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The importance of β-hCG values in prediction of the effectiveness of single dose methotrexate therapy in tubal ectopic pregnancy

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ABSTRACT

Objectives: To investigate the importance of β-hCG values on the day of onset and on the fourth and seventh day after treatment in the effectiveness of treatment in tubal ectopic pregnancies treated with a single dose of methotrexate (MTX).

Material and methods: One hundred sixty-two patients with tubal ectopic pregnancy treated with a single dose MTX treatment were retrospectively evaluated. β-hCG values and changes on Days 0, 4 and 7 of the MTX treatment successful group and the unsuccessful group were analyzed.

Results: MTX treatment was successful in 125 (77.2%) and unsuccessful in 37. When the β-hCG values on Days 0, 4 and 7 were compared in pairs, the differences between groups were statistically significant ($p < 0.001$).

The mean β-hCG value was 783.0 in the MTX successful group and 1802.0 in unsuccessful group ($p < 0.001$). There was a 21.6% decrease in β-hCG values between Days 0 and day 4 in the MTX successful group and a 25.7% increase in the MTX unsuccessful group ($p < 0.001$). On Days 0, 4 and 7, ROC curve analysis's values are, respectively; 755/939/486 for cut off, 86.49/83.78/94.59% for sensitivity and 48.80/69.60/72.36% for specificity.

Conclusions: Success rates of single-dose MTX treatment increase in tubal ectopic pregnancies with low initial β-hCG value. Patients with a decrease in β-hCG value and/or a cut-off decrease of 20% or more on the fourth day of treatment can be called for weekly β-hCG monitoring without the need for close follow-up. The change in β-hCG between Day 0 and Day 4 can be used to predict the efficacy of treatment.

Key words: ectopic pregnancy; methotrexate; beta-human chorionic gonadotrophin

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INTRODUCTION

An ectopic pregnancy is an implanted pregnancy outside of the uterine cavity, and most occurs in the fallopian tube (96%) [1]. Ectopic pregnancies, whose incidence has increased in recent years, are still one of the most important causes of maternal mortality and morbidity in the first trimester [2, 3].

Three approaches to the treatment of ectopic pregnancy are; surgical, medical (MTX) or expectant management. While surgical treatment was the gold standard treatment, advances in early diagnosis in the 1980s facilitated the initiation of medical treatment with MTX [4]. With the combined use of human chorionic gonadotropin (hCG) β subunit and transvaginal sonography (TVS) in early pregnancy, the diagnosis of ectopic pregnancy can be made early and medical treatment can be applied in many cases. The overall success rate of medical treatment in properly selected women is approximately 90% [5, 6]. The decision to continue with expectant management or medical therapy once or to seek surgery later depends mainly on the patient's symptoms and on-treatment serum β-hCG values. The most important predictor of MTX failure is high level of β-hCG [7, 8].

Many advantages of medical treatments over surgical treatment have been emphasized, such as lower cost, reduced morbidity and possible complications related to anesthesia and surgery, less tubal damage and higher probability of subsequent fertility. In many studies, it has been

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stated that the reproductive results of surgical treatment and medical treatment are similar [6, 9].

Today, the most commonly used agent worldwide in the treatment of ectopic pregnancy is methotrexate due to its low side effects and high efficacy [10]. Different medical treatment protocols (oral or parenteral) such as single dose, multiple doses, hybrid protocols have been the subject of numerous studies [11, 12].

In this study, we aimed to determine the importance of β-hCG values and changes in predicting the effectiveness of MTX in the medical treatment of tubal ectopic pregnancy and to determine the markers that can predict the success of treatment before the 7th day.

MATERIAL AND METHODS

Data of 186 patients who applied to Izmir Kâtip Çelebi University, Atatürk Training and Research Hospital, Gynecology and Obstetrics Clinic between January 2012 and September 2019, diagnosed with tubal ectopic pregnancy and administered a single dose MTX treatment protocol as medical treatment were compiled retrospectively from files and Hospital Information Management System records. Data, age, gravity, parity, serum β-hCG values, response to MTX treatment, need for additional doses and/or surgical treatment were examined. After evaluation with the inclusion criteria, 162 patients who were followed up with β-hCG for seven days, who were treated with a single dose of MTX, were included in the study.

The β-hCG values of the patients were categorized. Days 0, 4 and 7 β-hCG values, numerical changes in these values were determined and compared. Ratios and percentages were determined. Receiver operating characteristics (ROC) analyzes were performed to determine both a cut-off value and to reveal sensitivity, specificity, positive predictive and negative predictive values.

In our clinic, medical treatment comes to the fore in hemodynamically stable, non-ruptured ectopic pregnancy cases, if liver and renal function tests are normal, and there are no contraindications for MTX treatment. Medical treatment is applied to patients who accept medical treatment and sign the informed consent form about MTX and meet the criteria.

Definitive diagnosis of ectopic pregnancy was made by β-hCG positivity, absence of intrauterine gestational sac on TVS and ectopic focus. A single dose of MTX protocol recommended by the Memphis group (50 mg/m^2 intramuscularly) was administered to the patients. Serum β-hCG values were measured on the day of treatment (Day 0), as well as Days 4 and 7. The 4th and 7th day β-hCG values were compared and an additional dose of MTX was administered to patients with less than 15% decrease or increase in β-hCG value. Patients who received additional doses of MTX and underwent surgical treatment on any day of medical treatment were included in the treatment-failure group. The patient group whose medical treatment was considered successful was called for weekly follow-up until the β-hCG value was negative (< 5 IU/L).

Statistical analysis

Data were evaluated in the statistical package program IBM SPSS Statistics Standard Concurrent User V 25 (IBM Corp., Armonk, New York, USA). Descriptive statistics were given as number of units (n), percent (%), mean ± standard deviation (x ± sd), median (M), 25th percentile (C1), 75th percentile (C3). The normal distribution of the data of numerical variables was evaluated with the Shapiro Wilk test of normality and QQ charts. Two-group comparisons were made with two independent samples t-test for normally distributed variables, and Mann-Whitney U test for non-normally distributed variables. Friedman Analysis was used to compare within-group Days 0, 4 and 7 for β-hCG values. If there was a difference as a result of Friedman analysis, the Boferroni Corrected Friedman Comparison Test was used for comparisons between days. Receiver operating characteristics curve analysis was used to determine the β-hCG cutoff point for those who responded to treatment and those who did not. In the presence of significant breakpoints, the sensitivity and specificity values of these limits were calculated. A p value of < 0.05 was considered statistically significant.

RESULTS

Twelve of 186 patients were excluded from the study because their β-hCG values could not be reached on the 4th and 7th days. Surgical treatment was applied to 4 patients on Day 1, 3 on Day 5, and 3 after Day 7 because they were hemodynamically unstable and had signs of tubal rupture. One patient underwent surgical treatment voluntarily. Pathology result of one patient was reported as partial mole.

Response to treatment was evaluated in 162 patients who received a single dose of MTX and were followed up with β-hCG for seven days. Since 125 of 162 (77.2%) patients had a β-hCG reduction of more than 15% between Day 4 and Day 7, single-dose MTX therapy was considered successful. In 37 (22.8%) patients with β-hCG reduction less than 15% or an increase, the treatment was considered unsuccessful. The success rate of single dose MTX treatment was 77.2%.

Seven of 37 patients who failed single-dose MTX treatment underwent surgical treatment due to the urgent need for surgery. One patient underwent surgical treatment at her own request. A second dose of MTX treatment was applied to the remaining 29 patients. It was seen that the treatment was sufficient in the follow-ups.

Statistics of numerical variables between groups are given in Table 1.

Table 1. Comparison of single dose MTX successful and MTX unsuccessful groups in terms of clinical parameters and statistics

	Groups		Test statistics*	
	MTX Successful M (Q1–Q3)	MTX Unsuccessful M (Q1–Q3)	z value	p value
Mean age	30.83 ± 4.95	30.87 ± 5.92	0.032	0.975
Gravidity	2.00 (1.50–3.00)	2.00 (2.00–3.00)	0.093	0.926
Parity	1.00 (0.00–1.00)	1.00 (0.00–1.00)	0.506	0.613
B-hCG				
Day 0	783.00[a] (261.50–2139.50)	1802.00[a] (860.50–4370.00)	3.850	< 0.001
Day 4	454.00[b] (170.50–1298.25)	2453.00[b] (1284.50–5545.00)	5.973	< 0.001
Day 7	210.00[c] (76.00–649.00)	2389.00[c] (1197.50–5618.00)	7.329	< 0.001
Test statistics** χ^2 p	201.712 < 0.001	17.568 < 0.001		
Day 0 – Day 4	141.00 (9.00–513.50)	–757,00 [(–1293.50)–(–82.5)]	6.619	< 0.001
Day 0 – Day 7	456.00 (130.05–1134.00)	–279.00 [(–1315.00)–77.00)]	6.567	< 0.001
Day 4 – Day 7	177.00 (76.00–593.00)	11.00 [(–97.00)–294.00)]	4.205	< 0.001

a, b, c — It shows the between-day comparison for β-hCG in each group. The days with the same letters are similar; * Mann Whitney U Testi; ** Frieadman Testi; Q1: 25. Persantil; Q3:75. Persantil

In the group MTX unsuccessful, the β-hCG value on the 0th day was statistically significantly higher than the group MTX successful ($p < 0.001$). According to these data, as the β-hCG value on Day 0 increases, the success rate in response to a single dose of MTX treatment decreases (Tab. 2).

In the group MTX unsuccessful, both Day 4 and Day 7 β-hCG values were statistically significantly higher than the group MTX successful ($p < 0.001$).

When the β-hCG changes between Day 0 and Day 4 were examined, the β-hCG value in the group MTX successful decreased by an average of 141 (9.00–513.50) numerically; in the group MTX unsuccessful, it increased by an average of 757 (1293.50–82.5). This difference was statistically significant ($p < 0.001$).

When the β-hCG changes between Day 0 and Day 7 of the patients were examined, the β-hCG value in the group MTX successful decreased by an average of 456 (130.05–1134.00) numerically; in the group MTX unsuccessful, it increased by an average of 279 (1315.00–77.00). This difference was statistically significant ($p < 0.001$).

When the β-hCG changes between Day 4 and Day 7 of the patients were examined, the β-hCG value decreased by an average of 177 (76.00–593.00) in the group MTX successful; in the group MTX unsuccessful, it decreased by an average of 11 [(–97.00)–294.00]. This difference between the groups was found to be statistically significant ($p < 0.001$).

When the ROC curve values of the patients treated with a single dose of MTX on Day 0, Day 4 and Day 7 are evaluated together, it is seen that the sensitivity and specificity values increase as Day 0 gets closer to Day 7. According to these results; Day 0, Day 4 and Day 7 β-hCG values were found to have diagnostic value in predicting the success of patients with MTX (Fig. 1, Tab. 3).

Table 2. MTX success by day 0 β-hCG values

Day 0 β-hCG values	Cases (n)	Successful cases (n)	Success rate %
0–500	51	46	90.2
500–1000	33	27	81.8
1000–1500	12	9	75.0
1500–2000	16	11	68.8
2000–2500	8	6	75.0
2500–3000	6	4	66.7
3000–3500	8	6	75.0
3500–4000	9	7	77.8
4000–4500	5	3	60.0
4500–10000	8	3	37.5
> 10000	6	3	50.0
Total	162	125	77.2

After a single dose of MTX treatment, 105 (64.8%) of 162 patients had a decrease on Day 4 β-hCG values compared to Day 0 β-hCG values, and while the treatment was successful in 99 (94.3%) of these 105 patients. Treatment was unsuccessful in 6 (5.7%) of them. In 57 (35.2%) patients, an increase in β-hCG values on Day 4 was detected when compared to the β-hCG value on Day 0. While the treatment was successful in 26 (45.6%) of these 57 patients, in 31 (54.4%), the treatment was found to be unsuccessful. The change of β-hCG values between Day 0 and Day 4 were

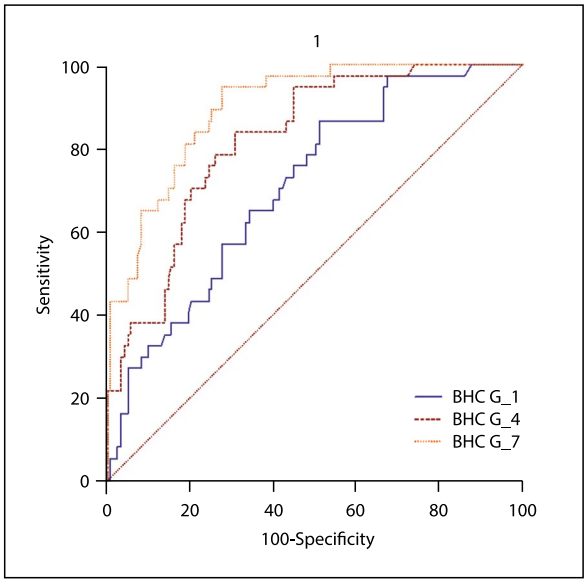

Figure 1. Receiver operating characteristics (ROC) curve for β–hCG values at Day 0, Day 4, and Day 7 in patients receiving single-dose MTX therapy

statistically significant in terms of response to treatment ($p < 0.001$).

In addition, in the group MTX successful (n = 125), a mean decrease of 21.6% (4.7–53.7) was found in Day 4 β-hCG values compared to Day 0 β-hCG values. In the group MTX unsuccessful (n = 37), Day 4 β-hCG values increased by 25.7% (12.7–76.7) compared to Day 0 β-hCG values. A statistically significant difference was found between the two groups in terms of the decrease in β-hCG value between Day 0 and Day 4 ($p < 0.001$).

A decrease on Day 4 β-hCG was detected in 96.1% of these 125 patients with successful treatment and 31.9% of 37 patients with treatment failure. This difference between the two groups was statistically significant ($z = -7.317$, $p < 0.001$).

DISCUSSION

Ectopic pregnancies is still one of the most important causes of first trimester maternal deaths [13]. For diagnosis, it is often sufficient to look at the serum β-hCG values of the patient and, if positive, to evaluate with TVS [5, 6].

It can be said that medical and surgical treatment have similar success rates in patients who are hemodynamically stable, have a small tubal mass, and have a serum β-hCG value < 5000 IU/L. Even if the chance of success is low in patients with a large tubal pregnancy diameter and higher β-hCG values, medical treatment can be tried by informing the patient in detail about the risk of surgical treatment [14].

The most prominent factor affecting the response to MTX treatment is the serum β-hCG value at the beginning of the treatment. There are many studies indicating that the higher the pre-treatment β-hCG level, the lower the success rate [14–17]. In Menon et al.'s review (503 patients treated with MTX), there was a significant and statistically significant increase in failure rates in patients with baseline β-hCG level > 5,000 mIU/mL compared to < 5,000 mIU/mL [3, 14].

With the medical treatment of ectopic pregnancy, the risks associated with surgery and anesthesia are avoided. However, compared to laparoscopic salpingectomy, medical treatment of ectopic pregnancy has a lower success rate and requires longer surveillance and patient visits. Randomized studies comparing medical treatment of ectopic pregnancy with laparoscopic salpingostomy showed a lower success rate with the use of single dose MTX (RR for success, 0.82%; 95% CI, 0.72–0.94); showed no statistically significant difference with multidose MTX use (RR for success, 1.8; 95% CI, 0.73–4.6) [18].

In another study, conflicting results were obtained when a single dose of MTX was compared with salpingostomy; Although tubal transmission and subsequent pregnancy rates are similar between the two groups, a single dose of MTX is generally less successful in treating ectopic pregnancy than laparoscopic salpingostomy [19].

One review concluded that MTX therapy was successful in 78–96% of patients [20]. There has been no randomized trial directly comparing two different MTX treatment protocols. In a meta-analysis (26 articles, 1.327 cases), the overall success rate for MTX treatment was 89%. The success rate of the multiple dose regimen was 92.7% (95% CI, 89–96%); this was statistically significantly higher than that achieved with the single dose regimen (88.1%; 95% CI, 86–90%) [5]. After controlling for first-day β-hCG values and the presence of embryonic cardiac activity, the failure rate for single-dose

Table 3. Receiver operating characteristics curve analysis results for Day 0, Day 4, and Day 7

	Cut off	Sensitivity	95% CI sens	Specificity	95% CI sens	PPV	NPV
Day 0*	> 755	86.49	71.20–95.40	48.80	39.80–57.90	33.3	92.4
Day 4**	> 939	83.78	68.00–93.80	69.60	60.70–77.50	44.9	93.5
Day 7***	> 486	94.59	81.80–99.20	72.36	63.60–80.00	50.7	97.8

CI — confidence interval; NPV — negative predictive value; PPV — positive predictive value; Sens — sensitivity; Spec — specificity; *area under the curve: 0.709, $p < 0.001$; **area under the curve: 0.824, $p < 0.001$; ***area under the curve: 0.898, $p < 0.001$

therapy was higher than for multiple-dose therapy [(OR) 4.75, 95% CI, 1.77–12.62] [21].

For the first time, a single-dose MTX regimen was introduced by Stovall et al. (1991) on 30 patients with a success rate of 94.2% [22]. In the study of single-dose MTX treatment regimen by Olofsson et al. (2001, 107 patients), the success rate was found to be 77% [23]. Lipscomp et al. (2000) published patients in the expanded Memphis cohort treated with a single dose of MTX; 287 (92.9%) of 315 patients were successfully treated with MTX [20]. As a result, MTX administration of a single dose study in 64 to 94.2% success rate was monitored from [20, 22, 24]. In our study (n = 162), the success rate was 77.2%, consistent with the literature.

A small, randomized clinical trial noted that single-dose therapy had a higher failure rate, but the difference was smaller ([RR] 1.50; 95% CI, 0.44–5.01) [25]. It was concluded that the difference in failure rates between the two protocols was undetectable in women with an overall good prognosis for successful medical treatment.

Nowak-Markwitz et al. (68 cases), it was shown that the chance of success is higher in patients with lower initial β-hCG values, and when the cut off value is taken as 1790 mIU/mL, the success rate in the treatment of ectopic pregnancy with MTX [17]. In another study involving 758 patients, the cut-off value of β-hCG was found to be 1435 to predict MTX success [3]. In addition, another study conducted (2016) emphasized that a single level of β-hCG is not diagnostic for ectopic pregnancy and that serial levels may show atypical trends in some cases [7]. Therefore, it is necessary to interpret these results together with clinical and sonographic findings and to focus on different variables in order to reach the correct diagnosis and achieve ideal results.

In our study, the difference between MTX successful and MTX unsuccessful patient groups in terms of mean baseline β-hCG value (783.0 versus 1802.0) was statistically significant ($p < 0.001$). In accordance with the literature, as β-hCG values increase on the day of treatment, the success rate of treatment decreases.

Response to treatment is considered successful if there is more than a 15% decrease in β-hCG values on the fourth and seventh days after MTX administration. With this treatment protocol, patients are followed closely for at least seven days. In fact, this follow-up is carried out in many centers (including our center) by hospitalizing the patients against the need for urgent surgical treatment. In order to shorten this period, the effectiveness of comparing the β-hCG values on the zero and four days of the patients in predicting success has been investigated for a long time. Gabbur et al. (2006, 83 cases) found that β-hCG change between Day 0 and Day 4 did not predict the response to treatment [26]. On the contrary, some studies conducted in the following years showed that the response to treatment can be predicted by comparing the value of β-hCG at Day 4 with the initial value (without waiting for Day 7) [27, 28].

In one study, Nguyen Q et al. found decreased β-hCG values between initial and day 4 in 12 (40%) of 30 patients, and all of these 12 patients had a successful response to treatment; response to treatment was successful in 11 (61.1%) of the remaining 18 patients whose β-hCG values increased on Day 4 [27].

In a study by Skubisz et al. (45 cases), β-hCG decreased on Day 4 in 73% of patients from baseline, and 88% of these patients had a successful response to treatment; Response to treatment was also successful in 42% of the remaining 27% patients who showed a slight increase in β-hCG [28].

Üstünyurt et al. (87 cases) found that treatment success rate increased when baseline β-hCG was less than 3000 mIU/mL, and the change in β-hCG between Day 0 and Day 4 was important in understanding the response to treatment [29].

In the study of Çelik et al. (93 cases), it was shown that the decrease in β-hCG values on Day 4 may be a predictor of response to treatment [24].

In a study by Bottin et al. (91 cases), it was seen that the 20% decrease in β-hCG values between Day 0 and Day 4 was taken as the cut-off value, and the response to treatment could be predicted [30]. Our study also supports taking 20% as the cut-off value.

In our study, a statistically significant difference was found between the MTX successful and MTX unsuccessful groups in terms of β-hCG change on Day 0 and Day 4, consistent with the literature ($p < 0.001$). In addition, in our study, there was a 21.6% (4.7–53.7) decrease in β-hCG values between Day 0 and Day 4 in the MTX successful group (n = 125). In the treatment unsuccessful group (n = 37), an increase of 25.7% (12.7–76.7) was shown. This difference between the groups was statistically significant ($p < 0.001$).

RESULTS

In accordance with the literature, we have shown that medical treatment success rates are increased in patients with low initial β-hCG values and tubal ectopic pregnancy. The success of the treatment increases when 755 mIU/mL is taken as the cut-off value for the initial β-hCG value.

Today, it cannot be concluded that the treatment is successful until the 7th day β-hCG values are observed after medical treatment of ectopic pregnancy with MTX. As the length of hospital stay is prolonged, it both causes patient anxiety and increases the cost of treatment. According to our data, patients with a decrease in β-hCG value and/or a 20% decrease (as a cut-off value) on the 4th day after a single dose of MTX treatment do not require close follow-up. They can be called for weekly β-hCG follow-ups without the 7th

day β-hCG value being seen. We believe that the serum β-hCG change between days 0 and 4 can be used to predict the efficacy of treatment earlier.

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Conflict of interest

All authors declare no conflict of interest.

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