

## Is it necessary to check $\beta$ -hCG levels on day 4 after single-dose methotrexate treatment of ectopic pregnancy? A retrospective cohort study

Dış gebelikte tek doz metotreksat tedavisinden sonra 4. günde  $\beta$ -hCG düzeyine bakılması gerekir mi? Retrospektif bir kohort çalışması

Emre Erdem TAS

Ankara Yıldırım Beyazıt Üniversitesi Kadın Hastalıkları ve Doğum Ana Bilim Dalı, Ankara Bilkent Şehir Hastanesi Kadın Doğum Kulesi, Türkiye

### ABSTRACT

**Aim:** This study aimed to investigate the usefulness of the percentage change in serum  $\beta$ -hCG levels from days 1 to 7 for predicting treatment success in patients treated with a single dose of methotrexate for tubal ectopic pregnancy.

**Materials and Method:** This retrospective observational study investigated 74 patients treated with a single-dose methotrexate regimen for tubal ectopic pregnancy at a tertiary hospital between January 2020 and December 2023. Patients were subdivided into two groups based on reduction in serum  $\beta$ -hCG levels between days 4 and 7:  $<15.0\%$  - "successful treatment" or  $\geq 15.0\%$  - "need a second dose methotrexate". Then, the percentage change in serum  $\beta$ -hCG levels between days 1 and 7 and its usefulness in predicting "successful treatment" were analyzed.

**Results:** Treatment was considered successful in 66 of the 74 patients (86.5%). There was a negative linear correlation between treatment success and percentage change in serum  $\beta$ -hCG levels from day 1 to day 7 ( $p<0.001$ ). ROC curve analyses revealed that the sensitivity of treatment success prediction decreased with increasing percentage change in serum  $\beta$ -hCG levels from days 1 to 7. The sensitivity and specificity of the  $-25.0\%$ ,  $0.0\%$ , and  $+25.0\%$  changes in serum  $\beta$ -hCG levels from day 1 to day 7 for predicting treatment success were  $100.0\%$ - $41.0\%$ ,  $90.0\%$ - $93.7\%$ , and  $80.0\%$ - $96.9\%$ , respectively.

**Conclusion:** Monitoring the percentage change in serum  $\beta$ -hCG levels from days 1 to 7 may effectively replace the traditional protocol, particularly when patient compliance is challenging or when day 4 measurements are impractical.

**Keywords:** Ectopic pregnancy, methotrexate, chorionic gonadotropin, treatment outcome

### ÖZ

**Amaç:** Bu çalışma, tubal ektopik gebelik nedeniyle tek doz metotreksat ile tedavi edilen hastalarda tedavi başarısını öngörmek için serum  $\beta$ -hCG düzeylerinde 1. ve 7. günler arasındaki yüzde değişimin yararlılığını araştırmayı amaçladı.

**Gereç ve Yöntemler:** Bu retrospektif gözlemsel çalışmada, Ocak 2020 ile Aralık 2023 arasında üçüncü basamak bir hastanede tubal ektopik gebelik nedeniyle tek doz metotreksat tedavisi uygulanan 74 hasta araştırıldı. Hastalar, 4. ve 7. günler arasında serum  $\beta$ -hCG seviyelerindeki azalmaya göre iki gruba ayrıldı:  $<15,0$  - "başarılı tedavi" veya  $\geq 15,0$  - "ikinci doz metotreksata ihtiyaç var". Ardından, serum  $\beta$ -hCG düzeylerinde 1. ve 7. günler arasındaki yüzde değişim ve bunun «başarılı tedaviyi» öngörmedeki faydası analiz edildi.

**Bulgular:** Yetmiş dört hastanın 66'sında (%86,5) tedavi başarılı kabul edildi. Tedavi başarısı ile 1. günden 7. güne kadar serum  $\beta$ -hCG seviyelerindeki yüzde değişim arasında negatif doğrusal bir korelasyon vardı ( $p<0.001$ ). ROC eğrisi analizleri, tedavi başarısı tahmininin duyarlılığının, 1. günden 7. güne kadar serum  $\beta$ -hCG düzeylerinde yüzdelik değişimin artmasıyla azaldığını ortaya çıkardı. Tedavi başarısını öngörmek için 1. ve 7. Günler arası serum  $\beta$ -hCG seviyelerindeki  $-25,0$ ,  $0,0$  ve  $+25,0$  değişikliklerin duyarlılığı ve özgülüğü sırasıyla  $100,0$ - $41,0$ ,  $90,0$ - $93,7$  ve  $80,0$ - $96,9$ 'du.

**Sonuç:** Birinci ve 7. günler arası serum  $\beta$ -hCG seviyelerindeki değişimin yüzdesel olarak izlenmesi özellikle hasta uyumunun zor olduğu veya 4. gün ölçümlerinin pratik olmadığı durumlarda geleneksel protokolün yerini etkili bir şekilde alabilir.

**Anahtar Kelimeler:** Ektopik gebelik, metotreksat, koryonik gonodotropin, tedavi sonucu

**Cite as:** Tas EE. Is it necessary to check  $\beta$ -hCG levels on day 4 after single-dose methotrexate treatment of ectopic pregnancy? A retrospective cohort study. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):297-300.

Geliş/Received: 19.09.2024 • Kabul/Accepted: 18.10.2024

Sorumlu Yazar/Corresponding Author: Emre Erdem TAS, Mehmet Akif Eroy Mahallesi Yesilay Caddesi 5A/121 Yenimahalle/Ankara, Türkiye

E-mail: doctortas83@gmail.com

Çevrimiçi Erişim/Available online at: <https://dergipark.org.tr/tr/pub/jgon>

## INTRODUCTION

Ectopic pregnancy (EP) is a potentially life-threatening condition that occurs when a blastocyst implants outside the uterine cavity, most commonly in the fallopian tubes (1). It affects approximately 1-2% of all pregnancies and remains a leading cause of maternal morbidity and mortality in the first trimester (2). Early diagnosis and prompt treatment are crucial to prevent complications, such as tubal rupture and internal bleeding. Management options for ectopic pregnancy include surgical intervention, medical treatment with methotrexate, or expectant management in select cases (3).

Single-dose methotrexate therapy has emerged as an effective non-invasive treatment option for hemodynamically stable patients with unruptured ectopic pregnancies (4). However, the optimal follow-up protocol for monitoring treatment success and potential complications remains debatable among healthcare providers (5, 6). Evaluation of treatment efficacy involves monitoring  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) levels at specific intervals: days 1, 4, and 7 after methotrexate administration. A universally accepted indicator of successful treatment is a reduction in  $\beta$ -hCG concentration of  $\geq 15\%$  between days 4 and 7 post-injection (7). In recent years, the effectiveness of the current protocol has been questioned, which has led to the proposal of alternative approaches. One such suggestion involves eliminating the  $\beta$ -hCG measurement on day 4 and predicting treatment success based on any reduction between day 0/1 and day 7 (5, 6).

This study investigated the necessity of checking  $\beta$ -hCG levels on day 4 after single-dose methotrexate administration, as recommended by the current guidelines, to assess treatment efficacy in tubal ectopic pregnancy cases. To this end, the relationship between treatment success and the percentage change in serum  $\beta$ -hCG levels from days 1 to 7 was evaluated.

## MATERIAL AND METHODS

This retrospective observational study was conducted at the Gynecology Department of Ankara Bilkent City Hospital between January 2020 and December 2023. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and approved by the Ethics Committee of the same institute (E.2.24.490). Oral informed consent was obtained from all participants prior to their participation in the study.

Eighty patients who were followed up and treated for tubal EP during the study period were assessed for eligibility using hospital records.

The inclusion criteria were EP confirmed by ultrasound examination and insufficient  $\beta$ -hCG increase between two measurements 48 h apart, management with a single-dose methotrexate regimen, and thorough follow-up of  $\beta$ -hCG levels on days 4 and 7 of injection. The exclusion criteria were pregnancy of unknown location, multiple-dose methotrexate regimen, emergency surgery after methotrexate administration, pretreatment  $\beta$ -hCG level  $\geq 10.000$  IU/L, positive fetal cardiac activity, expectant management, and operation without methotrexate administration.

According to our clinical protocol, hemodynamically stable women with no evidence of rupture are managed with methotrexate therapy, particularly a single-dose regimen. The single dose of methotrexate was calculated according to the body surface area of each patient ( $50 \text{ mg/m}^2$ ). The day of methotrexate injection was defined as day 1. During the follow-up,  $\beta$ -hCG levels were measured on days 4 and 7. If levels decreased by  $\geq 15\%$  between days, the treatment was accepted as successful, and  $\beta$ -hCG levels were followed up weekly until a negative result was obtained. However, if the serum  $\beta$ -hCG levels decreased by  $< 15\%$  between days 4 and 7, the treatment was considered unsuccessful, and a second dose of methotrexate was administered.

In this study, we first evaluated all the patients who were administered a single dose of methotrexate. After excluding patients who were undergone emergency surgery due to rupture of EP before day 7, the remains were subdivided into two groups: "successful treatment" and "need a second dose methotrexate". We then analyzed the percentage change in serum  $\beta$ -hCG levels between days 1 and 7 and its usefulness in predicting "successful treatment."

### Statistical analysis

Normally distributed data are expressed as the mean  $\pm$  standard deviation, whereas non-parametric data are presented as the median and interquartile range. The relationship between treatment success and percentage change in serum  $\beta$ -hCG levels from days 1 to 7 was determined using Spearman's correlation coefficient. The sensitivity and specificity of different percentage changes in serum  $\beta$ -hCG levels from days 1 to 7 for predicting treatment success were determined using receiver operating characteristic (ROC) curves. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 21.0 (IBM, SPSS Corp.; Armonk, NY, USA). Statistical significance was set at  $P < 0.05$ .

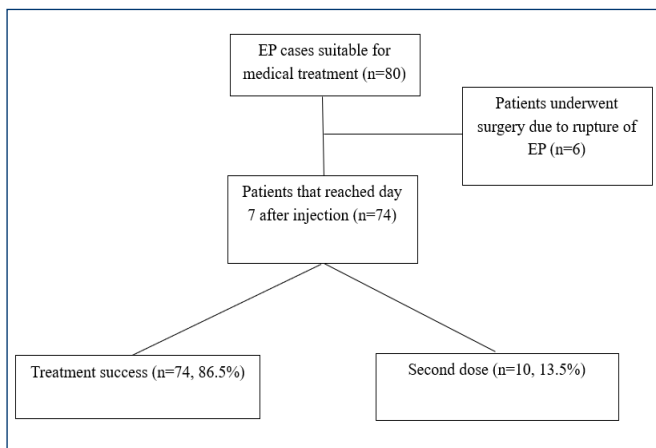
## RESULTS

A single dose methotrexate administered to 80 patients on day 1. Six patients (7.5 %) underwent surgery for rupture before day 7 and were excluded from the study. Treatment was considered successful in 86.5% (64/74) of the remaining patients, whereas 13.5% (10/74) received a second dose of methotrexate. Figure 1 shows the flowchart of the study population. The demographic and clinical characteristics of the 74 patients are summarized in Table 1.

When the changes in serum  $\beta$ -hCG levels during the follow-up period were analyzed, the mean percentage change in serum  $\beta$ -hCG levels was  $-2.2 \pm 45.2\%$  from days 1 to 4,  $-29.0 \pm 36.2\%$  from days 4 to 7, and  $-26.6 \pm 53.8\%$  from days 1 to 7. There was a negative linear correlation between treatment success and the percentage changes in serum  $\beta$ -hCG levels from day 1 to day 7 ( $P < 0.001$ , Spearman's correlation coefficient  $= -0.54$ ). ROC curve analyses revealed that the sensitivity of treatment success prediction decreased with increasing percentage changes in serum  $\beta$ -hCG levels from days 1 to 7 (Figure 2 and Table 2).

**Table 1.** Demographic and clinical characteristics of patients who were administered single-dose methotrexate for tubal ectopic pregnancy.

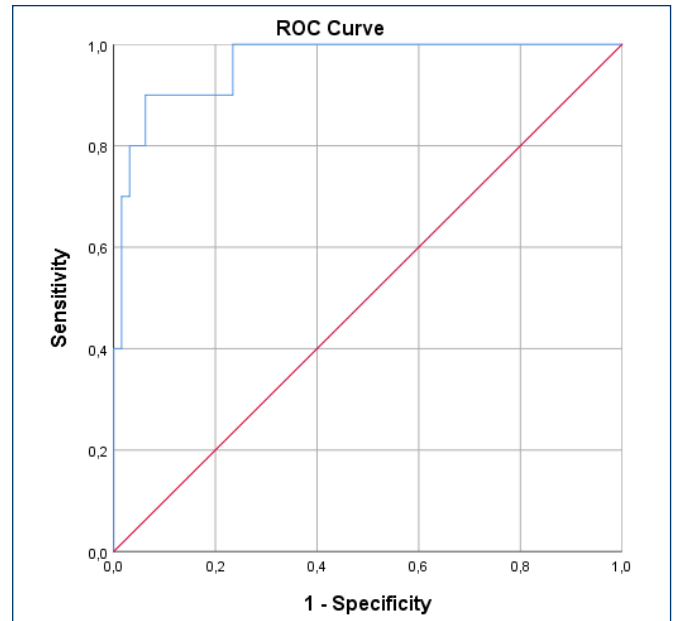
Age (years), mean $\pm$ SD	32.2 $\pm$ 4.8
Parity, median (IQR)	1 (1)
Gestational age (weeks), mean $\pm$ SD	5.2 $\pm$ 1.4
Day 1 serum $\beta$ -hCG level (IU/L), mean $\pm$ SD	1911.5 $\pm$ 1710
Day 4 serum $\beta$ -hCG level (IU/L), mean $\pm$ SD	1960.0 $\pm$ 2360.2
Day 7 serum $\beta$ -hCG level (IU/L), mean $\pm$ SD	1453.6 $\pm$ 1977.0



**Figure 1.** Flowchart of the study population.

**Table 2.** Sensitivity and specificity of treatment success predictions for different percentage changes in serum  $\beta$ -hCG levels from day 1 to day 7 ( $-50.0\%$ ,  $-25.0\%$ ,  $0.0\%$ ,  $+25.0\%$ , and  $+50.0\%$ ).

Percentage changes in serum $\beta$ -hCG levels from day 1 to day 7	Sensitivity	Specificity
$-50.0\%$	100.0%	41.0%
$-25.0\%$	100.0%	77.6%
$0.0\%$	90.0%	93.7%
$+25.0\%$	80.0%	96.9%
$+50.0\%$	60%	98.9%



**Figure 2.** Receiver operating characteristic curve analysis of the percentage changes in serum  $\beta$ -hCG levels from days 1 to 7 for predicting single-dose methotrexate treatment in patients with tubal ectopic pregnancy (area under curve = 0.96).

## DISCUSSION

Single-dose methotrexate is an effective treatment for ectopic pregnancy, with success rates influenced by the initial  $\beta$ -hCG levels and the rate of decrease in  $\beta$ -hCG post-treatment (8). These findings support the use of single-dose methotrexate as a viable alternative to surgical intervention in selected patients, potentially preserving future fertility and reducing the need for more invasive procedures (9).

The incidence of ectopic pregnancies varies with age and parity. Studies have shown that the incidence of disrupted ectopic pregnancy is most common in women aged 20-35 years and is more frequent in multigravida women, those who have been pregnant more than once (10). Our findings align with those in the literature, with a mean age of 32.2 years, median parity of 1. On the

other hand, EPs typically present clinically within the first trimester, with mean gestational ages reported at 7.2 weeks and 6.7 weeks (11,12). These figures suggest that the majority of ectopic pregnancies are identified relatively early in the pregnancy. In our study, the mean gestational age was 5.2 weeks and slightly lower than that reported in previous studies. Variations in study results may stem from patient demographics, clinical or socioeconomic factors, and differences in diagnostic tools, such as ultrasound quality.

The most widely adopted protocol for determining the success of single-dose methotrexate is based on a < 15% decrease in  $\beta$ -hCG levels between days 4 and 7 (7,13). Recently, alternative protocols have been introduced to establish a more economical and practical follow-up period after methotrexate administration (5,6,14,15). However, each of these new approaches has its own benefits and drawbacks. A prior investigation by Atkinson et al. examined various methods for forecasting treatment efficacy and suggested that the protocol measuring  $\beta$ -hCG reduction from days 0/1 to 7 was comparable in effectiveness to the currently employed approach (5). In their study, any reduction in serum  $\beta$ -hCG levels from days 1 to 7 had a 79% sensitivity and 86.0% specificity for predicting treatment success. Subsequently, Sukur et al. corroborated the findings of Atkinson et al., who concluded that any reduction in serum  $\beta$ -hCG levels on days 0/1–7 could replace the current method of determining treatment success in tubal EP management. In their study, Sukur et al. showed that any reduction in serum  $\beta$ -hCG levels from days 1 to 7 had 91.2% sensitivity and 80.0% specificity in predicting treatment success (6). Our findings were consistent with those of two previous studies. However, in the present study, we showed a negative linear correlation between treatment success and percentage changes in serum  $\beta$ -hCG levels from day 1 to day 7. Furthermore, our research indicates that treatment success can be reliably predicted not only by any decrease in serum  $\beta$ -hCG levels between days 1 and 7 but also by an increase of less than +25.0% in serum  $\beta$ -hCG levels.

In conclusion, this study provides valuable insights for predicting the success of single-dose methotrexate treatment in tubal ectopic pregnancies. These findings suggest that monitoring the percentage change in serum  $\beta$ -hCG levels from days 1 to 7 could be an effective alternative to the traditional protocol. This approach may prove particularly useful in cases where patient compliance is challenging or when day 4 measurements are not feasible owing to various constraints. Further research is warranted to validate these results and to potentially incorporate this method into clinical practice, ultimately improving the management of ectopic pregnancies and patient outcomes.

#### Ethics Committee Approval

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and approved by the Ethics Committee of the same institute (E.2.24.490)

#### Author Contributions

Data collection, analysis, interpretation, conception, design, and drafting of the manuscript were performed by Emre Erdem TAS.

#### Conflict of Interest

The author declares no conflict of interest.

## REFERENCES

- Awadalla Abdelwahid S, Ibtelhal Jaffer Youssef A, Abdallah Omer Elzein E, Safa Mohamed I, Kabbashi Mohammed Adam H, Mohamed Abdalla Elamin A, et al. Ectopic Pregnancy Risk Factors Presentation and Management Outcomes. *Clinical Journal of Obstetrics and Gynecology*. 2023 Sep 29;6(3):143–9.
- Thakur B, Shrimali T. Rare Concomitant Cesarean Scar Ectopic Pregnancy With Tubal Ectopic Pregnancy: A Case Report. *Cureus*. 2023 Apr 11;15(4).
- Gunawardena G, Priyananda K, Disanayake D, Jayalath G. A case series on current management options of tubal ectopic pregnancy in a tertiary care unit. *Sri Lanka Journal of Obstetrics and Gynaecology*. 2010 Apr 2;31(1):16.
- Khakwani M, Parveen R, Ali S. Treatment success with two doses of methotrexate vs single dose of methotrexate in Ectopic Tubal Pregnancy. *Pakistan journal of medical sciences*. 2022 Jan 1;38(6).
- Atkinson M, Mcgee T, Gupta S.  $\beta$ hCG monitoring after single-dose methotrexate treatment of tubal ectopic pregnancy: is the Day 4  $\beta$ hCG necessary? A retrospective cohort study. *The Australian & New Zealand journal of obstetrics & gynaecology*. 2014 Oct 1;54(5):475–9.
- Şükür YE, Çetinkaya E, Dökmeci F, Koyuncu K, Seval MM. Comparison of alternative  $\beta$ hCG follow-up protocols after single-dose methotrexate therapy for tubal ectopic pregnancy. *Archives of gynecology and obstetrics*. 2017 Sep 20;296(6):1161–5.
- Murray H. Diagnosis and treatment of ectopic pregnancy. *Canadian Medical Association Journal*. 2005 Oct 11;173(8):905–12.
- Kim J, Jung YM, Jee BC, Lee DY. Pretreatment serum human chorionic gonadotropin cutoff value for medical treatment success with single-dose and multi-dose regimen of methotrexate in tubal ectopic pregnancy. *Obstetrics & gynecology science*. 2017 Jan 1;60(1):79.
- Dhar H, Rath B, Hamdi I. Methotrexate Treatment Of Ectopic Pregnancy: Experience at Nizwa Hospital with Literature Review. *Oman Medical Journal*. 2011 Mar 25;26(2):94–8.
- Pemaron IBM, Bandem IKMP, Seputra DKA. The relationship between age and parity of pregnant women with the incidence of disrupted ectopic pregnancy at Wangaya hospital. *International Journal of Advances in Medicine*. 2022 Dec 27;10(1):16.
- Sharma V, Wadhwa RD. Chronic Tubal Ectopic Pregnancy with Diagnostic Conundrum: A Case Report. *International Journal of Science and Healthcare Research*. 2021 Jun 29;6(2):192–4.
- Yasmin S, Zeb L, Shaheen U, Mehmood S. Fertility Outcome In Patients With Previous Ectopic Pregnancy. *American Journal of Health, Medicine and Nursing Practice*. 2022 Apr 2;7(4):26–33.
- Dai Y, Zhang G, Zhu L, Lang J, Liu Z. Routine  $\beta$ -Human Chorionic Gonadotropin Monitoring for Single-Dose Methotrexate Treatment in Ectopic Pregnancy. *The Journal of Minimally Invasive Gynecology*. 2017 Aug 8;24(7):1195–9.
- Ustunyurt E, Şimşek H, Duran M, Coskun E, Ustunyurt ÖB. Role of initial and day 4 human chorionic gonadotropin levels in predicting the outcome of single-dose methotrexate treatment in women with tubal ectopic pregnancy. *Archives of Gynecology and Obstetrics*. 2013 May 12;288(5):1149–52.
- Wong L, Cheung C, Fung LWY, Lao TT. Trends in serum human chorionic gonadotropin levels 0-4days after methotrexate administration for predicting tubal ectopic pregnancy treatment success. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2018 Jan 3;141(2):245–9.