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The role of day 0 and day 4 β-human chorionic gonadotropin values and initial ultrasound findings in predicting the success of methotrexate treatment in ectopic pregnancy

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ABSTRACT

Objectives: To determine the role of baseline ultrasound findings and the changes between β- human chorionic gonadotropin (hCG) values on day 0 to day 4 in patients receiving single-dose methotrexate (MTX) therapy for tubal ectopic pregnancy.

Material and methods: One hundred fourteen patients who were hospitalized with a diagnosis of ectopic pregnancy and treated with single-dose methotrexate were included in this retrospective study. The successful treatment group (n = 88) comprised patients in whom serum β-hCG levels were resolved with single-dose methotrexate treatment, and the failed treatment group (n = 26) included patients who received second dose methotrexate and/or surgery. Ultrasound findings, laboratory findings, and serum β-hCG values at the time of admission and D4 and D7 β-hCG values were compared.

Results: The success rate of single-dose methotrexate treatment was 77.2%. In the successful treatment group, the initial β-hCG values of the patients were lower than the unsuccessful treatment group (1479.14 ± 1253.49, 4442.88 ± 3392.58, respectively) (p = 0.0001). A decrease of more than 35% between D0-D4 increased the probability of successful treatment (p = 0.017). Although ectopic focus size and abdominal free fluid showed no significant difference between the two groups, endometrial stripe thickness was significantly higher in the unsuccessful treatment group (12.61 ± 5.79, 9.28 ± 3.53) (p = 0.002).

Conclusions: In addition to the basal β-hCG value, endometrial stripe thickness of ultrasound findings should also be considered in determining patients with a high chance of success in single-dose MTX treatment.β-hCG changes between D0-D4 may be advantageous in the clinical management of ectopic pregnancy for earlier evaluation.

Key words: ectopic pregnancy; methotrexate; serum β-hCG; treatment success

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INTRODUCTION

Ectopic pregnancy (EP) is a condition in which the developing blastocyst is implanted in a tissue other than the uterine cavity endometrium, most commonly in the fallopian tube (98%) [1]. The incidence of ectopic pregnancy, which can cause severe maternal morbidity and mortality, is around 2% [2]. However, its frequency increases with each passing day due to increasing assisted reproductive technology (ART) applications and increasing pelvic inflammatory disease (PID) [3]. Nowadays, serial β-human chorionic gonadotropin (hCG) measurements and high-resolution ultrasound can be used for early diagnosis. Early diagnosis and treatment reduce maternal mortality, protects from tubal rupture, and allows fertility to be maintained.

Methotrexate (MTX), a folate antagonist, shows anti-mitotic activity in tissues with high proliferative capacity such as chorionic villi [4]. Medical treatment is a good alternative to surgery because it is effective, safe, and economical [5]. It was first reported by Tanaca et al. [6] that MTX was used successfully in the treatment of ectopic pregnancy in 1982. Single-dose, fixed multi-dose, and variable multi-dose regimens have been defined for MTX applications [7]. The most preferred single-dose protocol was developed by Stovall et al. [8] in 1991. Success in the single-dose protocol was defined as a decrease in β-hCG of > 15% between days 4 and 7 of MTX administration. The positive predictive value reaches 93% [9]. However, one-week follow-up increases the length of hospital stay or requires patient compliance

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for β-hCG follow-up. Also, during this time, tubal rupture may occur and emergency surgery may be required. Thus, an earlier predictive value, including baseline ultrasound data, to assess success may allow earlier intervention to those with a potential for treatment failure and make clinical management of ectopic pregnancy more effective.

Objectives

Evaluating the role of baseline ultrasound findings for determining patients with a high chance of success in single-dose MTX treatment. Although the cornerstone of MTX treatment monitoring is the change in β-hCG values between days 7 and 4, we are looking for an answer to the question of whether early prediction of the treatment success by evaluating change in β-hCG values between days 4 and 0 can bring a new perspective to clinical management of ectopic pregnancy.

MATERIAL AND METHODS

The data and patient files of patients who were hospitalized at our Training and Research Hospital with a diagnosis of ectopic pregnancy between May 2016 and December 2018 and treated with methotrexate were retrieved from the hospital's electronic registry system and retrospectively reviewed. Patient age, obstetric history, transvaginal ultrasound findings (ectopic focal size, endometrial stripe thickness, presence and amount of free fluid in the pouch of Douglas), complete blood count parameters, β-hCG values from days 0, 4, and 7 and following weeks, and treatment results were recorded.

The definitive diagnosis of ectopic pregnancy was made if the gestational sac and/or embryo were seen in the adnexal area and trophoblastic tissue was not observed in the uterine cavity on pathologic examination. Possible ectopic pregnancy diagnosis was defined as the presence of suspected adnexal mass or free fluid in the pouch of Douglas in the existence of abnormally increased or plateau β-hCG values or β-hCG values > 1500–2000 IU/L, with no intrauterine pregnancy observed on transvaginal ultrasound (TVUSG). These patients were candidates for methotrexate treatment in the absence of any contraindications to medical treatment; hemodynamic instability, acute abdominal findings, abnormal hematologic, renal, hepatic laboratory values, acute pulmonary disease, active peptic ulcer and breastfeeding mother.

While deciding on medical treatment/surgical treatment in our clinic, the patient's hemodynamic status, desire for fertility, ectopic focus size, serum β-hCG value, fetal heartbeat positivity, and compliance of the patient with the treatment process are considered. A single-dose MTX treatment protocol is applied to patients who are eligible as recommended in the American College of Obstetricians and Gynecologists Application Bulletin [10]. Day 0: β-hCG value, whole blood count, blood group, renal and hepatic function tests and lung radiography are evaluated in patients with a history of lung disease. Day 1: 50 mg/m^2 body surface area, intramuscular MTX is applied. Day 4: β-hCG, and day 7: complete blood count and β-hCG are examined. Successful treatment with single-dose MTX is a > 15% reduction in β-hCG between days 7 and 4, and a decrease in β-hCG of less than < 5 IU/L during weekly β-hCG follow-ups. Failure of single-dose MTX treatment was considered as the requirement for a repeated MTX dose due to a decrease in β-hCG values of days 7 and 4 < 15%, or surgical treatment of tubal rupture due to hemodynamic instability at any stage of treatment.

The study was started after receiving approval from the local ethics committee. The patients were divided into two groups according to the results of single-dose MTX treatment. Age, gravida, parity, laboratory findings, TVUSG findings, and β-hCG values at the start, 4th and 7th days were compared retrospectively between the groups.

Data were analyzed using the IBM SPSS Statistics 18© (SPSS Inc., 1989 2010) software package. The compatibility of continuous variables with normal distribution was examined using the Kolmogorov-Smirnov test. The categorical variables in the study are presented as frequency and percentage, and continuous variables as mean and standard deviation values. Chi-square and Fisher's Chi-square tests were used to analyze categorical variables. Since the independent comparisons of two groups did not meet the parametric test assumptions, the Mann-Whitney U test for independent measures of two group, and dependent groups were analyzed using the Friedman test. Furthermore, the possible factors determined by univariate analyzes were then analyzed by a multiple logistic regression model. The level of statistical significance was accepted as 0.05.

RESULTS

In this retrospective cohort study, the data of 304 patients admitted to our clinic with a diagnosis of ectopic pregnancy between May 2016 and December 2018 were reviewed; 21 patients were excluded from the study due to insufficient data or refusal of treatment. Expectant management was applied to 16 patients, spontaneous resolution was observed, and no additional treatment was required during the follow-up. One hundred fifty-three patients underwent primary surgical treatment.

Single-dose MTX was administered to 114 patients, 88 patients were treated successfully, and the success rate was 77.2%. Of the 26 patients who failed single-dose MTX treatment; 14 patients received a second dose of MTX, 10 patients underwent surgical treatment, and 2 patients had surgical treatment after a second dose of MTX.

The demographic data, and ultrasound and laboratory findings of the groups were divided according to MTX treatment success/failure (Tab. 1). Among the groups, there was no difference in terms of age (31.76 ± 5.77 vs 30.35 ± 5.66 years), gravida (2.84 ± 1.48 vs 2.46 ± 1.30), and parity (1.41 ± 1.09 vs 1.00 ± 0.89). Initial β-hCG values were found as 1479.14 ± 1253.49 in the successful treatment group and 4442.88 ± 3392.58 in the failed treatment group, which was statistically significantly different (p = 0.0001). β-hCG values at day 0, day 4, and day 7 were statistically lower in the successful treatment group than in the unsuccessful treatment group. Ectopic focal size showed no significant difference between the two groups (20.65 ± 10.48, 19.40 ± 5.95, respectively); however, endometrial stripe thickness was significantly higher in the unsuccessful treatment group (12.61 ± 5.79 vs 9.28 ± 3.53) (p = 0.002).

There was no correlation between the presence and amount of free fluid in the abdomen and the success or failure of treatment (Tab. 2).

In a multivariate logistic regression analysis, only two independent determinants; day 4 β-hCG values and day 7 β-hCG values were significantly associated with treatment success (Tab. 3).

The overall success rate of MTX treatment was 77.2%. The success rate was found as 87.5% for those with β-hCG values falling between D0-D4, and 59.5% in those whose values rose in the same period (Tab. 4).

A decrease of more than 35% between D0-D4 increases the probability of successful treatment (p = 0.017). Between D0–D4, 97.1% of those with a reduction of more than 35% had successful treatment (Tab. 5).

Table 1. Demographic data, and laboratory and ultrasonography data

	Successful (n = 88)	Unsuccessful (n = 26)	p value
Age	31.76 ± 5.77	30.35 ± 5.66	0.241
Gravida	2.84 ± 1.48	2.46 ± 1.30	0.288
Parity	1.41 ± 1.09	1.00 ± 0.89	0.131
Endometrial Thickness [mm]	9.28 ± 3.53	12.61 ± 5.79	0.002
Ectopic focus size [mm]	20.65 ± 10.48	19.40 ± 5.95	0.066
Hb	11.75 ± 1.38	11.87 ± 1.08	0.663
Plt	246.35 ± 82.69	253.67 ± 71.71	0.968
WBC	7.99 ± 2.49	8.02 ± 1.74	0.844
Neutrophils	7.94 ± 1.70	4.93 ± 1.54	0.891
Lymphocytes	2.02 ± 0.64	2.19 ± 0.40	0.584
β-hCG Day 0	1479.14 ± 1253.49	4442.88 ± 3392.58	0.0001
β-hCG Day 4	1133.81 ± 1044.38	5315.92 ± 4153.30	0.0001
β-hCG Day 7	609.59 ± 652.20	4779.96 ± 3525.71	0.0001

*Mann-Whitney U Test; Hb — Hemoglobin; Plt — Platelet count; WBC — White Blood Cell

DISCUSSION

Despite the advances in diagnostic and treatment methods, EP, which causes 6–13% of pregnancy-related deaths, is still an important cause of first trimester maternal deaths [1, 11]. Medical treatment with MTX is a good alternative to surgery

Table 2. The relationship between the presence of free fluid in the abdomen and treatment success

	Successful n (%)	Unsuccessful n (%)	Total n (%)	p value
Free liquid in the abdomen				
None	71 (77.2%)	21 (22.8%)	92 (100.0%)	0.149
Minimal	16 (84.2%)	3 (15.8%)	19 (100.0%)	
Plentiful	1 (33.3%)	2 (66.7%)	3 (100.0%)	

Minimal — < 3 cm free fluid; Plentiful — > 3 cm free fluid

Table 3. Multivariate logistic regression analysis of the factors associated with treatment success

Variable	OR	95% CI	p
Endometrial Thickness	1.211	0.942–1.557	0.135
β-hCG Day 0	0.999	0.998–1.000	0.220
β-hCG Day 4	0.996	0.993–1.000	0.027
β-hCG Day 7	1.008	1.003–1.012	0.001

*Nagelkerle R Square: 0.838; OR — Odds Ratio; CI — confidence interval

Table 4. Relationship between β-hCG 0-4 days change values and success rate

	Successful n (%)	Unsuccessful n (%)	Total n (%)	p value
Falling	63 (87.5%)	9 (12.5%)	72 (100.0%)	0.001
Rising	25 (59.5%)	17 (40.5%)	42 (100.0%)	
Total	88 (77.2%)	26 (22.8%)	114 (100.0%)	

*Chi-square test

Table 5. Effect of β-hCG change rates between D0-D4 on treatment success

	Successful n (%)	Unsuccessful n (%)	Total n (%)	p value
Decrease between D0-D4				
≤ 35%	29 (78.4%)	8 (21.6%)	37 (100.0%)	0.017
> 35%	34 (97.1%)	1 (2.9%)	35 (100.0%)	
Total	63 (87.3%)	9 (12.7%)	72 (100.0%)	
Increase between D0–D4				
≤ 18%	14 (66.7%)	7 (33.3%)	21 (100.0%)	0.346
≥ 18%	11 (52.4%)	10 (47.6%)	21 (100.0%)	
Total	25 (59.5%)	17 (40.5%)	42 (100.0%)	

* Chi-square and Fisher Chi-square test

because it is economical, effective, and non-invasive, but may not always be the best treatment option. Hemodynamic stability, the absence of fetal heartbeat, and absence of tubal rupture findings, which are accepted as indication for MTX treatment by most authors, but patient selection remains controversial with regard to the presence of abdominal free fluid and ectopic focus size [7, 10]. Some authors state that the ectopic focal size should be < 3.5 cm [10]. Kimiaei et al. [12] reported that in addition to initial β-hCG, ectopic focus size was also significant in evaluating treatment success. There are also studies reporting that ectopic focal size has no effect on treatment outcome [13, 14].

Gnıscı et al. [15] reported that hemoperitoneum was strongly associated with treatment failure and was more valuable than ectopic focal size and initial β-hCG value in predicting failure, but still found that MTX treatment was successful in more than half of all patients with hemoperitoneum. Lipscomb et al. [16] reported that free peritoneal fluid detection on ultrasound posed no risk for treatment failure in their study of 350 patients treated with MTX. The presence of free fluid in the abdomen may also be physiological [17]. Sargin et al. [18] stated that the first choice in treatment was medical treatment with expectant management or MTX, even if there was free fluid in the abdomen at the initial evaluation in a hemodynamically stable patient.

In our study, neither ectopic focus size nor the presence of free fluid in the abdomen was found to be associated with treatment failure. However, endometrial thickness was found to be significantly higher in the group with unsuccessful treatment (12.61 ± 5.79 mm) than in the successful MTX treatment group (9.28 ± 3.53 mm) (p = 0.002). Similarly, in a study where MTX treatment was successful, the mean endometrial thickness was 6.4 mm and the β-hCG value was 1936.2 mIU/mL, whereas in the group that failed, endometrial thickness was 11.7 mm and the mean β-hCG was found as 6831.3 mIU/mL [19]. In another study, it was reported that the rate of treatment failure with MTX increased if endometrial thickness > 12 mm [20]. Endometrial thickness was said to reflect the serum β-hCG level of the patient.

Soares et al. [21] reported that fast rising β-hCG values before treatment, as another predictive variable in the selection of patients for medical treatment of ectopic pregnancy with MTX, were effective in predicting treatment failure. In previous studies, baseline β-hCG is the most recommended parameter for successful treatment prediction. In the literature, close β-hCG thresholds for MTX treatment success have been reported. Rabischong et al. [22] found this value as 1300 IU/L, Markwitz et al. [23] reported 1790 IU/L, Pulatoglu et al. [24] found 1362 IU/L, and Corsan et al. [25] reported 1500 IU/L. In the current study contrary to expectations initial β-hCG value was not found to be an independent factor for the treatment outcome, similar with Levin at al. [26] Large range (72–12660) of the initial β-hCG values; including patients with a higher β-hCG concentration above the upper concentration limit allowed for single-dose regimen in the American College of Obstetricians and Gynecologists Application Bulletin [10] may have been effective on this finding.

The fact that cytotrophoblasts had a doubling time of 48 hours led investigators to evaluate earlier than 7 days to determine the efficacy of MTX, which inhibits cellular DNA synthesis by inactivating dihydrofolate reductase [27]. In a retrospective study of 30 patients, Nguyen et al. reported treatment success as 100% in patients with a decrease in β-hCG values on day 4, a decrease between D0–D4 was highly predictive, and that these patients might not need to be followed up on day 7, also avoiding an unnecessary second MTX dose [28]. Again, in a retrospective study of 45 patients, the single-dose MTX success rate was 76%, and the treatment success rate was reported as 88% in patients with decreased D0–D4 β-hCG [29]. In a prospective study of 129 patients, Agostini et al. [30] reported that a > 20% reduction in D0-D4 β-hCG values was effective in predicting MTX success with a positive predictive value of 97%. In a case-control study of 140 patients by Mashiach et al. [31], it was reported that an increase of more than 50% of β-hCG between D0–D4 indicated MTX treatment failure; however, it may help clinical management by giving an idea of MTX treatment outcomes in borderline situations rather than making a surgical decision based on this increase. In a recent retrospective study of 121 patients, it was stated that monitoring could be reduced in patients with a > 30% decrease in D0–D4 β-hCG values, and in patients with a > 70% increase, second-dose MTX could be administered [32]. Finally, Levin et al. advocated that β-hCG increment of less than 17% in the 24 hr pretreatment, and a decrease of more than 22% between day1 and day 4 β-hCG concentations might predict the success of single-dose MTX treatment [26]. In our study, the overall success rate was comparable to the literature with 77.2% [13, 24, 28, 29]. The success rate of single-dose MTX treatment for those whose β-hCG values fell between D0–D4 was 87.3%, and 59.5% in those whose levels rose. Single-dose MTX treatment was successful in 97% of patients with D0–D4 β-hCG values with a > 35% decrease. However, an increase rate that predicted success was not determined in patients with increased D0–D4 β-hCG values. A small number of successful patients who had an increase in β-hCG values between D0-D4 might be restrictive.

CONCLUSIONS

Determining the most appropriate patient for MTX treatment and evaluating the early changes in β-hCG values in the medical treatment of EP with MTX will contribute to cost reduction, reduce the patient's anxiety, and provide

further treatment options if needed. Timely surgical intervention will contribute to the preservation of the fertility of the patient. Large-scale prospective studies are needed to determine the direct effect of early changes in β-hCG on clinical outcomes.

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