
9. Talwar P, Sandeep K, Naredi N, Duggal BS, Jose T. Systemic methotrexate: an effective alternative to surgery for management of unruptured ectopic pregnancy. Med J Armed Forces India. 2013;69(2):130-3. doi: 10.1016/j.mjaf.2012.08.032. Epub 2012 Dec 1
10. Boots CE, Gustafson RL, Feinberg EC. Does methotrexate administration for ectopic pregnancy after in vitro fertilization impact ovarian reserve or ovarian responsiveness? Fertil Steril. 2013;100(6):1590-3. doi: 10.1016/j.fertnstert.2013.08.007
11. Moragianni VA. Methotrexate treatment of ectopic pregnancies does not affect ovarian reserve in in vitro fertilization patients. Fertil Steril. 2014;101(2):337-8. doi: 10.1016/j.fertnstert.2013.11.010
12. Oriol B, Barrio A, Pacheco A, Serna J, Zuzuarregui JL, Garcia-Velasco JA. Systemic methotrexate to treat ectopic pregnancy does not affect ovarian reserve. Fertil Steril. 2008;90(5):1579-82. doi: 10.1016/j.fertnstert.2007.08.032
13. Gervaise A, Masson L, de Tayrac R, Frydman R, Fernandez H. Reproductive outcome after methotrexate treatment of tubal pregnancies. Fertil Steril. 2004;82(2):304-8. doi: 10.1016/j.fertnstert.2004.04.023
14. Ohannessian A, Loundou A, Courbière B, Cravetto L., Agostini A. Ovarian responsiveness in women receiving fertility treatment after methotrexate for ectopic pregnancy: a systematic review and meta-analysis. Hum Reprod. 2014;29(9):1949-56. doi: 10.1093/humrep/deu174
15. Tabatabaii Bafghi A, Zaretezerjani F, Sekhavat L, Dehghani Firouzabadi R, Ramazankhani Z. Fertility outcome after treatment of unruptured ectopic pregnancy with two different methotrexate protocols. Int J Fertil Steril. 2012;6(3):189-94. PMID: 24520438 PMCID: PMC3850298
16. Dhar H, Hamidi I, Rathi B. Methotrexate treatment of ectopic pregnancy: experience at Nizwa Hospital with literature review. Oman Med J. 2011;26(2):94-8. doi: 10.5001/omj.2011.24
17. Smorgick N, Vaknin Z, Pansky M, Halperin R, Herman A, Maymon R. Combined local and systemic methotrexate treatment of viable ectopic pregnancy: outcomes of 31 cases. J Clin Ultrasound. 2008;36(9):545-50. doi: 10.1002/jcu.20506
18. Mol F, van Mello NM, Strandell A, Strandell K, Jurkovic D, Ross J, et al. Salpingotomy versus salpingectomy in women with tubal pregnancy (ESEP study): an open-label, multicentre, randomised controlled trial. Lancet. 2014;383(9927):1483-9. doi: 10.1016/S0140-6736(14)60123-9
19. Li J, Jiang K, Zhao F. Fertility outcome analysis after surgical management of tubal ectopic pregnancy: a retrospective cohort study. BMJ Open. 2015;5(9):e007339. doi: 10.1136/bmjopen-2014-007339
20. de Bennetot M, Rabischong B, Aublet-Cuvelier B, Belard F, Fernandez H, Bouyer J, et al. Fertility after tubal ectopic pregnancy: results of a population-based study. Fertil Steril. 2012;98(5):1271-6.e1-3. doi: 10.1016/j.fertnstert.2012.06.041
21. Fernandez H, Capmas P, Lucot JP, Resch B, Panel P, Bouyer J, et al. Fertility after ectopic pregnancy: the DEMETER randomized trial. Hum Reprod. 2013;28(5):1247-53. doi: 10.1093/humrep/det037
22. Hill MJ, Cooper JC, Levy G, Alford C, Richter KS, DeCherney AH, et al. Ovarian reserve and subsequent assisted reproduction outcomes after methotrexate therapy for ectopic pregnancy or pregnancy of unknown location. Fertil Steril. 2014;101(2):413-9. doi: 10.1016/j.fertnstert.2013.10.027
23. Krag Moeller LB, Moeller C, Thomsen SG, Andersen LF, Lundvall L, Lidegaard Ø, et al. Success and spontaneous pregnancy rates following systemic methotrexate versus laparoscopic surgery for tubal pregnancies: a randomized trial. Acta Obstet Gynecol Scand. 2009;88(12):1331-7. doi: 10.3109/00013409013891912
24. Turan V. Fertility outcomes subsequent to treatment of tubal ectopic pregnancy in younger Turkish women. J Pediatr Adolesc Gynecol. 2011;24(5):251-5. doi: 10.1016/j.jpag.2010.12.007
25. Varma R, Gupta J. Tubal ectopic pregnancy. BMJ Clin Evid. 2012;2012. PMID: 22321966 PMCID: PMC3285146
26. Jamard A, Turck M, Pham AD, Dreyfus M, Benoist G. Fertilité et risque de récidive après traitement chirurgical d’une grossesse extra-utérine: salpingotomie versus salpingectomie [Fertility and risk of recurrence after surgical treatment of an ectopic pregnancy (EP): salpingotomy versus salpingectomy]. J Gynecol Obstet Biol Reprod (Paris). 2016 Feb;45(2):129-38. (in French). doi: 10.1016/j.jgyn.2015.08.005. PMID: 26384840
27. Chen L, Zhu D, Wu Q, Yu Y. Fertility outcomes after laparoscopic salpingectomy or salpingotomy for tubal ectopic pregnancy: a retrospective cohort study of 95 patients. Int J Surg. 2017 Dec;48:59-63. doi: 10.1016/j.ijsu.2017.09.058. PMID: 28951291
28. Lagana AS, Vitale SG, De Dominicis R, Padula F, Rapisarda AM, Biondi A, et al. Fertility outcome after laparoscopic salpingostomy or salpingectomy for tubal ectopic pregnancy: a 12-year retrospective cohort study. Ann Ital Chir. 2016;87:461-5. PMID: 27480601.
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 chi²-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