Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Reproductive Outcomes After Methotrexate Therapy for Ectopic Pregnancy

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Article Info

10.24200/jogcr.11.4.323

Received: 2025/08/16
Accepted: 2025/11/26
Published Online: 23 Mar. 2026

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ABSTRACT

Background & Objective: Ectopic Pregnancies (EP) account for about 2% of pregnancies. If diagnosis and treatment are not rapidly performed, it may result in an acute emergency status that can account for about 6% of pregnancy-related deaths. The present study was conducted with aim to evaluate reproductive outcomes following methotrexate therapy for ectopic pregnancy, including probabilities of spontaneous pregnancy, use of Assisted Reproductive Technology (ART), live birth, abortion, and recurrent Ectopic Pregnancy (EP).

Materials & Methods: This retrospective-prospective cohort study was conducted at Shariati Hospital in Tehran, Iran. The outcomes of pregnancy were analyzed in 123 women treated with methotrexate for EP. Data collected from hospital records included maternal age, gestational age, parity, smoking status, and medical history. Patients were followed up to assess future pregnancy outcomes, including spontaneous pregnancy, live birth, abortion, recurrent EP, and need for ART.

Results: The mean age of women was 31.3±6.0 years and the mean gestational age was 6.6±2.1 weeks. The average number of prior pregnancies was 1.2±1.2. Among the participants, 21% had a history of infertility, 33% had prior miscarriages, and 13% had a history of ectopic pregnancies. Over a two-year follow-up, 44% pursued additional pregnancies, 38% conceived naturally, and 18% used Assisted Reproductive Technology (ART). More than half of the pregnancies occurred within 7 to 48 months after methotrexate treatment, and there were no recurrences of ectopic pregnancy or abortions reported.

Conclusion: The findings of this study suggest that experiencing an ectopic pregnancy should not be a cause for concern regarding adverse outcomes in future pregnancies. Women can be reassured that the likelihood of achieving a subsequent pregnancy is favorable within two years after methotrexate treatment for EP.

Keywords: Ectopic pregnancy, Methotrexate, Salpingectomy, Pregnancy outcome

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1. Introduction

Ectopic Pregnancies (EP) account for about 2% of pregnancies (1). More than 96% of ectopic pregnancies occur in the fallopian tubes (2). While in the ovary, the cornua of the uterus and even inside the abdomen may be occur (3). EP occurs when a growing blastocyst is implanted in a location other than the endometrium of the uterine cavity. Theoretically, the predisposing factors for tubal EP are that prevent migration of zygote to the endometrium. These may be inherent anatomical defects in the fallopian tube epithelium, hormonal factors that interfere with the normal transmission of the zygote, or pathological conditions that affect the normal functioning of the fallopian tube.

If diagnosis and treatment not rapidly performed, it may be result to an acute emergent status that can account for about 6% of pregnancy-related deaths (4). Advances in diagnostic and therapeutic methods globally significantly reduced maternal mortality from EP, but its prevalence has increased in developed countries following the use of assisted reproductive techniques (5,6). A review of studies shows that EP has increased in Iran in recent years (7). Diagnosis is made with 100% accuracy with the concentration of β-HCG ≥1500 IU/L and absence of observation of gestational sac inside the uterine cavity via transvaginal ultrasound. Therefore, the level of β-HCG titrate together with transvaginal ultrasound findings allows early diagnosis of EP (8). Treatment is surgical or medical, usually surgical methods are the basis of treatment, but early diagnosis allows the use of medical

treatments **(3)**. Treatment for ectopic pregnancy may result in the loss of a fallopian tube and possibility of infertility, reduced chances of future fertility, and stress of recurrence. Therefore, it can affect the life of women in the reproductive age **(9)**.

Methotrexate (MTX), as a folic acid analog, inhibits dihydrofolate reductase enzyme activity and purine and pyrimidine synthesis that required for DNA and RNA production in rapidly dividing cells, including trophoblast tissue. This drug was first introduced in the early 1980s for management of EP **(10)**. Intramuscular MTX can be considered in patients who are hemodynamically stable, have no absolute contraindications, and are willing to comply with ongoing surveillance until complete pregnancy resolution. Absolute contraindications to methotrexate therapy include breastfeeding, intrauterine pregnancy, hepatic, renal, or hematologic disorders and known sensitivity to methotrexate. Relative contraindications to methotrexate therapy include gestational sac greater than 4 cm, embryonic cardiac motion via transvaginal ultrasound and high initial β-hCG concentration (>5,000 mIU/mL) **(11)**. A time interval of 6 months after methotrexate therapy until the future pregnancy is necessary to reduce the damaging effects of MTX on chromosomes **(12)**.

Since few studies have been conducted on this field in Iran, the present study was conducted with aim to investigate the outcomes of future fertility in women who received methotrexate for EP.

2. Materials and Methods

This retrospective- prospective cohort study was conducted at Shariati Hospital, Tehran, Iran.

The records of all women (n=150) with a history of ectopic pregnancy who were hospitalized at Shariati Hospital in Tehran between 2017 and 2022 were reviewed, resulting in the inclusion of 123 participants (27 women did not participate in telephone follow-up). The extracted data included: maternal age, gestational age, parity, number of children, daily smoking, and history of miscarriage, infertility, ectopic pregnancy, abdominal surgery, Pelvic Inflammatory Disease (PID), and β-hCG concentration. These patients were followed and their information regarding future fertility after treatment of ectopic pregnancy with methotrexate, including spontaneous pregnancy, need for Assisted Reproductive Technology (ART), live birth, abortion, and recurrent ectopic pregnancy were recorded.

Women's demographic information and records were extracted from the hospital's HIS files; then the patients were followed up by telephone to ask about their potential for future pregnancy, and above spontaneous pregnancy or need for ART, and to document the pregnancy outcomes.

Data were analyzed using SPSS software (version 24) (Inc., Chicago, Illinois, USA). Frequency and percentage were used to describe qualitative variables, and mean and standard deviation were used for quantitative variables. $P<0.05$ was considered statistically significant.

3. Results

In the current study, 123 women with a mean age of 31.25±5.97 years were included. The mean gestational age was 6.63±2.12 weeks. The mean number of pregnancies was 1.23±1.21. Twenty-one percent of participants had a history of infertility, about 33% had a history of abortion, and more than 13% had a history of ectopic pregnancy. Sixty-six percent had a history of abdominal surgery. More than 80% of women had never smoked. Additionally, 23% of the women had a history of PID (Table 1).

During a two-year follow-up, approximately 44% of the women did not pursue future fertility. Fifty-six percent elected to pursue future pregnancy, with 38% achieving pregnancy spontaneously and 18% conceiving with ART. Most pregnancies occurred within 7 to 48 months after methotrexate treatment (Figure 1).

There was no case of recurrent ectopic pregnancy or abortion among the participants (Table 2).

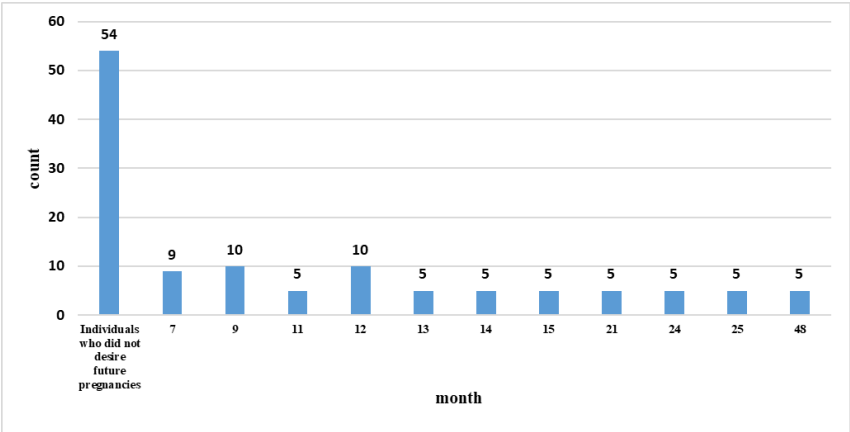


Figure 1. Time interval for pregnancy after treatment with methotrexate

Table 1. **Patient baseline demographics characteristics**

Characteristics		Total (N=123) N (%)
Mean of maternal age (years)		31.25±5.97
History of abortion	yes	41(33.33)
	no	82(66.67)
History of infertility	yes	26(21.14)
	no	97(78.86)
History of ectopic pregnancy	yes	17(13.82)
	no	106(86.18)
History of abdominal surgery	Cesarean section	54(43.90)
	Diagnostic laparoscopy	9(7.32)
	EP laparoscopy	9(7.32)
	Appendectomy	3(2.44)
	other	7(5.69)
History of Smoking	no	41(33.33)
	yes	20 (16.28)
	no	103(83.74)
History of PID	yes	28(22.76)
	no	95(77.24)

Table 2. **Future pregnancy after treatment with methotrexate**

Characteristics		Total(N=123) N (%)
Pregnancy	Natural	47(38.21)
	IVF	22(17.89)
	Individuals who did not desire future pregnancies	54(43.90)
Abortion	yes	0(0.0)
	no	69(100.0)
Recurrent ectopic pregnancy	yes	0(0.0)
	no	69(100.0)

4. Discussion

Ectopic pregnancy is usually treated with minimally invasive surgical methods or methotrexate injection **(13)**. Approximately 35% of ectopic pregnancies are candidates for primary therapy with methotrexate **(14)**. Methotrexate therapy can be considered for patients with confirmed or high suspicion for ectopic pregnancy who are hemodynamically stable with no evidence of rupture **(15)**. The purpose of the present study was to investigate the pregnancy rate and its consequences after methotrexate therapy for ectopic pregnancy. This study identified a history of cesarean section and prior abortion as the most significant risk factors for ectopic pregnancy. There has been a marked rise in abdominal surgical procedures, particularly cesarean sections, over the past few decades **(16,17)**. Scientific sources suggest that uterine damage following a miscarriage may increase the risk of subsequent ectopic pregnancy **(18)**, which could help explain the findings observed in this study. It is noteworthy that administration of methotrexate may correlate with a reduced incidence of miscarriage; however, this assertion cannot be conclusively substantiated at this time.

In the present study, about 44% of women did not try to pregnancy again, which is somewhat consistent with the study of Tabatabaii Bafghi et al., **(19)**. In their study, 33% of women had not pregnancy during the follow-up after treatment with methotrexate, which is less than the present study. The observed difference could be due to the different sample size with our study.

In our study, approximately 56% of women opted for future pregnancy. In the present study, more than 38% of women achieved spontaneous pregnancy after treatment, which is consistent with the results of other studies **(12,20,21)**. Several studies have shown that subsequent spontaneous intrauterine pregnancy rates are similar between women treated with methotrexate and those treated with salpingostomy, with rates ranging from 36% to 64% **(22,23)**. Studies evaluating ovarian reserve after treatment with methotrexate for EP showed no impact on future ovarian reserve **(24,25)**. In our study, more than half of the women became pregnant between 7 and 48 months after receiving methotrexate, which is similar to other studies in this field with a slight difference. On the other hand, it may be advisable to allow a 6-month interval after methotrexate treatment to mitigate potential chromosomal risks during follicular division **(26,27)**. In the present study, about 18% of women used ART for their future pregnancy, which is in line with other studies **(28)**.

The results of the present study indicated no recurrence of ectopic pregnancy among the women. Research shows that the risk of recurrent EP in women with a history of EP is approximately 6-18% **(29)**. This risk may be influenced by the treatment method for EP, a history of pelvic infections, hemoglobin levels **(30)**,

maternal age, and higher gravidity **(30,31)**. The observed differences between this study and others may be partially attributable to the difference in the sample size. The risk of subsequent ectopic pregnancy is approximately 10% following either methotrexate or salpingostomy **(32)**. Generally, 50-80% of women treated with methotrexate subsequently achieve a viable intrauterine pregnancy, while 10-20% experience a recurrent ectopic pregnancy **(33)**. In essence, fertility outcomes after ectopic pregnancy depend more on individual patient characteristics than on the treatment method **(34)**.

One limitation of this study is that it was conducted at a single center, which may limit the generalizability of the results to other centers. The strengths of this study include its longitudinal design with a 48-month follow-up, enabling a thorough evaluation of long-term clinical outcomes after methotrexate therapy. Additionally, no cases of recurrent ectopic pregnancy or miscarriage were observed during follow-up, reinforcing the efficacy and safety of the treatment approach.

5. Conclusion

Evidence from studies of pregnancy outcomes in women treated with methotrexate for ectopic pregnancy does not suggest that the treatment adversely affects future pregnancy outcomes or ovarian reserve. The occurrence of EP should not raise concerns about adverse outcomes in future pregnancies. Women can be reassured that the success rate of a subsequent intrauterine pregnancy after EP treatment with methotrexate within two years is high.

6. Declarations

Acknowledgments

The authors gratefully acknowledge the financial support provided by the Research and Technology Vice-Chancellor of Tehran University of Medical Sciences. Additionally, the authors would like to express their sincere appreciation to Hossein Rahimi for his valuable contributions in this study.

Ethical Considerations

This article is the result of a research project that was approved by the ethical committee of Tehran University of Medical Sciences, Tehran, Iran (Code of Ethics: IR.TUMS.MEDICINE.REC.1401.013). Information from the records was used, and patients gave consent for the use of their file information for scientific research upon admission, with the patients' names kept confidential.

Authors' Contributions

M.T and S.H designed and conducted the research. M.T reviewed the article. Both authors approved the final manuscript and took responsibility for the integrity of the data.

Conflict of Interest

The authors declare no conflict of interest.

Fund or Financial Support

The authors declare no fund.

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How to Cite This Article:

Talebian M, Hosseinimousa S. Reproductive Outcomes After Methotrexate Therapy for Ectopic Pregnancy. J Obstet Gynecol Cancer Res. 2026;11(4):323-328.

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