



Prediction of Single Dose Methotrexate Success in Ectopic Pregnancy Treatment

© Berna Aslan Çetin¹, © Begüm Aydoğan Mathyk²

¹University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey

²University of North Carolina Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Chapel Hill, North Carolina, USA

Abstract

Objective: To investigate the efficacy of single-dose methotrexate treatment and the factors affecting its success in the treatment of ectopic pregnancy.

Methods: Ectopic pregnancy cases treated with single dose methotrexate treatment between January 2013 and December 2017 were compared as successful and unsuccessful. Demographic characteristics of patients, ectopic mass size, beta human chorionic gonadotropin (β -hCG) values at the beginning of treatment and at 4th and 7th days were evaluated.

Results: A total of 462 patients, who underwent single dose methotrexate treatment as initial ectopic pregnancy treatment, were included in the study. Single dose methotrexate treatment was successful in 350 patients (75.8%) and failed in 112 patients (24.2%). Serum β -hCG levels on the day of methotrexate administration, β -hCG values at 4th day and at 7th day, and ectopic mass size were significantly higher in the failed group ($p < 0.001$).

Conclusion: There are a number of factors affecting the success of single dose methotrexate treatment in ectopic pregnancy in hemodynamically stable patients. The most important of these are ectopic mass size and initial β -hCG value.

Keywords: Ectopic pregnancy, single dose, methotrexate

INTRODUCTION

Ectopic pregnancy is the implantation of a blastocyst somewhere other than the endometrial cavity (1). It is one of the most important causes of mortality and morbidity in the first trimester (2). The incidence in all pregnancies varies between 0.5 and 2% (1). The incidence of ectopic pregnancy has increased in recent years due to the increase in the frequency of previous pelvic infections, increased use of intrauterine devices, increased incidence of pelvic inflammatory disease, and increased pregnancy assisted reproductive techniques (3). Early diagnosis and treatment of ectopic pregnancies can be made thanks to the fact that beta human chorionic gonadotropin (β -hCG) values can be routinely examined and transvaginal ultrasonography becomes widespread (4). Medical treatment, surgical treatment or wait and see method are the treatment options. Patients can benefit from medical treatment when the diagnosis can

be made while the patients are hemodynamically stable and before rupture (5,6). Medical treatment has many advantages over other treatments; these include less tubal damage, lower cost and preservation of fertility. Single dose methotrexate treatment is an effective and safe medical treatment and success rates vary between 64% and 94% (7). Methotrexate dose may be repeated or surgery may be performed in patients who fail single dose treatment (8-11). In this study, we aimed to compare successful and unsuccessful patients who underwent single-dose methotrexate treatment for ectopic pregnancy in our hospital and to determine the factors affecting success.

METHODS

Our study is a retrospective case-control study involving patients who were treated for ectopic pregnancy in the Clinic of Obstetrics and Gynecology, Kanuni Sultan Süleyman Training



Address for Correspondence: Berna Aslan Çetin, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
Phone: +90 533 220 13 14 E-mail: bernaaslan14@hotmail.com ORCID ID: orcid.org/0000-0001-6856-1822

Cite this article as: Aslan Çetin B, Aydoğan Mathyk B. Prediction of Single Dose Methotrexate Success in Ectopic Pregnancy Treatment. Eur Arch Med Res 2019; 35 (4): 201-4

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European Archives of Medical Research published by Galenos Publishing House.

Received: 09.04.2018

Accepted: 27.08.2018

and Research Hospital between January 2013 and December 2017. After the approval of the ethics committee, the records of 461 patients who were hospitalized with ectopic pregnancy and who received single-dose methotrexate treatment were evaluated retrospectively. Diagnosis of ectopic pregnancy was made when serum β -hCG level >1500 mIU/mL and transvaginal ultrasonography failed to show intrauterine gestational sac or succeeded to show ectopic focus, or less than 60% increase in β -hCG levels in 48 hours or plateau when β -hCG level <1500 mIU/mL, or absence of chorionic villus in pathological examination after dilatation curettage and/or patency of elevated β -hCG values despite curettage. The definite contraindications of methotrexate treatment were unstable hemodynamics, active hepatic or renal disease, and relative contraindications were β -hCG >10.000 mIU/mL and fetal cardiac activity. A single dose of 50 mg/m^2 methotrexate was administered intramuscularly. Treatment was considered successful if β -hCG levels decreased by more than 15% between the 4th and 7th days of treatment and the serum β -hCG levels decreased below 5 mIU/mL at weekly follow-up. Patients who had an increase in serum β -hCG concentration, less than 15% decrease on the 7th day of treatment or rupture were treated with a second dose of methotrexate or surgical treatment. Treatment was considered to be unsuccessful in patients who required surgery or second dose methotrexate.

Statistical Analysis

Statistical analyzes were performed using the Statistical Package for Social Sciences 20.0 (SPSS Inc., Chicago, IL, USA) program. The distribution of the data was evaluated by Kolmogorov-Smirnov test. Descriptive statistical methods (mean, standard deviation) as well as independent t-test were used for the comparison of the normally distributed data. Results were evaluated at $p < 0.05$ level of significance. In ROC analysis, serum β -hCG levels and cut-off values, sensitivity and specificity were determined for methotrexate success at the 1st, 4th and 7th days.

RESULTS

A total of 462 patients who were diagnosed as ectopic pregnancy between January 2013 and December 2017 and treated with single dose methotrexate as initial treatment were included in the study. Single dose methotrexate treatment was successful in 350 (75.8%) patients, but failed in 112 (24.2%) patients and the second dose methotrexate or surgical treatment was applied in these patients.

Table 1 shows a comparison of the demographic and clinical characteristics of successful and unsuccessful groups. There was no significant difference between the two groups in terms of age,

gravidia, parity, hemoglobin and hematocrit values. Serum β -hCG values on the day of methotrexate administration, β -hCG levels at the 4th and 7th day and ectopic mass size were significantly higher in the unsuccessful group ($p < 0.001$). Figure 1 shows ROC analysis for methotrexate success and β -hCG levels and mass size. According to the ROC analysis, when the cut-off value of β -hCG was taken as 2.000 mIU/mL on the day of methotrexate administration, the sensitivity and specificity were 81% and 83%, respectively. When the cut-off value of β -hCG was taken as 2.500 mIU/mL at the 4th day, sensitivity was 82%, specificity was 90%, and when the cut-off value of β -hCG was taken as 2.100 mIU/mL at the 7th day, sensitivity was 83%, specificity was 92%. When the cut-off value for ectopic mass size was calculated as 20 mm, the sensitivity and specificity of predicting methotrexate success were 75% and 56%, respectively.

Table 1. Comparison of demographic and clinical characteristics of the two groups

	Successful (n=350)	Unsuccessful (n=112)	p
Age	29.97 \pm 5.62	29.95 \pm 5.32	0.963
Gravida	2.90 \pm 1.54	2.81 \pm 1.60	0.593
Parity	1.19 \pm 1.07	1.13 \pm 1.08	0.624
Abortus	0.63 \pm 0.60	0.58 \pm 0.52	0.646
Gestation week	5.88 \pm 1.71	6.12 \pm 1.79	0.189
Hemoglobin (g/dL)	12.06 \pm 1.40	12.04 \pm 1.26	0.855
Hematocrit (%)	36.66 \pm 3.80	36.70 \pm 3.42	0.913
β -hCG 1 (mIU/mL)	1369.67 \pm 1013.71	3876.59 \pm 3108.21	<0.001
β -hCG 4 (mIU/mL)	1207.55 \pm 1157.48	4292.66 \pm 2718.72	<0.001
β -hCG 7 (mIU/mL)	866.70 \pm 799.39	4067.01 \pm 2314.14	<0.001
Mass size (mm)	12.97 \pm 11.53	23.35 \pm 13.03	<0.001

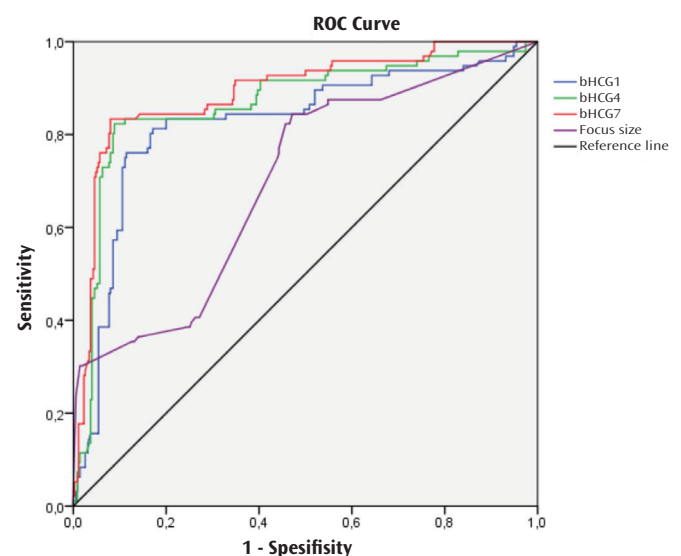


Figure 1. ROC analysis of factors influencing methotrexate success

DISCUSSION

In the treatment of ectopic pregnancy, wait and see method, medical and surgical treatment can be applied. Which of these methods is preferred is decided by considering the clinical and laboratory findings and fertility of the patient (12). In this study, we investigated the factors that affect the success of methotrexate in patients receiving single dose methotrexate treatment. With the early diagnosis of ectopic pregnancy cases, medical treatment options have started to be developed without damaging the tubes. Methotrexate is the most successfully used medical agent for this purpose. Methotrexate is a folic acid antagonist and inhibits the formation of tetrahydrofolate required for DNA, RNA and adenosine triphosphate synthesis (13). In ectopic pregnancies, methotrexate treatment can be administered as single dose or multiple doses, local or systemic. As experiences with methotrexate have increased, single-dose regimens have emerged to simplify treatment, improve compliance, and reduce side effects and cost. Successful results have been obtained with systemic administration of single dose methotrexate (14). In this study, all patients were initially treated with a single dose methotrexate protocol. Methotrexate is used as a medical agent in the treatment of ectopic pregnancy. The success of the drug is related to the clinical and laboratory findings of the patient (15). The definite contraindications of methotrexate treatment are unstable hemodynamics, active hepatic or renal disease, and relative contraindications are β -hCG >10.000 mIU/mL and fetal cardiac activity (16). Success rates of single dose methotrexate use range from 64% to 94% (17). Similar to the literature, the success rate was 75.8% in our study. There are limited publications on the factors that affect the success of single dose methotrexate treatment in ectopic pregnancy. While high serum β -hCG levels were found to be the only effective prognostic factor in a study (17), Kimiaei et al. (18) found that ectopic mass size, in addition to initial β -hCG level, was a factor affecting the success of the single-dose methotrexate treatment. In some studies, in addition to the high initial β -hCG level, the decrease in β -hCG levels at the 4th day after methotrexate treatment was suggested to be the most important prognostic factor in predicting success (19,20). In a study performed by Mungan et al. (21) it was shown that the location of ectopic pregnancy in tubes was important in determining the success of single dose methotrexate treatment. The success of methotrexate has been shown to be better in periampular ectopic pregnancies compared to periistmic location (21). In our study, we determined ectopic mass size and serum β -hCG levels as factors affecting success. We found that treatment success was reduced when the ectopic mass was over 20 mm. Serum β -hCG levels are closely related to medical

treatment and success rates. In the study of Lipscomb et al. (22) β -hCG levels were significantly higher in the single-dose methotrexate unsuccessful group. Lipscomb et al. (22) reported that β -hCG at the beginning of treatment was the best prognostic data for predicting methotrexate success. In their study, they determined a success rate of 94% when the initial β -hCG level was below 10.000 and 75% when it was above 10.000. More recent publications have shown that this cut-off value is more effective between 2.000 and 3.000 (19). In our study, we found that treatment success was higher when the initial β -hCG cut-off value was below 2.000.

CONCLUSION

In conclusion, there are many factors affecting the success of single dose methotrexate treatment in ectopic pregnancy. The most important of these are the ectopic mass size and initial β -hCG level. The patient's fertility status, clinical and laboratory findings, and serum β -hCG follow-up are important considerations in the planning of appropriate treatment.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sadi Konuk Training and Research Hospital (2017/414).

Informed Consent: Informed consent is not obtained due to the retrospective nature of this study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A.Ç., Concept: B.A.Ç., B.A.M., Design: B.A.Ç., B.A.M., Data Collection or Processing: B.A.Ç., Analysis or Interpretation: B.A.M., Literature Search: B.A.M., Writing: B.A.Ç.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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