

Factors Affecting Success in Single-Dose Methotrexate Treatment in Ectopic Pregnancies and 10 Years of Clinical Experience

Emre Mat,¹ Ismail Bağlar,² Esra Keles,¹ Ahmet Özkul,²
Lokman Tekin Ertekin²

¹Department of Gynecologic Oncology, Kartal Lütfi Kırdar City Hospital, Istanbul, Türkiye

²Department of Obstetrics And Gynecology, Kartal Lütfi Kırdar City Hospital, Istanbul, Türkiye

Submitted: 08.07.2025

Revised: 31.07.2025

Accepted: 05.08.2025

Correspondence: Emre Mat,
Department of Gynecologic Oncology, Kartal Lütfi Kırdar City Hospital, Istanbul, Türkiye

E-mail: emremat63@gmail.com



Keywords: Ectopic pregnancy; methotrexate; β -hCG.



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ABSTRACT

Objective: The aim of this study was to evaluate the success rate of ectopic pregnancy cases treated with single-dose methotrexate in an advanced gynecology and obstetrics center over a 10-year period and the factors affecting the response to treatment.

Methods: A total of 120 patients who were diagnosed with ectopic pregnancy and treated with single dose systemic methotrexate between January 2014 and December 2024 were retrospectively included in the study. Demographic data, clinical findings, baseline β -hCG levels, treatment responses, and rates of conversion to surgery if necessary were analyzed.

Results: In the study, treatment success with a single dose of methotrexate was 78.3%. The rate of second dose methotrexate administration was 13.3% and the rate of surgical requirement was 8.3%. Baseline β -hCG level was found to be the most important factor affecting treatment success ($p<0.001$).

Conclusion: Single-dose methotrexate treatment is an effective and safe treatment option in cases of ectopic pregnancy with appropriate criteria. Careful patient selection based on baseline β -hCG level and ectopic mass characteristics may increase treatment success and decrease the need for surgery.

INTRODUCTION

Ectopic pregnancy is an obstetric emergency that occurs when the fertilized ovum implants outside the endometrial cavity and can have serious consequences, accounting for approximately 1.5-2% of pregnancies.^[1] With the development of early diagnosis possibilities, medical treatment options have come to the forefront as an alternative to surgery. Among these options, the most commonly used method is single dose systemic methotrexate administration.^[2]

Methotrexate is an antifolate agent that terminates pregnancy by stopping the proliferation of trophoblast cells. It is frequently preferred in clinical practice due to its ease of administration, low risk of complications and reduced hospital stay.^[3]

However, some factors affecting the success of this treatment method are still controversial. In particular, β -hCG level at the time of diagnosis, gestational week and characteristics of the ectopic mass may directly affect the treatment response.^[4] In this study, we evaluated the efficacy of single-dose methotrexate treatment administered in an advanced center in the last ten years and examined the factors affecting success.

MATERIALS AND METHODS

This retrospective descriptive study included ectopic pregnancy cases treated with single dose systemic methotrexate (MTX) at an advanced gynecology and obstetrics center between January 2014 and December 2024. Ethics committee approval was obtained (Approval No: 2025/010.99/15/25. Date: 30/04/2025) and the study was

conducted in accordance with the principles of the Declaration of Helsinki.

A total of 120 patients who were hemodynamically stable, without fetal cardiac activity, with a mass diameter of 4 cm and a β -hCG level below 5000 IU/L were included in the study. Patients with MTX contraindications, ruptured or unstable cases were excluded.

All patients received MTX 50 mg/m² intramuscularly according to body surface area. β -hCG levels were checked on days 4 and 7; $\geq 15\%$ decrease was considered as success criteria. A second dose was administered to patients who were deemed necessary, and those who did not respond to treatment were taken to surgery.

Data were obtained from patient files and analyzed with SPSS 26.0 program. Numerical variables were presented as mean $\pm$ standard deviation, categorical data were presented as frequency and percentage. Appropriate statistical tests were used for intergroup comparisons; $p < 0.05$ was considered significant.

RESULTS

In our study, 120 patients who were diagnosed with ectopic pregnancy and treated with single dose methotrexate in a 10-year period were retrospectively evaluated. The mean age of the patients was 30.6 ± 4.9 years and the mean gestational age was 6.4 ± 0.9 weeks. Fifteen percent of the patients ($n=18$) had a previous history of ectopic pregnancy. The mean serum baseline β -hCG level was 2340 ± 1080 IU/L and the mean mass size was 26.8 ± 6.2 mm on transvaginal ultrasonography. Sociodemographic findings of the patients are given in Table 1.

In the study, 94 patients (78.3%) were successfully treated with a single dose of methotrexate. 16 patients (13.3%) received a second dose of methotrexate because the decrease in β -hCG on days 4 and 7 was not sufficient. The remaining 10 patients (8.3%) underwent surgical interven-

tion due to non-response to treatment or clinical deterioration. In successfully treated patients, the mean time to decrease in serum β -hCG level to <5 IU/L was 23.4 ± 6.8 days. No patient developed complications after treatment. The patients' initial β -hCG levels and single-dose MTX treatment success levels are given in Table 2.

When the patients who successfully responded to single dose MTX treatment were compared with those who failed, the only variable that made a significant difference was baseline β -hCG level ($p < 0.001$). There was no statistically significant difference in age, gestational week, transvaginal ultrasonography mass diameter and history of infertility.

In line with these data, our study concluded that the baseline β -hCG level is the strongest factor determining the success of single dose methotrexate treatment. Especially in cases with >3000 IU/L, the failure rate increases.

DISCUSSION

In this study, 78.3% treatment success rate was obtained in ectopic pregnancy cases treated with a single dose of systemic methotrexate. This result is consistent with the range of 64-94% reported in the literature.^[5] The baseline serum β -hCG level, which is one of the most important determinants of success rate, was found to be significantly higher in the unsuccessful group in our study; this is in line with recent studies.^[6,7]

Jurkovic et al.^[8] showed that there was no difference between methotrexate and expectant management in patients with β -hCG levels <1500 IU/L, but methotrexate was more effective at higher levels. Similarly, studies by Papageorgiou D et al.^[9] identified the baseline β -hCG level as the strongest prognostic factor.

In our study, we observed that hCG levels above 3000 IU/L increased the risk of failure, which supports Capozzi et al.^[10] report of a 64% failure rate. Cases with a mass di-

Table 1. Demographic and clinical characteristics of the cases

Feature	Single dose MTX Successful (n=94)	Single dose MTX Failure (n=26)	p value
Age (years, mean $\pm$ SD)	30.2 ± 4.6	31.4 ± 5.2	0.18
Gestational week (weeks)	6.3 ± 0.8	6.7 ± 1.1	0.15
Baseline β -hCG (IU/L)	1925 ± 890	3960 ± 1110	<0.001
Ectopic mass diameter (mm)	25.6 ± 5.4	29.8 ± 7.1	0.07
History of ectopic pregnancy (%)	12 (12.8)	6 (23.1)	0.21
History of infertility (%)	14 (14.9)	6 (23.1)	0.37
History of pelvic surgery (%)	22 (23.4)	6 (23.1)	0.96
Time to reset β -hCG (days)	23.4 ± 6.8	-	-
Need for second dose of methotrexate (n, %)	10 (10.6)	6 (23.1)	0.09
Rate of transition to surgery (n, %)	0	10 (38.4)	<0.001

MTX: Methotrexate, p value of <0.05 indicates a significant difference.

Table 2. Treatment success and failure rates according to baseline β -hCG level

Baseline β -hCG Level (IU/L)	Number of Patients (n)	With a single dose of MTX	
		Successful Treatment (n, %)	Failed Treatment (n,%)
<500	10	10 (100)	0 (0)
500-999	16	15 (93.7)	1 (6.3)
1000-1499	18	16 (88.8)	2 (11.2)
1500-1999	20	17 (85.0)	3 (15.0)
2000-2499	16	13 (81.2)	3 (18.8)
2500-2999	12	9 (75.0)	3 (25.0)
3000-3499	10	5 (50.0)	5 (50.0)
3500-3999	8	3 (37.5)	5 (62.5)
4000-4499	6	2 (33.3)	4 (66.7)
≥ 4500	4	1 (25.0)	3 (75.0)

MTX: Methotrexate, p value of <0.05 indicates a significant difference.

ameter >3.5cm on transvaginal ultrasonography have also been associated with lower success rates.^[11]

In failed cases, a second dose of methotrexate was sufficient in some patients, while other patients required surgical intervention. This shows that the second dose can be a safe and effective option.^[12] However, it is emphasized that patient selection criteria should be determined more carefully to reduce this need.^[13]

In the literature, the advantages of the single-dose protocol such as short hospitalization time and low cost are pointed out, but it is also stated that it may not be suitable for all patients and individualized patient selection gains importance.^[14,15] In the systematic review by Tang et al.,^[16] it was emphasized that low progesterone levels and mild clinical symptoms may also predict success.

No serious complications were reported in our study, supporting the safety of the protocol. Nevertheless, patients should be closely monitored due to rare hepatotoxicity and gastrointestinal side effects.^[17,18]

In conclusion, early diagnosis, appropriate patient selection and regular β -hCG monitoring increase the success of single-dose methotrexate treatment and decrease the need for surgery. To reduce the risk of failure, β -hCG level, mass diameter and clinical findings should be evaluated together.^[19,20]

The strengths of our study include the fact that it was based on 10 years of data, the number of patients was sufficient and the treatment protocol was standardized. However, its retrospective nature, lack of some clinical data, and single-center nature are factors that limit the generalizability of the results. These findings should be supported by multicenter, prospective studies.

Conclusion

Single dose methotrexate offers an effective and safe treatment option in appropriately selected cases of ectopic

pregnancy. The 78.3% success rate obtained in our study is consistent with the literature. It has been observed that baseline β -hCG level, especially at values above 3000 IU/L, increases the risk of treatment failure. Therefore, this parameter should be one of the main determinants in patient selection. The absence of complications supports the safety of the protocol and the second dose is an effective alternative that reduces the need for surgery. Evaluation of hormonal and biochemical markers in further studies may further strengthen patient selection processes.

Ethics Committee Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of University of Health Sciences Turkey, Kartal City Hospital (Date: 30.04.2025, Decision No: 2025/010.99/15/26).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: E.M., İ.B., E.K., A.Ö.; Design: L.T.E., İ.B., E.K., A.Ö.; Supervision: E.M., E.K., A.Ö.; Fundings: E.M., E.K., İ.B., L.T.E.; Materials: İ.B., E.K.; Data collection &/or processing: E.K., İ.B.; Analysis and/or interpretation: A.Ö., E.K.; Literature search: E.K., A.Ö., L.T.E.; Writing: E.M., İ.B., L.T.E.; Critical review: E.M., E.K., İ.B.

Conflict of Interest

None declared.

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Ektopik Gebeliklerde Tek Doz Metotreksat Tedavisinde Başarıyı Etkileyen Faktörler ve 10 Yıllık Klinik Deneyim

Amaç: Bu çalışmada, ileri düzey bir kadın hastalıkları ve doğum merkezinde, 10 yıllık süreçte tek doz metotreksat ile tedavi edilen ektopik gebelik olgularının başarı oranı ile tedaviye yanıtı etkileyen faktörlerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya Ocak 2014-Aralık 2024 tarihleri arasında ektopik gebelik tanısı konmuş ve tek doz sistemik metotreksat tedavisi uygulanan toplam 120 hasta retrospektif olarak dâhil edilmiştir. Hastaların demografik verileri, klinik bulguları, başlangıç β -hCG düzeyleri, tedavi yanıtları ve gerekirse cerrahiye geçiş oranları analiz edilmiştir.

Bulgular: Çalışmada tek doz metotreksat ile tedavi başarısı %78.3 olarak saptanmıştır. İkinci doz metotreksat uygulaması %13.3, cerrahi gereksinim oranı ise %8.3 olarak bulunmuştur. Başlangıç β -hCG düzeyinin tedavi başarısını etkileyen en önemli faktör olduğu tespit edilmiştir ($p<0.001$).

Sonuç: Tek doz metotreksat tedavisi, uygun kriterleri taşıyan ektopik gebelik olgularında etkili ve güvenli bir tedavi seçeneğidir. Başlangıç β -hCG düzeyi ve ektopik kitle özellikleri dikkate alınarak hasta seçiminin dikkatli yapılması, tedavi başarısını artırabilir ve cerrahiye olan gereksinimi azaltabilir.

Anahtar Sözcükler: Ektopik gebelik; metotreksat; β -hCG.