ORIGINAL ARTICLE

The Importance of 24-hour β-hCG Change Before Treatment and β-hCG Change between 1-4 days in Predicting the Success of a Single Dose Methotrexate Treatment

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Abstract:

Background: Ectopic pregnancy treatment with a single dose of methotrexate, causes patients to stay in hospital for a long time, increases the cost of treatment, decreases the compliance of the patient, and leads to loss of work force. *Aim and Objectives:* The aim of this study was to predict the success of single dose Methotrexate (MTX) treatment in ectopic pregnancy at an early period. *Material and Methods:* Between 1st January 2018 –31st December 2019 at the University of Health Sciences, Tepecik Education and Research Hospital, ectopic pregnancy patients who were treated with single dose MTX (50 mg/m^2) were included in the study. Clinical and laboratory parameters were evaluated. *Results:* The data of 100 patients that met our criteria were analyzed. Patients enrolled in the study, were divided into 2 groups. Group 1 MTX treatment failed group (n = 50) and Group 2 MTX treatment successful group (n = 50). Pre-treatment of beta-human Chorionic Gonadotrophin (β-hCG) values of the patients was of the MTX treatment failed group to be higher than those of the MTX treatment successful group ($p < 0.001$). Although the pre-treatment β-hCG change within 24 hour was higher in the MTX treatment failed group, the difference was not significant in the groups. The β-hCG change between 1st and 4th days, the average β-hCG value in the treatment failed group tended to increase, whereas in the group where the treatment successful, it tended to decrease and the results were significant ($p = 0.004$). *Conclusion:* Ectopic pregnancy is a serious obstetric complication that causes maternal morbidity and mortality. Therefore, early diagnosis and treatment is important. Especially, a single dose MTX treatment is an effective and safe option in the treatment of ectopic pregnancy. In this study, pre-treatment β-hCG values were significantly higher in the MTX failed group. The β-hCG values 24 hour before the start of the treatment and the β-hCG change at the beginning of the treatment were examined, and no difference was found between the groups in terms of predicting success in a single dose of MTX. On the other hand, the β-hCG change between the 1st and 4th days was an early predictor of the medical treatment success.

Keywords: Ectopic Pregnancy, Methotrexate, Human Chorionic Gonadotrophin, Predictor

Introduction:

In normal pregnancy, the fertilized ovum settles into the uterine cavity. Ectopic pregnancy is the placement of the blastocyst outside the endometrial cavity, and one of the major causes of maternal losses in the first trimester [1]. Ectopic pregnancies account for 1-2% of all pregnancies and their prevelance has increased day by day [1]. This increase is due to advances in early diagnosis, increased risk factors and increased use of assisted reproductive techniques [2-3].

Ectopic pregnancy can be treated medically or surgically. Preference varies depending on clinical status, ectopic pregnancy localization and hemodynamic stability [4]. Tubal damage is a

significant risk for patients who want a repeat pregnancy after an ectopic pregnancy. Tubal damage may develop depending on the ectopic pregnancy itself and/or the surgical treatment applied [5]. Therefore, medical treatment to be applied in ectopic pregnancies has many advantages over surgical treatment. These include less tubal damage, lower costs and elevation of subsequent fertility potential [6-7]. Today, Methotrexate (MTX) is the most commonly used agent worldwide for the treatment of ectopic pregnancy [8]. The most important factors in preference are low side effects and high effectiveness [7,9].

Treatment and follow-up of ectopic pregnancy with MTX is done by hospitalization with follow-up of vital signs and by following the serum β-hCG exchange. In the commonly used protocol, serum β-hCG concentration is measured on the 4th and 7th days and if the decrease in β-hCG between days 4 and 7 is less than 15%, a second dose of MTX or surgery is applied [10-11]. This causes patients to be hospitalized for a long time, increase the cost of treatment, decrease the compliance of the patient, and leads to loss of work force. These factors direct researchers to investigate early predictors of the success of medical treatment. Therefore, this study aimed to determine the role of 24-hour β-hCG change before treatment and β-hCG change between 1-4 days in predicting the success of a single dose MTX treatment.

Material and Methods:

Study Design:

Ectopic pregnancy patients who were treated with MTX at the University of Health Sciences, Tepecik Education and Research Hospital, between 1st January 2018 and 31st December 2019 were included in the study. Ectopic pregnancy was diagnosed based on the following signs and symptoms; serial β-hCG measurements and / or ectopic focus on Transvaginal Ultrasound (TVUS) without intrauterine sac. Dilation and Curett age (D&C) were performed on all patients. The results of pathology materials were followed up and the diagnosis of ectopic pregnancy was confirmed by "decidual reaction".Patients with normal liver [(Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)) and renal function (urea and creatine)] tests, serum beta-human Chorionic Gonadotropin (β-hCG) concentration ⩽ 5000 mIU/mL, no fetal cardiac activity detected on transvaginal ultrasound, hemodynamically stable, no contraindication for MTX [10] and who gave informed consent for MTX treatment were included in the study. MTX was administered to each patient at a dose of 50 mg/m^2. In all patients, β-hCG measurement was repeated on the 4th and 7th days of treatment, and levels were monitored, and patients with less than 15% reduction between the 4th and 7th days received 2nd dose of MTX or underwent surgery, and this group was named the failed group.

Ethical committee approval (2019/18-31) was obtained from the University of Health Sciences Tepecik Education and Research Hospital Ethics Committee.

Study Participants:

Women who met the following criteria were included in the study: patients diagnosed with ectopic pregnancy and treated with a single dose of MTX, unruptured ectopic pregnancies, hemodynamically stable patients, patients without acute abdomen or intra-abdominal bleeding, patients who underwent D&C and had a "decidual reaction" pathology report. Patients undergoing alternative therapy prior to MTX treatment (laparotomy or laparoscopic surgery), those who

received a multiple dose MTX regimen, who had ruptured ectopic pregnancies, hemodynamically unstable patients, those with acute abdomen or intra-abdominal bleeding, those who conceived with Intrauterine Device (IUD) or assisted reproductive techniques were excluded.

Statistical Analysis:

The Statistical Package for the Social Sciences 22.0 software program (IBM Corporation, Armonk, New York, US) was used for statistical analysis. Kolmogorov–Smirnov (n>30), Shapiro–Wilk (n<30) tests and suitable graphics were used for testing normality of quantitative data. Groups were compared using Student's *t*-test or Mann–Whitney *U*-test according to variable distribution. Data are expressed as mean ± standard deviation, median (min–max) and n, (%). Chi-square tests was used for categorical variables. $p<0.05$ was accepted as statistically significant. Receiver operating characteristic curves were computed, and the Area Under the Curve (AUC) was used to evaluate the performance of the variable as a predictor.

Results:

A total of 100 patients who met the inclusion criteria were included. These 100 patients were classified either as Group 1 MTX treatment failed group (n=50) or Group 2 MTX treatment successful group (n=50). The demographic and medical characteristics of the patients are given in Table 1. There was no significant difference between the failed group and the successful group in terms of age, adolescent pregnancy rates or advanced age pregnancy rates. Furthermore, no significant difference was found between the groups in terms of BMI values or parity (Table 1). Treatment characteristics of the patients are shown in Table 2. Mean ectopic focal size was 27.4±12.8 in the failed group and 17 ± 6.4 in the successful group, with a statistically significant difference ($p < 0.001$).

Similarly, the estimated gestational age of the patients was 53.2 ± 6.3 in the MTX treatment failed group and 40.1 ± 6.3 MTX treatment successful group, the difference between them was statistically significant ($p < 0.001$). As the size of the ectopic focus and estimated gestational age decreased, treatment success increased. There was no significant difference between the groups in terms of localization of ectopic focus (right tuba-left tuba) and endometrial thickness. Pre-treatment β-hCG values of the patients was of the MTX treatment failed group to be higher than those of the MTX treatment successful group (3381.78 ± 3424.39 vs 1475.83 ± 1442.66) ($p < 0.001$). MTX was more successful at lower β-hCG levels. Although the pre-treatment β-hCG change within 24 hour was higher in the MTX treatment failed group, the difference between the groups was not significant (10.39 ± 20.70% vs 6.64±19.04%). Mean β-hCG change between the 1st and 4th days was 25.01 ± 53.89% and -4.64 ± 47.26% for the MTX treatment failed and successful groups respectively, the difference between them was statistically significant ($p = 0.004$) (Table 2).

Fig.1 shows receiver operating characteristic curve analysis of the 24 hour pretreatment increment in hCG (%) (AUC = 0.469 ± 0.058; 95% CI 0.354 - 0.583) with a sensitivity of 42.9%, specificity of 59.0%, and the change in hCG concentration from day 1 to day 4 (%) (AUC= 0.670 ± 0.055; 95% CI 0.562 – 0.777) with a sensitivity of 69.9%, specificity of 73.0% in terms of identifying which patients were successfully treated with a single dose of MTX (Fig. 1).

Table 1: Demographic and Medical Characteristics of Women Involved in the Study

Parameters	Failed Treatment (n=50)	Successful Treatment (n=50)	*P*
Maternal age (year) (Mean ± SD)	29.5 ± 5.4	30.1 ± 6	0.614
Adolescent pregnancy ⩽19 (n, %)	2 (4%)	3 (6%)	0.646
Advanced age pregnancy ⩾35 (n, %)	10 (20%)	12 (24%)	0.629
BMI (kg/m^2) (Mean ± SD)	23.9 ± 1.9	24.5 ± 2.1	0.705
Parity (n, %)			0.074
Nulliparous	10 (20%)	18 (36%)	
Multiparous	40 (80%)	32 (64%)	

BMI-body mass index

Table 2: Antibiotic Resistance Pattern of Enterobacter Isolates

Parameters	Failed Treatment (n=50)	Successful Treatment (n=50)	*P*
Mean Ectopic Pregnancy Size (mm) (Mean ± SD)	27.4 ± 12.8[a]	17 ± 6.4[b]	**<0.001**
Estimated Gestational Age (days) (Mean ± SD)	53.2 ± 6.3	40.1 ± 6.3	**<0.001**
Location (n, %)			
Right	22 (52.3%)	21 (55.2%)	0.796
Left	20 (47.7%)	17 (44.8%)	
Endometrial thickness (mm) (Mean ± SD)	9.8 ± 6.3	10.2 ± 7.1	0.646
Pre-treatment HCG (mIU/ml) (Mean ± SD)	3381.78 ± 3424.39	1475.83 ± 1442.66	**<0.001**
24-h pre-treatment increment in HCG (%)(Mean ± SD)	10.39 ± 20.70	6.64 ± 19.04	0.347
Change in HCG 1-4 day (%) (Mean ± SD)	25.01 ± 53.89	-4.64 ± 47.26	**0.004**

[a]: 8 data could not be found. [b]: 12 data could not be found.

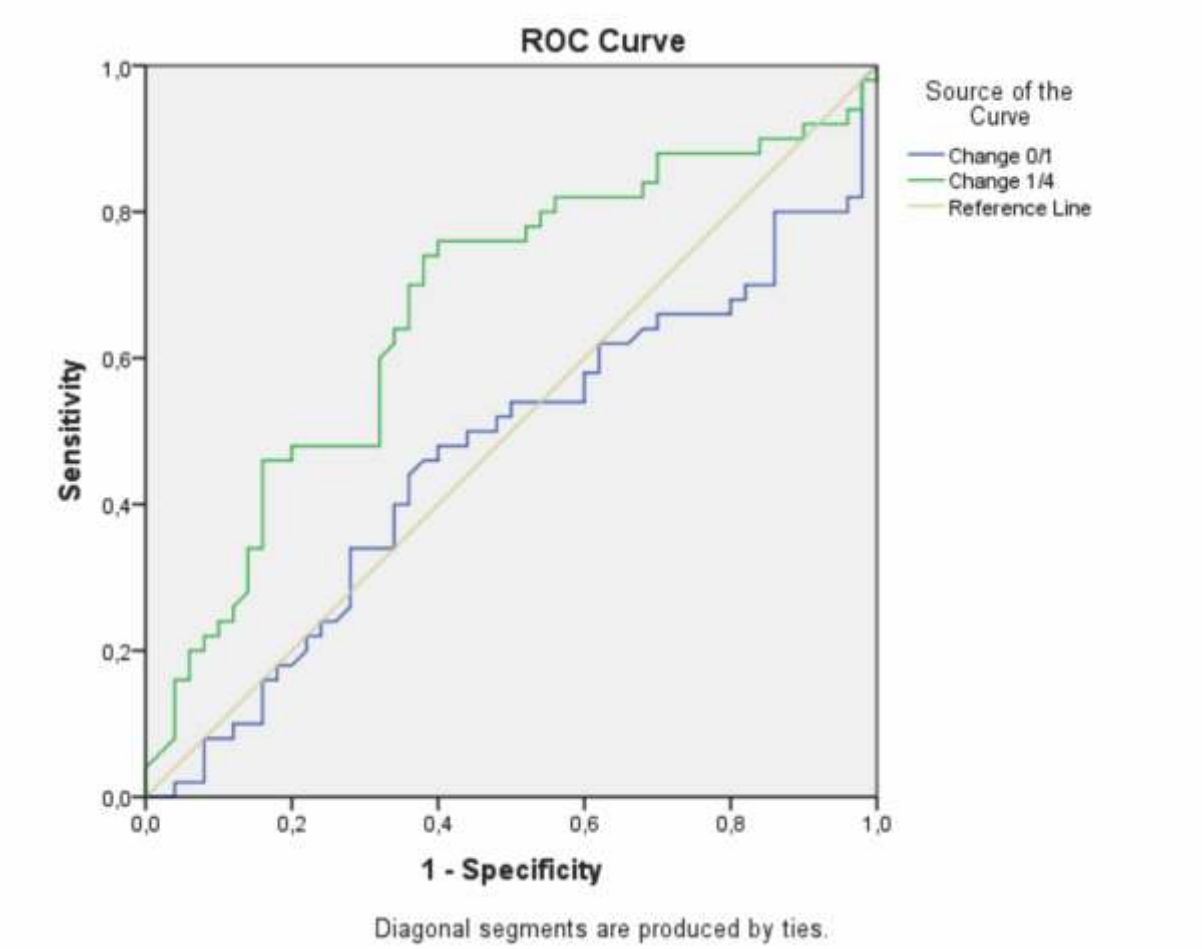

Fig. 1: Receiver Operating Characteristic Curve Analysis of the 24 h Pre-treatment Increment in HCG (%) and the Change in HCG Concentration from Day 1 to day 4 (%)

Discussion:

MTX reversible inhibits the conversion of folic acid to tetrapholic acid by inhibiting the dihydrofolate reductase enzyme [12]. It also acts by inhibiting other folate-bound enzymes such as 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (AICAR) [13]. There are two accepted protocols for MTX; single and multiple dose regimens. The overall resolution rate of ectopic pregnancy reported in the literature is about 90%, which is similar for both single and multiple dose protocols [14-15]. The single dose regimen is cheaper, requires less follow-up, and does not require calcium folinate support. Multiple dose protocols appear to cause more side effects [14]. Therefore, the single dose regimen appears to be more advantageous and is preferred more frequently. For women with tubal pregnancy treated with MTX, we suggest a single dose protocol in most cases.

The single dose protocol is administration of a single Intramuscular (IM) dose of MTX. The dose is administered as 50 mg/m^2. While most women

respond to a single dose of treatment, about 15-20% of women require a second dose of MTX. A third dose may be required in less than 1% patients [14].

The success of the treatment is evaluated based on the changes in β-hCG between days 4 and 7. If the decrease in β-hCG between days 4 and 7 is less than 15%, a second dose of MTX or surgery is applied [10-11]. In this process, patients are usually hospitalized and monitored. The long hospitalization period is an economic burden, causing loss of work force and making it difficult to adapt to treatment. If MTX success can be seen early, the second dose of MTX can be done earlier, with this prediction, early planning of treatment may increase the chance of success; while the trophoblastic tissue load is still low. Therefore, we looked for an answer to the question: "can treatment success be predicted earlier in a single dose MTX regimen?" In our study, although the β-hCG change at 24 hours before treatment was higher MTX treatment failed group, the difference between the groups was not significant in this regard.

There have been two previous retrospective studies on this subject. Levin *et al.* retrospectively examined 99 women in 2017 [16] and 292 women in 2019 [17] and found by both studies β-hCG variation within 24 hours before treatment was statistically significant in predicting treatment success. In our study, although the β-hCG change was higher in the MTX treatment failed group, the difference between was not significant. When we compared our study with these two studies, the pre-treatment mean value of β-hCG was observed to be quite high in the MTX treatment failed group with a value of 3381.78 ± 3424.39. This may reflect the fact that our patients were admitted later to our hospital, which is a tertiary center, and therefore were diagnosed later. Our study populations may be quite different; therefore, our medical treatment success may have been less. Because the success of single dose MTX in ectopic pregnancy is higher in early diagnosis and patients with a lower initial β-hCG value respond better to MTX treatment [18-20]. In addition, Levin *et al.* the use of similar populations in both studies of may have caused them to receive similar successful results.

In our study, β-hCG change between the 1st and 4th days of the patients was 25.01 ± 53.89% and -4.64 ± 47.26% in the treatment failed and successful groups respectively, with a statistically significant difference. Our findings are supported by the studies of Levin *et al.* [16,17]. There are other studies with similar findings in the literature [21-22], as well as those that argue for an insignificant change between days 1 and 4 [23]. One of our limitations may be the limited sample size. We attempted to compensate for such limitations by using strict patient selection criteria.

Conclusion:

This study concluded that the first 24-h β-hCG change at the beginning of treatment was not effective in predicting the success of MTX treatment. On the other hand, the β-hCG change between the 1st and 4th was an early predictors of the medical treatment success. To make the subject clear, there is a need for randomized controlled prospective and multicenter studies involving a larger number of patients.

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