

The Impact of Different Management Options of Ectopic Pregnancy on Future Fertility

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ABSTRACT

In this study, our aim was to evaluate the subsequent fertility status of women treated with different methods for ectopic pregnancy.

Patients diagnosed with ectopic pregnancy between January 2012 and July 2020 were included in the study. Fertility outcomes of the patients treated with medical or surgical options were questioned.

In the study, 659 patients who met the eligibility criteria were included. A single dose of MTX was administered in 37 patients (32.2%) and two doses of MTX were applied in 14 patients (12.2%) and surgery was preferred in 64 patients (55.7%) in the infertile group. In 213 patients (39.2%) in the fertile group, MTX was administered as a single dose while two doses of MTX and surgery was preferred in 49 patients (9.0%) and 282 patients (51.8%), respectively. No statistically significant difference was detected between the groups according to treatment approaches.

There was no significant difference regarding fertility outcomes following different types of treatments for ectopic pregnancy. For this reason, the methods to be chosen for the treatment of ectopic pregnancy should be evaluated according to the individual factors of the patient.

Keywords: Ectopic pregnancy, methotrexate, salpingectomy, salpingostomy, fertility

Introduction

Ectopic pregnancy is the implantation of the embryo outside the uterine cavity, most commonly located in the Fallopian tubes. The incidence of ectopic pregnancy which is diagnosed clinically and located anywhere is approximately 2% of all pregnancies (1). The most common extrauterine-located pregnancy is observed in the tuba uterina with a rate of 96% (2).

In recent years, early diagnosis of extrauterine pregnancies has become easier due to the advancements owing to imaging methods and the increased frequency of follow-up. The proper management of ectopic pregnancy has also increased as well. The mortality rate due to

ectopic pregnancy constitutes approximately 4% of all pregnancy-associated deaths (3, 4).

History of previous tubal surgery including ectopic pregnancy surgery has been accepted as the highest risk factor for development of ectopic pregnancy (5). Other risk factors that can cause ectopic pregnancy are pelvic inflammatory disease, infertility, having been treated with assisted reproductive techniques, cigarette smoking and in utero exposure to diethylstilbestrol (DES) (5-7).

The treatment method depends on the location of the gestational tissue, the gestational week, the demographic and clinical characteristics of the patients. Management modalities include conservative approach, medical or surgical treatment.

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The treatment model for ectopic pregnancy is important for the patient's future fertility expectations. There are several studies in the literature evaluating future fertility or recurrence risk following treatment of ectopic pregnancy (8,9).

Our aim in this study was to investigate the effect of different treatment options on future fertility in women who were diagnosed as ectopic pregnancy and managed with different treatment methods according to their fertility status.

Materials and Methods

Patients who were treated with different options for ectopic pregnancy at University of Health Sciences Istanbul Kanuni Sultan Suleyman Training and Research Hospital between January 2012 to July 2020 were included in this retrospective cohort study. This study which was conducted according to the principles of the Declaration of Helsinki was approved by the institution's Ethics Committee (KAEK/2020.06.09). At this center, informed consent was obtained from all patients, allowing the use of their blinded clinical data for research purposes.

In our study, we collected data of the patients from the hospital records and we only used medical information in this scientific publication. Current status about the fertility of the participants was obtained through phone call. Patients with previous history of ectopic pregnancy and diagnosis of infertility treated with or without in vitro fertilization (IVF) were excluded from the study. Patients who could not be reached by phone were also excluded from the study.

Age, delivery route, body mass index (BMI), smoking, serum beta human chorionic gonadotropin (β hCG) level value at diagnosis, the localization and size of ectopic pregnancy, treatment modality, fertility status and contraceptive method following ectopic pregnancy treatment were questioned. Surgical method was investigated in women managed with surgery while methotrexate (MTX) dose and success of methotrexate treatment were recorded in those treated with medical options. The presence of suspected ectopic pregnancy mass, gestational sac (GS) and Crown Rump Length (CRL) detected by transvaginal ultrasonography at the time of ectopic pregnancy diagnosis were noted.

The criteria which were used for the diagnosis of ectopic pregnancy are listed hereafter:

- β hCG value showing a plateau course,
- β hCG value over 2000 mIU/mL and no observed gestational sac in the uterine cavity by transvaginal ultrasonography,
- Observation of a pregnancy image outside of the uterus or rupture of ectopic pregnancy on ultrasound examination.

The preferred management methods were single or multiple methotrexate treatment, tubal surgery regarding salpingostomy or salpingectomy through laparoscopy or laparotomy. Methotrexate therapy was preferred in cases with hemodynamic stability, serum β hCG value below 5000, fetal cardiac activity not detected on transvaginal ultrasonography and the patient's compliance with follow-up. Before methotrexate treatment, liver and kidney functions were evaluated, complete blood count and urinalysis were requested. If the results were normal, methotrexate treatment was applied. A single dose of MTX (50 mg/m²) was applied and serum β hCG levels were measured on days 0, 4, and 7 after MTX injection. If the decrease in β hCG values between days 4 and 7 is <15 percent, a second dose of MTX 50 mg/m² IM is administered. Failure of medical therapy was considered when an increase in β hCG levels was observed despite recurrent MTX injections or when the patient's clinical stabilization deteriorated after the first or second MTX injections. They were advised to use a method of contraception for 3 months after the last injection of MTX.

Surgical treatment was preferred in patients who were hemodynamically unstable or with suspected ectopic pregnancy rupture, in breast-feeding patients, in patients with contraindications for methotrexate and in those who could not continue to follow-up. Patients who did not accept medical treatment or had unsuccessful MTX treatment were also considered for surgical therapy. Specimens were sent to the pathologic examination.

Laparoscopy was preferred in patients who were stable hemodynamically for anesthetic consultation. Surgery by laparotomy was performed in remaining patients who were hemodynamically unstable and anesthesia was not suitable for laparoscopy.

In terms of future fertility, the diagnosis was made in cases where there was no pregnancy detected despite unprotected intercourse for 1 year under

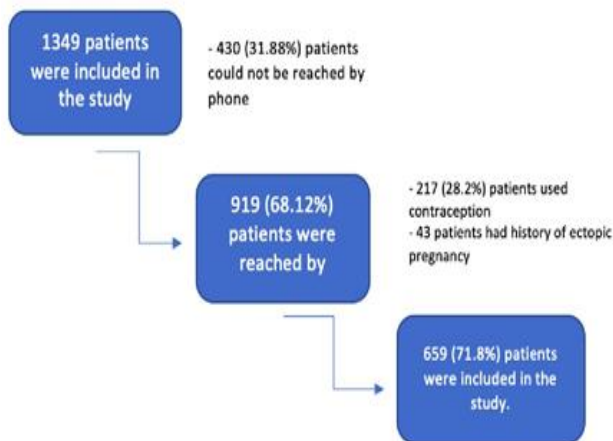


Fig.1. Flow-Chart of the Study Population

the age of 35 and 6 months above the age of 35 in the absence of any other infertility factor.

The study population was divided into two groups according to their fertility status. All demographic and clinical characteristics of the patients were compared between the groups.

Statistical Analysis: SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Normality of demographic data was evaluated with the Shapiro-Wilk test. Interquartile range and median were accepted for data that did not show normal distribution and standard deviation and mean value were accepted for data with normal distribution. Independent Samples T test was used for normal distributed data. The Chi-square test was used in the analysis of categorical variables. Significant was defined as a p value less than 0.05.

Results

A total of 1349 women between the ages of 18-44 who were diagnosed with ectopic pregnancy was assessed for our study. Of those, 430 patients could not be reached by phone call. Since there was no expectation of pregnancy due to contraceptive use (104 patients with IUD (Intrauterin device), 74 patients with COC (combined oral contraceptive), 2 patients with coitus interruptus, 2 patients with BTL, 35 patients with condom), 217 women were not included. Additionally, 43 patients did not meet the eligibility criteria for the study due to having a history of previous ectopic pregnancy. Figure 1 summarizes the eligibility criteria of the study.

As shown in Figure 1, 659 (71.8%) patients were included in the study. Infertility was detected in

115 patients (17.5%). The mean age of patients was 31.9 ± 6.5 years in the infertile group and 29.0 ± 5.2 years in the fertile group (Table 1). There was a statistically significant difference between the groups in terms of age ($p < 0.001$). However, no statistically significant difference was found regarding BMI, delivery type and smoking between the groups ($p > 0.005$).

In Table 2, the treatment options including MTX single dose, MTX multiple doses and surgery were evaluated in the infertile and fertile groups. A single dose of MTX was administered in 37 patients (32.2%) and two doses of MTX were applied in 14 patients (12.2%) and surgery was preferred in 64 patients (55.7%) in the infertile group. In 213 patients (39.2%) in the fertile group, MTX was administered as a single dose while two doses of MTX and surgery was preferred in 49 patients (9.0%) and 282 patients (51.8%), respectively. No statistically significant difference was detected between the groups according to treatment approaches ($p = 0.290$).

In Table 3, fertility outcomes were evaluated in patients undergoing different treatment modalities. Infertility was diagnosed in 48 patients (18.3%) who were managed successfully with MTX injection while it was detected in 3 patients (6%) who were operated due to unsuccessful MTX treatment. There was no statistically significant difference between the groups in terms of success of MTX treatment ($p = 0.085$).

Groups were also compared based on their ultrasonographic findings of ectopic pregnancy including only a mass, GS and CRL. There was no significant difference between the infertile and fertile groups regarding this characteristics ($p = 0.598$) (Table 4). There was no significant difference between the groups in terms of hospitalization requirement and serum β hCG levels ($p = 0.516$) (Table 5). Table 6 shows the comparison of groups according to surgical methods (salpingectomy vs salpingostomy) and no statistically significant difference was found ($p = 0.329$). When the patients were compared based on surgical route (laparoscopy vs laparotomy), no statistical significance was found ($p = 0.825$) (Table 7).

Discussion

We aimed to evaluate the fertility outcomes of patients treated for ectopic pregnancy in the future. In our study, the fertility outcomes of the patients who were treated for ectopic pregnancy during the post-treatment period were evaluated.

Table 1. Demographic and Clinical Characteristics of The Patients

	All population (n=659) (mean±SD or no(%)) (min-max)	Infertile group (n=115) (mean±SD or no(%)) (min-max)	Fertile group (n=544) (mean±SD or no(%)) (min-max)	p***
Age (years)	25.2±5.5 (18-44)	31.9±6.5 (19-44)	29.0±5.2 (18-43)	<.001*
BMI (kg/m2)	26.8±6.1 (17.1-47.8)	27.7±6.4 (17.2-47.8)	26.6±6.0 (17.1±45.2)	.496*
Type of birth				
No birth	219 (33.2%)	49 (42.9%)	170 (31.3%)	
Vaginal delivery	210 (31.9%)	34 (29.6%)	176 (32.4%)	.052**
CS	230 (34.9%)	32 (27.8%)	198 (36.4%)	
Cigarette use				
Present	32 (4.9%)	7 (6.1%)	25 (4.6%)	.499**
Absent	627 (95.1%)	108 (93.9%)	519 (95.4%)	

Abbreviations: BMI: body mass index; CS: cesarean delivery

*Independent Samples T test, **Chi-Square tests

*** p value <0.05 is significant

Table 2. The Relationship Between Treatment Options and Fertility

	Infertile group (n=115) (number (%))	Fertile group (n=544) (number (%))	p**
MTX single dose	37 (32.2%)	213 (39.2%)	
MTX multiple dose	14 (12.2%)	49 (9.0%)	
Surgery	64 (55.7%)	282 (51.8%)	.290*

Abbreviations: MTX: methotrexate

*Chi-Square Tests

** p value <0.05 is significant

Table 3. Comparison of Patients Who Had MTX Therapy Alone and Who Underwent Surgery After MTX Failure

	Infertile group (n=51) (number (%))	Fertile group (n=262) (number (%))	p**
MTX	48 (18.3%)	215 (81.7%)	
Surgery following MTX failure	3 (6%)	47 (94%)	.085*

Abbreviations: MTX: methotrexate

*Chi-Square Tests

** p value <0.05 is significant

It has been found that only age affects fertility status after management of ectopic pregnancy. No statistically significant difference was found between infertile and fertile groups regarding treatment approaches. In addition, serum β hCG levels during the diagnosis of ectopic pregnancy

and the size of ectopic pregnancy did not result in a significant difference about fertility status. Considering the preservation of fertility, it was observed in our study that the choice of treatment for ectopic pregnancy was not the only criterion.

Table 4. Fertility Comparison According To Ectopic Pregnancy Mass

	Infertile group (n=115) (number (%))	Fertile group (n=544) (number (%))	p**
Gestational mass	102 (17.2%)	492 (82.8%)	
GS	3 (14.3%)	18 (85.7%)	
CRL	10 (22.7%)	34 (77.3%)	.598*

Abbreviations: GS: gestasyonel sac, CRL: Crown Rump Length

*Chi-Square Tests

** p value <0.05 is significant

Table 5. Comparison of Patients According To Serum Beta-hCG Values At The Time of Diagnosis of Ectopic Pregnancy

	Infertile group (n=115) (mean±SD)	Fertile group (n=544) (mean±SD)	p***
Hospitalization (days)	4.6±3.4	4.7±3.2	.210*
Serum βhCG levels (IU/mL)			
<1000	30 (15.4%)	165 (84.8%)	
1001-5000	55 (17.2%)	265 (82.8%)	.516**
5001-10000	15 (18.8%)	65 (81.3%)	
>10000	15 (23.4%)	49 (76.7%)	

Abbreviations: beta-hCG: beta-human chorionic gonadotropin

*Independent Samples T test,

**Chi-Square Tests

*** p value <0.05 is significant

Table 6. Comparison of Patients In Terms of The Difference Between Surgical Methods

Surgical methods	Infertile group (n=67) (number (%))	Fertile group (n=329) (number (%))	p**
Salpingectomy	61 (16.4%)	310 (83.6%)	.329*
Salpingostomy	6 (24%)	19 (76%)	

*Chi-Square Tests

** p value <0.05 is significant

Among the studies comparing salpingectomy and salpingostomy in the literature, Becker et al. previously recommended laparoscopic salpingostomy in patients at risk for infertility. However, no significant difference was found between conservative and radical treatments in patients without risk factors (10). In parallel to our results, other studies in the literature comparing salpingostomy and salpingectomy did

not detect a significant difference in terms of fertility (11-14).

In the study of Chen et al. with 96 patients, similar to our study, no significant difference was detected between salpingotomy and salpingectomy in terms of fertility (15). In the study of Bennetot et al., no significant difference was observed between methotrexate treatment and laparoscopic salpingostomy and salpingectomy in terms of fertility which is consistent with our study.

Table 7. Comparison of patients in terms of Laparoscopy and Laparotomy

	Infertile group (n=67) (number (%))	Fertile group (n=329) (number (%))	p**
Laparoscopy	35 (17.3%)	167 (82.7%)	.825*
Laparotomy	32 (16.5%)	162 (83.5%)	

*Chi-Square Tests

** p value <0.05 is significant

However, it is emphasized that it would be more appropriate to choose conservative treatments in patients with risk factors for infertility. It is recommended that the treatment should be chosen according to the patient's clinical characteristics, presence of tubal rupture and serum β hCG levels (16).

In another study conducted in patients who underwent salpingotomy due to ectopic pregnancy, infertility was found in 21.3% and no difference was observed between salpingectomy and salpingotomy in terms of fertility outcomes (15). Pereira et al., in a study conducted with 144 patients, compared MTX therapy and salpingectomy in women with ectopic pregnancy. They concluded that it did not change the ovarian response and IVF results in the subsequent IVF treatment (17).

Baggio et al. compared MTX injection, surgery and expectant management in patients with ectopic pregnancy and observed that intrauterine pregnancy was higher in follow-up group. For this reason, they recommended waiting for treatment in patients with fertility expectations as long as the patient's clinic would be appropriate. Methotrexate treatment option should be kept in the foreground for women who cannot be administered expectant management (18). These results may be interpreted that tubal tissue may deteriorate structurally or functionally causing infertility although it is preserved during the surgical treatment of ectopic pregnancy.

Our study made a significant contribution to the literature due to large sample size and comparison of three different treatment options. Retrospective data collection and reaching the patients about fertility status through phone call could be accepted as the limitations of the study.

The methods preferred for the treatment of ectopic pregnancy were not found to be superior to each other on subsequent fertility. The most important thing to decide on the treatment method should be the patient's clinical condition.

For this reason, these women should be evaluated and informed in detail.

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