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CLINICAL ARTICLE

Success rates of single-dose methotrexate and additional dose requirements among women with first and previous ectopic pregnancies

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ABSTRACT

Objective: To compare the success of the single-dose methotrexate regimen and the requirement for a second or third dose of methotrexate between women with their first ectopic pregnancy (EP) and those with previous EP. *Methods:* In a retrospective cohort study, data were analyzed from women treated for EP by single-dose methotrexate at a Turkish tertiary referral center between January 2010 and December 2013. Data were compared between women with at least one previous EP and those with their first EP. *Results:* The success rate of the protocol in the first and previous EP groups was similar: 93.0% (320/344) and 87.3% (48/55), respectively. History of previous EP was not a predictor of treatment failure. However, the requirement for additional methotrexate doses was significantly higher in the previous EP group (16/48 [33.4%]) than in the first EP group (55/320 [17.2%]; $P = 0.03$). Multivariate analysis showed that history of tubal surgery ($P = 0.006$) and initial levels of the β-subunit of human chorionic gonadotropin ($P = 0.001$) were significant predictors of treatment failure. *Conclusion:* Although the single-dose regimen had similar success rates in the previous EP and first EP groups, additional doses of methotrexate were more frequently required in the previous EP group.

1. Introduction

Ectopic pregnancy (EP) is defined as the implantation and subsequent development of the embryo outside the endometrium. EP constitutes 1%–2% of all pregnancies, and its incidence has increased in the past four decades [1,2]. Despite earlier diagnosis and appropriate treatment, EP still accounts for 3%–4% of all pregnancy-related deaths, even in high-income countries [3]. Women are most commonly diagnosed with a first EP when aged 18–24 years, and are at increased risk (5–10-fold) for recurrent EP until the end of their reproductive life. Therefore, approximately 10%–15% of women who have had an EP once will have a second EP during their reproductive period [4–7].

In terms of counseling and monitoring patients with increased risk of subsequent EP, it is important to determine the predisposing risk factors for recurrence. Conducting a prospective observational study to investigate the recurrence of EP might require follow-up for decades; as a result, only a few retrospective studies have investigated the risk factors and success of treatment among women with previous EP [8,9].

A single-dose methotrexate regimen is a safe and effective treatment option with a proven success rate for first EP. Although data are limited, it has been speculated that women who have had previous EP could have an increased risk of treatment failure with the single-dose regimen [10]. However, whether one dose of methotrexate (50 mg/m^2) is sufficient for effective treatment or whether additional doses might be necessary has not been clarified.

The primary aim of the present study was to compare the success rate of the single-dose methotrexate regimen and the requirement for additional doses of methotrexate between women with a first EP and those with previous EP. A secondary aim was to determine potential risk factors for first and previous EP.

2. Materials and methods

In a retrospective cohort study, the medical records of women treated for EP at the early pregnancy clinic of a Turkish tertiary referral center in Ankara, Turkey, between January 1, 2010, and December 31, 2013, were reviewed. The inclusion criterion was single-dose methotrexate treatment for EP. Women who had a non-tubal EP, had been treated at another center, or had insufficient data were excluded from the study. Institutional ethical committee approval was obtained for the study, and all patients gave written informed consent before participation.

All pregnant women presenting at the emergency room with complaints of bleeding and pelvic pain were evaluated for EP. Women with a serum level of the β-subunit of human chorionic gonadotropin (β-hCG) of 1500 IU/L or higher, and no intrauterine gestational sac with or without an ectopic mass on transvaginal ultrasonography were admitted with a diagnosis of EP. Women with a β-hCG level of

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less than 1500 IU/L were followed up with transvaginal ultrasonography and serial β-hCG measurements to confirm the diagnosis.

Women who presented with hemodynamic instability, severe pain, or signs of intra-abdominal bleeding were referred for immediate surgery. If the β-hCG value was lower than 1000 IU/L and tending to decrease, the women were treated with expectant management (waiting without any intervention). All other hemodynamically stable women with EP were candidates to receive the single-dose methotrexate regimen unless they had a contraindication to methotrexate or were unable to complete the required follow-up period. There were no upper limits for ectopic mass size or β-hCG level for the single-dose regimen.

A dose of methotrexate (50 mg/m^2) was administered intramuscularly on day 1 of the single-dose regimen. After a 15% decrease or more in β-hCG between days 4 and 7, the β-hCG levels were repeatedly measured until they reached 10 mIU/L. If the β-hCG levels decreased by less than 15%, a second dose of methotrexate was injected. Similar to this protocol, if the β-hCG levels decreased by less than 15% between days 4 and 7 after the second dose, a final third dose was given. If the β-hCG levels did not adequately decrease after repeated methotrexate doses and the patient was referred for surgery, or if the patient underwent emergency surgery for a tubal rupture during the treatment period, the treatment was considered to have failed.

The study data were collected from specific EP files that were compiled for each patient during the treatment period. For analysis, the patients were divided into two groups: those with previous EP (group 1) and those with first EP (group 2).

SPSS for Windows version 15.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Percentages were compared via the χ^2 test, and continuous variables by the Mann–Whitney *U* test. An initial assessment of the first 10 women with first EP demonstrated a success rate of 90% for the single-dose methotrexate regimen; this proportion was 70% for women with previous EP. On the basis of these values, the DSS Research Sample Size Calculation Program statistical package (http://www.dssresearch.com/toolkit/sscalc/) indicated that a minimum of 48 participants would be required in each group to demonstrate a difference at an α value of 0.05 and a β value of 0.20.

A logistic regression model was used to determine the effect of confounders on methotrexate success. In the regression analysis, eight variables were tested as possible predictors of treatment failure: group (first EP and previous EP), age, number of previous EPs, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), size of ectopic mass, β-hCG level on day 1 of methotrexate treatment, smoking, and history of previous tubal surgery. Possible predictors were compared by univariate analyses using the Enter method in SPSS. Predictors that were thought to be clinically significant were assessed by backward logistic regression analysis. The procedure eliminated all variables that were not statistically significant at the 0.05 level.

3. Results

During the study period, 504 women with a diagnosis of EP met the study criteria and were included in the study. Overall, 77 (15.3%) women had a history of previous EP (Table 1). Women in group 1 were older than those in group 2 (31.5 vs 29.9 years; $P = 0.012$). Women in group 1 had higher gravidity (3.8 vs 2.4; $P = 0.001$) and higher rates of abortion (52.0% vs 25.5%; $P = 0.001$) as compared with those in group 2. Women in group 1 had a higher incidence of well-known EP risk factors such as history of intrauterine device (IUD) use ($P = 0.024$), tubal surgery ($P = 0.001$), and pelvic surgery ($P = 0.027$). The difference in history of previous pelvic inflammatory disease (PID) between the two groups also approached significance ($P = 0.066$).

Overall, 59 (13.8%) women in group 2 and 15 (19.5%) in group 1 underwent immediate laparoscopic surgery. Spontaneous resolution occurred with expectant management for 31 (6.2%) women: 24 in group 2, and 7 in group 1. The remaining 399 women with EP were referred to the single-dose methotrexate protocol (Fig. 1). Overall, 320 (93.0%) of 344 women with first EP and 48 (87.3%) of 55 women with previous EP were successfully treated. Additional doses of methotrexate were required for 55 (17.2%) women with first EP and 16 (33.4%) women with previous EP ($P = 0.03$). Table 2 summarizes the clinical variables and treatment success for women given the single-dose methotrexate protocol for EP.

Table 1
Comparison of patient characteristics by first and previous EP.[a]

Characteristic	First EP group (n = 427)	Previous EP group (n = 77)	*P* value
Age, y	29.85 ± 5.78	31.51 ± 5.27	0.012
BMI	26.03 ± 4.93	26.04 ± 4.90	0.954
Smoker	85 (19.9)	11 (14.3)	0.274
Gravidity	2.44 ± 1.28	3.75 ± 1.32	0.001
Parity	0.98 ± 0.92	1.10 ± 0.96	0.266
Previous abortions			0.001
0	318	37	
1	78	19	
≥2	31	21	
Intrauterine device use	86 (20.1)	25 (32.5)	0.024
History of pelvic inflammatory disease	50 (11.7)	15 (19.5)	0.066
History of tubal surgery	23 (5.4)	19 (24.7)	0.001
Pelvic surgery	91 (21.3)	26 (33.8)	0.027
Infertility treatment	52 (12.2)	8 (10.4)	0.848

Abbreviations: EP, ectopic pregnancy; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
[a] Values are given as mean ± SD or number (percentage), unless indicated otherwise.

To examine whether previous EP is a risk factor for failure of the single-dose regimen, data from the women treated with single-dose methotrexate (n = 399) were also analyzed by regression analysis (Table 2). Initial β-hCG values were slightly but not significantly higher among women with previous EP than among those with first EP (1556 vs 1400 IU/L; $P = 0.051$). However, the single-dose regimen failed at a similar rate among women with first and those with previous EP (7.0% vs 12.7%; $P = 0.17$).

In the univariate analysis, prior tubal surgery and initial β-hCG values were found to be significant predictors of treatment failure. Having a previous EP was not a significant predictor of methotrexate failure among women treated with the single-dose regimen (odds ratio 0.51, 95% confidence interval 0.21–1.25; $P = 0.145$). After multiple logistic regression analysis, only history of tubal surgery ($P = 0.006$) and higher β-hCG values on the first day of the methotrexate protocol ($P = 0.001$) remained as the independent predictors of single-dose methotrexate failure (Table 3).

In group 1 (n = 77), 38 patients had more than one previous EP, and the previous EP treatment could not be clarified for nine patients. Eighteen of the remaining 30 patients were medically treated in their previous EP; in this subgroup, the failure rate of treatment of the index EP by single-dose methotrexate regimen was 11.1% (2/18). Twelve of the 30 patients were treated surgically in their previous EP and the failure rate of treatment of the index EP by single-dose methotrexate regimen was 16.7% (2/12); thus, the treatment failure rates were statistically similar ($P > 0.99$). Therefore, the treatment modality used in previous EP was not a predictor of treatment failure in the subsequent EP.

4. Discussion

In the present study, the effectiveness of the single-dose methotrexate regimen and the requirement for additional methotrexate doses were investigated among women with first and previous EP. It was found that the success of the single-dose methotrexate regimen—with use of second and third doses when indicated—was highly satisfactory in both groups of women. It was also demonstrated that the requirement for a second or third methotrexate dose was significantly higher for women with previous EP than for those with first EP. Although previous tubal surgery and initial β-hCG value significantly predicted