Do the change in β-hCG values between the 0th and 4th day in tubal ectopic pregnancy treatment with a single-dose methotrexate (MTX) protocol, predict the need for a second dose of MTX?

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Abstract

Aim: The single-dose methotrexate (MTX) regimen is effective and minimizes side effects but an additional 2nd dose is needed in case of failure in an ectopic pregnancy (EP). We aimed to predict the additional MTX dose by evaluating the change in β-hCG values between day 0 and day 4 in EPs with administered single-dose MTX regimen.

Method: A total of 454 tubal EPs between 2013 and 2019 were evaluated retrospectively. *Cases cured with a single dose of MTX without an additional dose were accepted as the control group, and cases under a single-dose regimen were cured by applying a second dose of MTX on the 7th day were accepted as the study group. Obstetric and demographic characteristics and the change in β-hCG values compared in both groups.*

Results: Age, body mass index (BMI), gravida, smoking, abdominal surgery, presence of IUDs, initial β-hCG levels (0th day), and EP size were similar in both groups, but the presence of previous EP history was significantly higher in the study group. The change of β-hCG from days 0 and 4 determined that a 20% increase predicts the need for a 2nd dose of MTX with 72.4% sensitivity, and 87.8% negative predictive value (NPV).

Conclusion: The single-dose MTX protocol is successful in 83.3% of convenient cases (as the control group), but, an increase of 20% in β-hCG between days 0 and 4 predicts the patients that need to be administered 2nd dose MTX, and thus, a double-dose MTX protocol will be achieved early.

What does this study adds to the clinical work?

In tubal ectopic pregnancies, the single-dose methotrexate protocol is successful in 83.3% of convenient cases, but, under this protocol, an increase of 20% in β-hCG change between days 0 and 4 predicts the cases (16.7 %) that need to be administered 2nd dose MTX, and thus, by applying the 2nd dose of MTX to these cases on the 4th day without delay, a double-dose MTX protocol will be achieved early.

Introduction

Ectopic pregnancy (EP) is defined as the implantation of the fertilized ovum outside the uterus, frequently in the fallopian tubes, and occurs in approximately 2% of all pregnancies (1.) In patients diagnosed with EP, methotrexate (MTX) as medical treatment or surgical treatment is preferred, or expectant follow-up is performed according to the current condition of the patient, and ultimately, the decision on treatments methods to depends on many variables such as the patient's clinical findings, desire for fertility, beta-human chorionic gonadotropin (β-hCG) levels, localization and size of the lesion (2).

In the absence of contraindications, the recommended (GRADE A) protocol for the medical treatment of ectopic pregnancy is a single intramuscular MTX injection at a dose of 50 mg/m^2 and off-label use should be avoided (3). A single-dose MTX regimen is easy to administer, and as effective as a multiple-

dose regimen, minimizing side effects and eliminating the need for folinic acid (4). In the single-dose MTX regimen, serum β-hCG levels are evaluated on days 4th, and 7th after treatment, and a 15% reduction in β-hCG levels from day 4th to day 7th is considered an indication of successful treatment (5). However, if there is no 15% decrease on the 7th day, the same dose of MTX is repeated a second time (5).

The success rate of MTX treatment varies between 63% and 97%, depending on the treatment protocol and patient response (6). Although MTX treatment is quite effective, considering the success rates, it is not always successful in similar cases diagnosed with EP without contraindications for a single dose MTX regimen, and a second additional dose of MTX is required. Differences in patient response are also significant in MTX treatment success, due to treatment failure can be life-threatening with EP rupture, and it is necessary to predict a possible failure early. In addition, an increase in β-hCG is observed on the 4th day, although the etiology is not fully elucidated (7).

As a result, the need for a 2nd dose of MTX becomes clear only on the 7th day, and an increase in β-hCG levels can be observed on the 4th day. Clinicians and patients are faced with circumstances such as delays and failures in treatment, or overtreatment in this process. In this study, we aimed to predict the cases requiring an additional 2nd dose of MTX by evaluating the change between β-hCG values on the 0th and 4th days.

Methods

The study was designed retrospectively and female patients who were admitted to the early pregnancy service with the diagnosis of tubal EP between 2013 and 2019 were evaluated. In our clinic, tubal EP is diagnosed when there is no intrauterine gestational sac and tubal EP mass is observed in transvaginal ultrasonography (TVUS), chorionic villi are not observed in histopathology analysis after dilatation and curettage, and subsequent serum b-hCG levels are plateaued or increased irregularly and inappropriately. Patients with β-hCG value >10000 IU/ml, with lesion size larger than 4 cm, with a positive fetal heartbeat, cases with liver or kidney failure, and who underwent emergency surgical treatment during medical treatment were excluded from the study. A total of 454 tubal EPs administered to a single-dose MTX regimen of 50 mg/m^2 were applied intramuscularly were included in this study. In our clinic, the diagnosis, treatment, and follow-up of EP are applied according to the 2018 American College of Obstetrics and Gynecology (ACOG) guideline (5). Tubal EPs cured with a single dose of MTX without an additional dose were accepted as the control group, and tubal EPs under a single dose regimen were cured by applying a second dose of MTX on the 7^{th} day were accepted as the study group.

β-hCG follow-ups were recorded on the first day of MTX administration as day 0^{th} (or day 1^{st} in some studies), day 4^{th} (96 hours after MTX administration), and day 7^{th} (168 hours after MTX administration). The primary outcome of interest was the percent change in β-hCG from day 0^{th} to day 4^{th} and compared between groups. Also, in both groups, obstetric and demographic characteristics such as age, body mass index (BMI), gravity, parity, abortion, EP history, previous cesarean section, smoking, abdominal surgery history, and intrauterine device use (IUD) were determined. In addition, the size of EP, gestational age,

intra-abdominal free fluid, whether MTX was administered single or double, and cure (β-hCG < 0.5 mUI/ml) were also evaluated.

Statistical analysis

Analyzes were made with the SPSS 21.0 program and were studied at a confidence level of 95%. It is considered sufficient for the normal distribution that the kurtosis and skewness values obtained from the measurements are between +3 and -3. Numbers(n) and percentages(%) were calculated for categorical variables, and mean ± standard deviation (SD) was calculated for numerical variables. Statistical significance was taken as $p<0.05$. In two independent groups, parametric variables were analyzed with a t-test. The relationship between categorical variables was analyzed with the Chi-square test. The receiver operating characteristic (ROC) curve was used to show the sensitivity and specificity for the requirement of 2nd dose of MTX using a percentage change of β-hCG from day 0^{th} to 4^{th}. The detection value of β-hCG increases close to 1 when the area under the curve (AUC) value is greater than 0.5.

Results

Medical records of a total of 558 patients diagnosed with tubal EP and treated with a single-dose MTX treatment protocol were reviewed retrospectively. However, 4 patients with β-hCG value > 10000 mIU/ml, 12 patients with EP size greater than 4 cm, 1 patient with a positive fetal heartbeat, and 87 patients who underwent emergency surgical treatment due to medical treatment failure were excluded from the study, and a total of 454 patients were included in the study. A single dose of MTX for treatment was successful in 378 (83.3%) of the cases (control group), and 76 (16.7%) cases required a second dose of MTX on the 7th day of treatment (study group).

The demographic and clinical characteristics of both groups are presented in Table 1. The mean parity of the control group was higher than the study group (1.1 ± 1.1 vs. 0.7 ± 1.0, p = 0.004). The rate of previous EP was found to be higher in the study group (17.1%) than in the control group (8.2%) (p = 0.017). When the ultrasonographic findings were examined, the mean EP size of both groups was similar (study group 16.8 ± 6.9 mm vs. control group 17.9 ± 6.9 mm, p = 0.168). Pelvic-free fluid was observed in 27.6% of the study group and 28.6% of the control group (p = 0.868).

Table 1
Demographic and clinical characteristics of patients who received single-dose and two-dose methotrexate

	Single-dose MTX Control Group N = 378	**Two-dose MTX Study Group N = 76**	**P value**
Age (year)	29.9 ± 5.9	29.7 ± 5.2	0.856
Gravida	2.7 ± 1.5	2.4 ± 1.6	0.088
Parity	1.1 ± 1.1	0.7 ± 1.0	**0.004**
BMI (kg/m^2)	25.3 ± 4.3	25.5 ± 4.5	0.462
Presence of abortus	102(%27.0)	17 (%22.4)	0.404
Presence of previous EP	31 (%8.2)	13 (%17.1)	**0.017**
Presence of previous CS	113 (%29.9)	14 (%18.4)	**0.042**
Presence of smoking	96 (%25.6)	14 (%18.4)	0.184
Presence of abdominal surgery	136 (%36.0)	22 (%28.9)	0.240
Presence of IUD	30 (%7.9)	4 (%5.3)	0.419
Gestational age (day)	38.9 ± 15.0	41.8 ± 13.8	0.152
Size of EP (mm)	17.9 ± 6.9	16.8 ± 6.9	0.168
Persence of pelvic-free fluid	108 (%28.6)	21 (%27.6)	0.868
Data are presented as mean ± standard deviation or number (%). T-test and Chi-square test were used in statistical analysis.			
Abv: MTX; methotrexate, BMI; Body Mass Index, EP; Ectopic Pregnancy, CS; Cesarean section, IUD; Intrauterine Devices			

β-hCG levels were as seen in Table 2. On the 0th day, β-hCG levels of both groups were similar ($p > 0.05$). On the 4th day (803,2 ± 1307,8 vs. 1432,9 ± 1701,2 mIU/ml, $p = 0.003$) and 7th day (480,0 ± 792,4 vs. 1313,3 ± 1451,4 mIU/ml, $p < 0.001$) treatment group, β-hCG levels were lower in the control group than in the study group. On the 4th day of treatment, the total number of patients with decreased β-hCG values was 283 (62.3%), and the total number of patients with increased β-hCG values was 172 (37.8%). While the rate of patients with a decrease in β-hCG level between the 0th and 4th day of treatment in the control group was 69.6%, it was 26.3% in the study group ($p < 0.001$). The rate of patients with an increase in β-hCG level was found to be higher in the study group than in the control group (75.0% vs. 30.4%, $p < 0.001$).

Table 2
BHCG levels of patients who received single and two doses of methotrexate

	Single-dose MTX Control Group N = 378	Two-dose MTX Study Group N = 76	P value
β-hCG value on 0th day (mIU/ml)	1034,5 ± 1633,5	1177,3 ± 1294,9	0.465
β-hCG value on 4th day (mIU/ml)	827,0 ± 1384,2	1397,9 ± 1681,3	**0.006**
β-hCG value on 7th day (mIU/ml)	490,9 ± 841,7	1284,6 ± 1435,3	**< 0.001**
Amount of change in β-hCG between 0th and 4th day (mIU/ml)	-207,8 ± 1139,8	220,7 ± 663,3	**0.001**
Rate of change in β-hCG between 0th and 4th day (mIU/ml)	-0,16 ± 0.55	0,27 ± 0,55	**< 0.001**
Rate of patients with decreased β-hCG between 0th and 4th day	263 (%69,6)	20 (%26.3)	**< 0.001**
Percentage of decrease in β-hCG between 0th and 4th day	-0,41 ± 0,27	-0,23 ± 0,19	**< 0.001**
Rate of patients with increased β-hCG between 0th and 4th day	115 (%30,4)	57 (%75.0)	**< 0.001**
Percentage of increase in β-hCG between 0th and 4th day	0,43 ± 0,57	0,46 ± 0,52	0.714
Data are presented as mean ± standard deviation or number (%). T-test and Chi-square test were used in statistical analysis.			
Abv: β-hCG ; beta-human chorionic gonadotropin, MTX; methotrexate			

The percentage change of β-hCG between days 0th and 4th was evaluated, and a mean increase of 27% in the study group was observed, although it decreased by a mean of 16% in the control group ($p < 0.001$). ROC analysis has used the percentage of the change of β-hCG from days 0th and 4th, it was determined that a 20% increase could predict the need for 2nd dose of MTX with 72.4% sensitivity and 70.4% specificity (AUC 0.761, 95%CI 0.707–0.814, seen in Table 3). The positive predictive value (PPV) was 32.7%, and the negative predictive value (NPV) was 87.8% for the 20% cut-off value.

Discussion

Numerous publications have demonstrated comparable efficacy of medical treatment to surgical treatment in stable EPs if there are no contraindications (8). The multiple-dose protocol is beneficial for patients requiring additional doses but has the disadvantage that it has a high rate of side effects and requires the addition of folinic acid rescue alternately with MTX doses (9). A single-dose protocol may sometimes require additional doses during follow-up (5). Consequently, the two-dose protocol was developed to strike a balance between the benefits of increased treatment success from additional doses of MTX while using the same convenient visit schedule as the single-dose protocol (10). Unfortunately, data on which patients should receive a single or double dose of MTX are still limited. As in our clinic, clinicians apply a second dose of MTX if there is no 15% decrease in the single dose protocol on the 7th day (5). Our aim in this study is to evaluate the change of β-hCG between the 0th and 4th days, to predict the cases that require the 2nd dose of MTX application, and as a result, to apply the 2nd dose of MTX on the 4th day without delay in the treatment and achieve the two-dose protocol early.

In our study, age, BMI, gravida, abortion, smoking status, history of abdominal surgery, and presence of IUDs were similar in both groups, but the presence of previous EP history was significantly higher in the study group who received an additional 2nd dose of MTX on the 7th day. Tubal damage after an EP episode can impair the passage of the zygote from the fallopian tube into the uterine cavity, thus predisposing women to another EP (11). Data on MTX response in recurrent EPs caused by tubal injury are limited (12), and it is difficult to identify a unilateral and contralateral recurrence EP, due to the retrospective design of our study.

In fact, characteristics of EPs such as the size, the presence of a fetal heartbeat, and especially β-hCG levels, are key prognostic factors for predicting and evaluating the success of MTX therapy (13). However, initial β-hCG levels (0th day), gestational age, and EP size were similar in both groups in this study. Both groups with similar β-hCG levels on day 0th (1034,5 ± 1633,5 vs 1177,3 ± 1294,9 mIU/ml) responded differently to MTX treatment on day 4th, as seen in Table 2. Shatkin Hamish et al. (14), in their study with 159 patients, similarly found that 58.9% of the single-dose MTX regimen group had a successful decrease in β-hCG values between 0 and 4 days, while an increase in β-hCG values was observed by 76.2% in the unsuccessful group and, a > 18% reduction in β-hCG levels predicted treatment success (PPV 92%). However, in their study (14), baseline B-HCGs of both groups were significantly different and included both those who received a second dose of MTX and those who went to emergency surgery during treatment in the unsuccessful group. Akselim et al. (15) stated that the change in β-hCG value between the 1st and 4th days in the single-dose MTX protocol predicts the need for an additional dose and if there is a decrease of less than 4% (with 88.6% PPV), an additional dose of MTX on the 4th day. Lavie et al. (16) categorized levels of serum β-hCG were defined as follows: initial β-hCG level on the day of admission; β-hCG level on the day of MTX administration (0. day); rate of change per hour in the β-hCG level before MTX administration (calculated by dividing the difference between initial and day 0. by the number of hours between the two measurements); and the percent change in β-hCG levels before MTX administration. In their study with 119 patients, the initial β-hCG levels were significantly different in the successful and unsuccessful groups (763.1 vs. 1429.63 mIU/L, respectively) and the percent change in β-hCG level was 13.1%, which did not show a significant difference between the groups, however, hourly

change in β-hCG level was significantly lower in the successful group. (16). In another study (17), similarly, a β-hCG index value of 0.2 in the ROC curve (20% decrease in β-hCG value between day 1st and 4th) was found to be the best predictor for the success of single-dose MTX in EP treatment (sensitivity 0.6, specificity 0, 92, PPV 0.97 and NPV 0.35).

The strengths of our study were, in a large sample of 454 cases, with strict inclusion (those who were successfully treated with a single dose of MTX or an additional 2nd dose of MTX) and exclusion (exclusion of the group that went to surgery), determined the change of β-hCG between 0 and 4 days after a single dose of MTX in both groups with similar tubal EP characteristics and β-hCG values. As the limitations of the study, the only difference characteristically in tubal EP cases with similar features is the recurrence of EP, but due to the retrospective design of the study, the unilateral and contra-laterality of the recurrence could not be determined and its effect on the treatment response could not be investigated.

Conclusion

In tubal ectopic pregnancies, the single-dose methotrexate protocol is successful in 83.3% of convenient cases, but, under this protocol, an increase of 20% in β-hCG change between days 0 and 4 predicts the cases (16.7%) that need to be administered 2nd dose MTX, and thus, by applying the 2nd dose of MTX to these cases on the 4th day without delay, a double-dose MTX protocol will be achieved early.

Declarations

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There is no financial disclosure to be made for this study.

Disclosure statement

The authors declare no conflicts of interest.

Ethical Approval and Human Rights

Ethics committee approval was taken for this retrospective study from the Local Ethics Committee

All authors and the study protocol have complied with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving human subjects.

Consent to participate

Informed consent was obtained from patients who participated in this study.

Availability of data and materials

The data supporting this study is available through the corresponding author upon reasonable request.

Authorship Contributions

YA Reis: Project Development, Data Collection or Management, Manuscript Writing/Editing

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table

Table 1 is available in the Supplementary Files section.

Supplementary Files

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- Table3.docx