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Original Article

# Predictors of failure of the commonly used single-dose methotrexate protocol for treating tubal ectopic pregnancies

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ABSTRACT

*Objectives:* This study identified patients who would benefit from an earlier additional medical intervention and/or continuing close surveillance even if commonly used parameters indicated sufficient medical treatment to determine markers of treatment failure.

*Materials and methods:* A retrospective analysis of patients with a preliminary diagnosis of ectopic pregnancy treated with the single-dose methotrexate protocol. *Group 1*: cases cured with a single dose of methotrexate; *Group 2*: cases who required more than one dose of methotrexate or surgery following the first dose. Demographics, clinical/sonographic findings, observation period, and β-human chorionic gonadotropin (hCG) levels were compared among the two groups. Thresholds were defined and a regression analysis was performed to define independent predictors of failure.

*Results:* Data from 120 patients were analyzed: Group 1 (n = 92); Group 2 (n = 28). β-hCG levels measured at all time points, and day (0–4) and day (4–7) changes, presence of adnexial masses, and infertility were significantly different among the two groups. Only the day (0–4) and day (4–7) changes in β-hCG levels were independent predictors of failure.

*Conclusion:* Day (0–4) thresholds or newly defined day (4–7) thresholds were not more sensitive than the conventional day (4–7) criteria. Day (0–4) β-hCG levels increased by more than 9.7% in half the patients who required additional methotrexate doses or surgery despite fulfillment of the conventional day (4–7) criteria. In contrast, no cases of treatment failure were observed if the day (0–4) decrease was >26.6%.



## Introduction

Ectopic pregnancy is the leading cause of pregnancy-related mortality in the first trimester. An earlier diagnosis combined with numerous treatment options has decreased related mortality [1].

The prevalence of ectopic pregnancy has been increasing in the last four decades due to increasing rates of pelvic infections, smoking, infertility, and more sensitive laboratory methods and imaging technologies providing an earlier diagnosis [2].

The proportion of indeterminate cases with a later definite diagnosis has increased with more sensitive diagnostic methods [3].

The classic assessment of treatment success defined by Stovall et al. and revalidated by Kirk et al. has 88–93% sensitivity but eliminates a large number of patients as false negatives, if not a large proportion in a population with high pregnancy rates [4,5].

Our aim was to analyze independent markers of treatment failure to identify patients who would benefit from an earlier additional medical intervention and/or continuing close surveillance even if conventional parameters indicated sufficient medical treatment.

## Materials and methods

This was a retrospective analysis of patients with a preliminary diagnosis of ectopic pregnancy, who applied to the Bagcilar Research and Training Hospital Obgyn Department emergency section or ambulatory clinic from September 2012 to March 2016 and who were treated with the methotrexate (Mtx) single-dose protocol defined by Stovall et al. [4]. This study was approved by

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the Medical Ethics Committee (Project number: 406/2015). The patients' data were obtained from the patients' database (MEDIN 2.0.0) using the following queries: "ectopic pregnancy" as the diagnostic input. The surgical records were revised for the diagnosis of "ectopic pregnancy".

Ectopic pregnancy was a preliminary diagnosis when blood β-human chorionic gonadotropin (hCG) levels were >1500 mIU/ml and no intrauterine gestational sac was detected (examined with 5–8 MHZ transvaginal sonography) or when blood β-hCG levels were <1500 mIU/ml but the level was increasing and was <50% during the previous 48 h and blood β-hCG levels did not regress despite a uterine evacuation. Following the preliminary diagnosis of ectopic pregnancy, an observation period of 1–8 days elapsed before the first dose of Mtx. In the intervening period, the patients were regularly monitored for abnormalities in hemodynamics by measuring blood counts and blood β-hCG levels every other day. If the blood β-hCG level did not regress spontaneously (≥15%/24 h drop during serial β-hCG measurements with or without a uterine evacuation performed according to findings of endometrial thickness ≥10 mm, sonographic view of intrauterine conception or passage of tissues with uterine bleeding), medical treatment was started.

The single-dose Mtx treatment protocol was used for patients with a preliminary diagnosis of ectopic pregnancy and a β-hCG level <10,000 mIU/mL; with nonhomogeneous adnexial masses ≤5 cm; absence of fetal cardiac activity, absence of signs of hemoperitoneum or hypovolemia; and normal blood counts and renal/liver function tests. Mtx was administered at a single intramuscular (IM) dose of 50 mg/m$^2$ on day 0, unless there were contraindications. The patients were hospitalized and watched expectantly following the drug administration while being checked for signs of acute abdomen and serious intraabdominal bleeding until a surgical intervention was indicated or for 7 days. Blood tests (biochemistry, blood parameters, and β-hCG) were measured on day 4. If a ≥15% decrease was not observed in the blood β-hCG level from days 4–7 or if a plateauing or rising blood β-hCG level was observed during follow-up of resolution, a second dose of 50 mg/m$^2$ Mtx was administered IM, followed by the same cycle of follow-up as for the first Mtx dose. If a ≥15% drop was observed, the patients were observed weekly.

Failure of the single-dose Mtx treatment was considered if extra doses of methotrexate were required, or if a surgical intervention was made due to an intervening clinical picture of tubal rupture.

*Exclusion criteria from the analysis* included: spontaneous regression during observations with or without a uterine evacuation; lost to follow-up; nontubal ectopic pregnancy; and surgery prior to medical treatment.

Data extracted from the database included demographics and clinical presentations of the patients; sonographic findings, length of the observation period before treatment, and all β-hCG levels measured including those measured on days 0, 4, and 7 following Mtx administration. Intervening surgeries and clinical outcomes are summarized in Table 1 and Fig. 1. Data derived for analysis were the percentage changes in blood β-hCG levels: [β-hCG] ((Day 0–Day 4)/Day 0) and [β-hCG] ((Day 4–Day 7)/Day 4); also represented by [β-hCG] (Day 4/Day 0) and [β-hCG] (Day 7/Day 4), respectively; and daily changes during the observation period were derived by logarithmic transformation of the ratios. In this study, we refer to changes in β-hCG as quotients of values measured on the annotated days (e.g., the conventional day 4 to day 7 change of 15% as ([β-hCG] level on day 7)/([β-hCG] level on day 4) represented by *the day (7/4) change of 0.85*, etc.)

Univariate tests were used to define significantly different variables among the single-dose Mtx successfully *(Group 1)* cured and the single dose Mtx failed *(Group 2)* groups requiring more than one dose of Mtx or surgery after the initial dose. A receiver operating characteristics (ROC) curve analysis of these variables defined the threshold values that were used to derive new dichotomized variables for the multivariate logistic regression analysis to predict

**Table 1**
Characteristics of the patients who were successfully treated (Group 1) or who failed medical treatment (Group 2).

| | Group 1[a] (n = 92) | Group 2[b] (n = 28) |
|---|---|---|
| Age | 30.6 ± 0.6 | 30.3 ± 0.9 |
| Gravida | 2.8 ± 0.2 | 3.3 ± 0.3 |
| Abortus | 1.9 ± 0.2 | 2.2 ± 0.6 |
| *Active Contraception, n (%)* | 14 (15.2) | 5 (17.9) |
| *Infertile couple, n (%)*[c] | 7 (7.6) | 6 (21.4) |
| *Smoking, n (%)* | 26 (28.3) | 10 (35.7) |
| *Previous Ectopic Pregnancy, n (%)* | 4 (4.3) | 2 (7.1) |
| *Previous abdominopelvic operations, n (%)* | 38 (41,3) | 10 (35,7) |
| *History of pelvic infection, n (%)* | 4 (4.3) | 2 (7.1) |
| Endometrial thickness (mm) | 8.6 ± 0.5 | 8.1 ± 0.8 |
| Number of cycles of single dose Mtx[c] | 1 | 1.6 ± 0.1 |
| Mtx Single-dosage administered (mg) | 80.7 ± 0.9 | 81.1 ± 1.7 |
| Watchfull period (days) | 2.3 ± 0.2 | 1.7 ± 0.1 |
| DailyΔ% (β-hCG) during observation[c,d] | 0.4 ± 0.1 | 6.9 ± 0.3 |
| Day 0:[β-hCG] of First Mtx Treatment (mIU/mL)[c] | 1472 ± 167.8 | 2319.7 ± 375 |
| Day 4:[β-hCG] of First Mtx Treatment (mIU/mL)[c] | 1418.1 ± 202 | 2942.2 ± 459.4 |
| Day 7:[β-hCG] of First Mtx Treatment (mIU/mL)[c] | 814.6 ± 122 | 2686.3 ± 493 |
| Day (4/0)[e,c] | 0.79 ± 0.05 | 1.27 ± 0.05 |
| Day (7/4)[f,c] | 0.55 ± 0.06 | 0.86 ± 0.06 |
| Hospitalization period (days)[c] | 7.1 ± 0.3 | 16 ± 1.1 |
| Missed Period/positive pregnancy test, n (%) | 32 (34,7) | 11 (39,3) |
| Pain/bleeding, n (%) | 57 (61,9) | 13 (46,4) |
| Adnexial Mass (+), n (%)[c] | 29 (31.5) | 21 (75) |
| Free peritoneal fluid, n (%) | 32 (34,4) | 9 (28,1) |

[a] Resolved with single dose methrotrxate (Mtx).
[b] Required additional Mtx doses/surgery for tubal rupture.
[c] $P < 0.05$.
[d] Daily change in β-human chorionic gonadotropin (hCG) levels during the waiting period (%/day).
[e] Ratio of β-hCG levels on day 4 to day 0 following the first Mtx dose.
[f] Ratio of β-hCG levels on day 7 to day 4 following the first Mtx dose.