

Predictive value of β -hCG decline for methotrexate success in ectopic pregnancy: A retrospective cohort with long-term fertility outcomes

¹Cansu ÖNAL KANBAŞ

²Esra KELEŞ

³Evrime BOSTANCI ERGEN

⁴Mustafa EROĞLU

¹Department of Obstetrics and Gynecology, University of Health Sciences, Kartal Dr. Lutfi Kırdar City Hospital, Istanbul, Turkey

²Department of Gynecologic Oncology, University of Health Sciences, Kartal Dr. Lutfi Kırdar City Hospital, Istanbul, Turkey

³Department of Obstetrics and Gynecology, Istanbul Medipol University, Istanbul, Turkey

⁴Department of Obstetrics and Gynecology, University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center, Istanbul, Turkey

ORCID ID

CÖK : 0009-0000-4638-7907

EK : 0000-0001-8099-8883

EBE : 0000-0002-1634-6781

ME : 0000-0002-2772-7248



ABSTRACT

Objective: This study aimed to validate various β -hCG decline thresholds for predicting the success of single-dose methotrexate (MTX) treatment, compare fertility outcomes across different treatment modalities, and identify predictors of treatment success in women with tubal ectopic pregnancy (EP).

Material and Methods: This retrospective study included 687 women diagnosed with tubal EP and treated with a single-dose MTX protocol between January 2013 and May 2018. Data collected included patient demographics, clinical presentation, serial β -hCG levels, ultrasound findings, treatment modalities, and subsequent fertility outcomes. The predictive value of different percentage declines in β -hCG levels between Days 0–4 and Days 4–7 was analyzed.

Results: The study included women with a mean age of 30.65 ± 5.64 years (range: 16–53). A decline of $\geq 40\%$ in β -hCG levels between Day 4 and Day 7 following MTX treatment ruled out the need for second-line intervention with 57% sensitivity and 96% specificity (AUC=0.87, 95% CI: 0.81–0.93, $p < 0.0001$). Patients successfully treated with MTX exhibited a significantly greater mean β -hCG decline (0.39 ± 0.24) compared with those requiring second-line intervention (0.08 ± 0.22 ; $p < 0.0001$).

Conclusion: Higher β -hCG decline thresholds between Day 4 and Day 7 demonstrate high specificity for predicting successful MTX treatment in tubal EP. Tubal-preserving strategies, such as salpingostomy and MTX, appear to be associated with improved subsequent pregnancy rates compared with salpingectomy.

Keywords: Ectopic pregnancy, methotrexate, salpingectomy, salpingostomy, β -hCG.

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Correspondence: Esra KELEŞ, MD. Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Sağlık Bilimleri Üniversitesi, Jinekolojik Onkoloji Kliniği, İstanbul, Türkiye.

Tel: +90 216 391 06 80

e-mail: dresrakeles@gmail.com

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INTRODUCTION

Ectopic pregnancy (EP) complicates 1–2% of pregnancies and accounts for 2.7% of pregnancy-related deaths globally, primarily due to rupture and hemorrhage.^[1,2] While surgical intervention remains definitive, medical management with MTX has emerged as a first-line therapy for hemodynamically stable patients, preserving fertility and reducing morbidity.^[3–6] However, 10–36% of MTX-treated patients require secondary interventions, necessitating reliable biomarkers to predict failure.^[7]

It is recommended that serial β -hCG monitoring be performed to assess MTX response, yet optimal thresholds for intervention remain contentious. A decline of $\geq 15\%$ in β -hCG levels during the Day 4–7 interval serves as a robust indicator of successful treatment outcome, characterized by a positive predictive value (PPV) of 93%, although recent studies propose higher thresholds for improved specificity.^[8,9] Additionally, long-term fertility outcomes following EP are inconsistently reported, with conflicting evidence regarding the impact of salpingectomy versus tubal-preserving surgeries.^[10] Therefore, to address these gaps, we retrospectively analyzed a large cohort of patients with EP to validate β -hCG decline thresholds, compare fertility outcomes across treatment modalities, and identify predictors of treatment success.

MATERIAL AND METHODS

Study Design and Setting

This retrospective study was conducted at Zeynep Kamil Women and Children's Diseases Training and Research Hospital, a tertiary referral center in Istanbul, Türkiye. Medical records of all patients diagnosed with EP between January 1, 2013, and May 30, 2018, were reviewed.

Ethical Approval

The study received ethical approval from the Institutional Review Board (IRB) of the same hospital (Approval number: 04; Date: January 9, 2019).^[11] This study was conducted in accordance with the Declaration of Helsinki. Due to its retrospective design, informed consent was waived by the Institutional Review Board (IRB). Patient confidentiality was maintained throughout the study by anonymizing all collected data.

Patient Selection

Inclusion criteria were: (1) women of reproductive age with a confirmed diagnosis of tubal EP; (2) primary treatment received at our institution (MTX, salpingectomy, salpingostomy, or tubal milking); and (3) complete follow-up records available, including baseline demographic data, clinical presentation, initial diagnostic findings, serial serum β -hCG values (at diagnosis, day of MTX administration [Day 0], and Days 4 and 7 post-MTX for medically managed patients), and details of subsequent fertility outcomes.

Diagnosis of EP was established based on a combination of transvaginal ultrasonography (TVS) demonstrating an extrauterine gestational sac (with or without fetal cardiac activity) or, in the absence of definitive TVS findings, persistently elevated or inappropriately rising serum β -hCG levels inconsistent with an intrauterine pregnancy (IUP), often accompanied by an empty uterine cavity.

Patients were excluded if follow-up information was unavailable or lost, or if they had hemodynamic instability, signs of acute abdomen, abnormal liver or renal function test results, presence of fetal cardiac activity, serum β -hCG levels > 5000 IU/L, or an adnexal mass larger than 4 cm in diameter. In addition, patients who did not meet institutional criteria for MTX treatment or had contraindications were excluded. Contraindications to MTX therapy included hemodynamic instability, signs of acute abdomen, abnormal liver or renal function test results, presence of fetal cardiac activity, serum β -hCG > 5000 IU/L, or an adnexal mass > 4 cm in diameter. Patients with cesarean scar EP or EP in non-tubal locations were also excluded.

Treatment Protocol

Eligible patients received a single intramuscular dose of MTX at 50 mg/m² according to the hospital's standard protocol.^[11] Surgical management was reserved for patients not eligible for MTX or in whom MTX therapy failed. Treatment success for MTX was defined as the resolution of EP, evidenced by a decline in serum β -hCG to non-pregnant levels, without the need for any secondary surgical intervention or additional MTX doses. Treatment failure was defined as any of the following: evidence of tubal rupture requiring emergency surgery, increasing or plateauing β -hCG levels after the initial expected decline, or failure of β -hCG to decline by at least 15% between Day 4 and Day 7 (unless a more substantial subsequent decline obviated intervention), ultimately necessitating secondary medical or surgical treatment.

Data Collection

Data collected included patient demographics, clinical presentation, serial β -hCG levels, ultrasound findings, treatment modalities (methotrexate, salpingectomy, salpingostomy, milking), and subsequent fertility outcomes. Baseline β -hCG was defined as the value at diagnosis; Day 0 β -hCG was defined as the value on the day of MTX administration. The percentage change in β -hCG between Days 0–4 and Days 4–7 was calculated using the formula: $([\beta\text{-hCG Day X} - \beta\text{-hCG Day Y}] / \beta\text{-hCG Day X}) * 100$.

Subsequent fertility outcomes were evaluated through a review of institutional medical records documenting later pregnancies, supplemented by patient-reported data obtained during follow-up visits and telephone interviews. The primary fertility outcome was the occurrence of a subsequent IUP after the index EP treatment.

Statistical Analysis

Statistical analysis of the research data was conducted using the SPSS for Windows 18 software package. Descriptive statistics, including percentage distribution, mean, and median, were used in the analyses. To compare two continuous variables, the Student t-test was employed for those with a normal distribution, the Mann–Whitney U test for those without a normal distribution, and the Kruskal–Wallis analysis of variance for comparisons involving more than two groups without a normal distribution. In correlation analyses, Pearson's correlation coefficient was used for continuous variables with a normal distribution, whereas Spearman's correlation coefficient was used for continuous variables without a normal distribution. The diagnostic decision-making properties of variables in predicting clinical outcomes were examined using receiver operating characteristic (ROC) curve analysis.

Table 1: Baseline characteristics (n=687)

Category	Variable	n (%)	Mean \pm SD	Range
Demographic characteristics	Age (years)		30.65 \pm 5.64	16–53
	Gravida		2.36 \pm 1.42	0–11
	Parity		0.83 \pm 0.99	0–5
	Living children		0.80 \pm 0.97	0–5
	Abortions		0.48 \pm 0.89	0–7
Ultrasound findings	Adnexal mass	494 (71.9)		
	Normal ultrasound	193 (28.1)		
Hemodynamic stability	Stable	552 (80.3)		
	Unstable	135 (19.7)		
Initial treatment modality	Methotrexate	294 (42.8)		
	Salpingectomy	283 (41.2)		
	Salpingostomy	96 (14.0)		
	Milking	14 (2.0)		
Second-line treatment	No further treatment	246 (83.0)		
	Additional MTX	21 (7.0)		
	Salpingectomy	18 (6.0)		
	Salpingostomy	9 (3.0)		
	Milking	2 (0.7)		

SD: Standard deviation; MTX: Methotrexate. Data are expressed as median (Q1–Q3), mean \pm SD or number (percentage) as appropriate.

Table 2: Predictive value of β -hCG decline between day 4 and day 7

β -hCG decline threshold	Sensitivity (%)	Specificity (%)	AUC	95% CI	p
\geq 40%	57	96	0.87	0.81–0.93	<0.0001
\geq 65%	85	98	N/A	N/A	N/A
\geq 73%	90	98	N/A	N/A	N/A

β -hCG: Beta-human chorionic gonadotropin; AUC: Area under the curve; CI: Confidence interval; N/A: Not available. A p value of <0.05 indicates a significant difference.

RESULTS

Patient Characteristics

A total of 687 patients with a mean age of 30.65 \pm 5.64 years (range: 16–53) were included in the study. Median gravidity was 2 (mean 2.36 \pm 1.42), and median parity was 0 (mean 0.83 \pm 0.99). The mean number of living children was 0.80 \pm 0.97, and the mean number of prior abortions was 0.48 \pm 0.89 (Table 1).

Diagnostic and Clinical Findings

At presentation, the majority of patients (80.3%, n=552) were hemodynamically stable, whereas 19.7% (n=135) were unstable (Table 1). Transvaginal ultrasonography at diagnosis identified an adnexal mass in 71.9% (n=494) of cases, while the remaining 28.1% (n=193) showed no abnormality (Table 2).

Initial Treatment Modalities and Outcomes

The most common initial treatment was MTX, administered to 42.8% of patients (n=294), followed by salpingectomy (41.2%, n=283), salpingostomy (14.0%, n=96), and milking (2.0%, n=14) (Table 1). A favorable response to first-line treatment was achieved in 92.4% (n=635) of cases.

Second-Line Treatment Outcomes

Among MTX-treated patients, 83.0% (n=246) required no further treatment. Second-line interventions included additional MTX (7.0%), salpingectomy (6.0%), salpingostomy (3.0%), and milking (0.7%) (Table 1). There was no statistically significant difference in β -hCG decline rates across second-line treatment modalities (p=0.276).

Table 3: Reproductive outcomes stratified by initial treatment modality

Initial treatment modality	Pregnant (n)	Not pregnant (n)	p
Methotrexate (MTX)	150	144	
Salpingectomy	111	172	
Salpingostomy	58	38	
Milking	9	5	0.001

MTX: Methotrexate. A p value of <0.05.

Predictive Value of β -hCG Decline

A decline of $\geq 40\%$ in β -hCG levels between Day 4 and Day 7 following MTX treatment ruled out the need for second-line intervention with 57% sensitivity and 96% specificity (AUC=0.87, 95% CI: 0.81–0.93, $p < 0.0001$). Increasing the threshold to $\geq 65\%$ improved sensitivity to 85% and specificity to 98%. At a $\geq 73\%$ decline, sensitivity and specificity reached 90% and 98%, respectively (Table 2).

Patients who achieved resolution with single-dose MTX exhibited a greater mean decline in β -hCG levels (0.39 ± 0.24) compared with those who required second-line intervention (0.08 ± 0.22 ; $p < 0.0001$).

Reproductive Outcomes

Following treatment, 150 patients (51.0%) achieved pregnancy, whereas 144 (49.0%) did not. The mean β -hCG decline did not significantly differ between those who achieved pregnancy (0.36 ± 0.26) and those who did not (0.32 ± 0.26 ; $p = 0.206$). Pregnancy outcomes were not significantly associated with initial ultrasound findings ($p = 0.293$), response to initial treatment ($p = 0.433$), or β -hCG decline ($p = 0.215$).

Pregnancy rates differed significantly according to treatment modality ($p = 0.001$). Patients who underwent salpingostomy or received MTX had higher rates of subsequent pregnancy compared with those who underwent salpingectomy (Table 3).

DISCUSSION

The findings of this study offer significant insights into the management of EP, particularly concerning the utility of serial β -hCG monitoring in predicting the success of MTX treatment and the subsequent reproductive outcomes associated with various therapeutic modalities.

Our findings underscore the critical role of fertility-preserving strategies in hemodynamically stable patients. Salpingostomy demonstrated the highest subsequent IUP rate (60.4%), followed by MTX (51.0%) and salpingectomy (39.2%). These results align with the DEMETER trial^[12] which reported a 1.7-fold increase in IUP rates after salpingostomy compared with salpingectomy, and a 2023 meta-analysis by Hao et al.^[13] concluding that MTX offers advantages over salpingectomy while remaining non-inferior to salpingostomy. The markedly lower pregnancy rates following salpingectomy (39.2%) highlight the clinical imperative to avoid radical surgery in stable

patients. While salpingectomy remains the standard for ruptured EP or hemodynamic instability, our data support prior reports advocating shared decision-making in stable patients prioritizing future fertility.^[14]

MTX emerges as a non-invasive, fertility-preserving option, consistent with van Mello et al.^[15] who found comparable long-term fertility outcomes between medical and conservative surgical management, particularly in patients with initial β -hCG levels < 2000 IU/L. However, conservative surgical approaches such as salpingostomy require rigorous postoperative β -hCG monitoring due to the risk of persistent trophoblastic tissue, observed in 7–15% of cases.^[16] The lower persistent trophoblast rate (3.0%) in our cohort may reflect stringent surgical techniques or adherence to follow-up protocols.

The findings of this study support the role of early β -hCG decline as a predictor of MTX treatment success. We observed that patients who achieved resolution with single-dose MTX demonstrated a significantly greater mean decline in β -hCG levels between Days 4 and 7 compared with those who required second-line intervention. This observation aligns with numerous studies identifying initial β -hCG levels as a key predictor of MTX treatment failure. A meta-analysis by Alur-Gupta et al.^[17] indicated the importance of initial hCG levels in predicting MTX success. Similarly, Dilbaz et al.^[18] identified initial β -hCG levels $> 3,000$ mIU/mL as a significant predictor of treatment failure. Aydın and Özgen^[19] also highlighted the utility of early hCG changes between Days 0/1 and 4 in predicting treatment outcomes, suggesting that earlier assessment may be beneficial. Furthermore, Ray et al.^[20] identified pre-treatment β -hCG levels, along with the rate of decline on Days 4 and 7 following MTX administration, as the most significant predictors of successful medical management. The consistent findings across various studies, including our own, emphasize the clinical utility of closely monitoring β -hCG levels in the early stages of MTX treatment to identify patients at higher risk of failure who may benefit from alternative or adjunctive interventions.

The present study has several strengths, including a large sample size, standardized MTX protocols, rigorous β -hCG monitoring, and the provision of long-term reproductive outcomes. Exclusion of non-tubal EP and hemodynamically unstable patients ensured a more homogeneous study population. Limitations include the retrospective study design, which inherently limits causal inferences. Additionally, the study could not account for other reproductive health variables, such as assisted reproductive technology use, partner fertility, or ovulatory function.

Our findings carry significant clinical implications. They may guide clinicians in choosing tubal-preserving strategies in hemodynamically stable patients, thereby avoiding unnecessary salpingectomy and improving reproductive outcomes. The robust predictive value of early β -hCG decline underscores the necessity of meticulous monitoring of β -hCG levels in patients undergoing medical management for ectopic pregnancy. Furthermore, adopting higher β -hCG decline thresholds may help clinicians avoid unnecessary interventions in women demonstrating a favorable early response to MTX, thereby reducing patient morbidity while preserving fertility potential.

Future research endeavors should focus on developing standardized protocols for assessing long-term reproductive outcomes following various EP treatments, thereby providing more

definitive guidance to both clinicians and patients. Further research on novel biomarkers offers promising avenues for refining risk stratification and treatment algorithms in EP. Additionally, studies comparing different MTX regimens and their impact on both treatment efficacy and subsequent fertility would be valuable in optimizing medical management approaches.

CONCLUSION

Our study provides further evidence supporting the critical role of β -hCG monitoring in the management of tubal EP treated with MTX. Higher β -hCG decline thresholds appear to offer improved specificity in predicting treatment success, while tubal-preserving strategies are associated with better subsequent fertility. Early β -hCG decline remains a significant predictor of successful medical management.

Disclosures

Ethics Committee Approval: The study was approved by University of Health Sciences, Zeynep Kamil Women and Children's Diseases Training and Research Hospital Ethics Committee (No: 04, Date: 09.01.2019).

Informed Consent: Due to its retrospective design, informed consent was waived by the Institutional Review Board (IRB).

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