



Clinical Characteristics of Patients with Ectopic Pregnancies Treated with Additional Doses of Methotrexate

Ek Doz Metotreksat ile Tedavi Edilen Ektopik Gebelik Hastalarının Klinik Özellikleri

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ÖZET

AMAÇ: Ektopik gebeliğin medikal tedavisinde kullanılan metotreksatın uygulama rejimleri farklılık göstermektedir. Bu çalışmada tek doz ve tekrarlayan doz metotreksat rejimlerini belirleyen faktörler araştırılmıştır.

GEREÇ VE YÖNTEM: 3. basamak bir merkezde, 1 Ocak 2012 ile 31 Ağustos 2022 tarihleri arasında, ektopik gebelik tanısı almış hastalar (n=383) retrospektif olarak incelendi. Takipten çıkan (n=36) ve cerrahi olarak tedavi edilenler (n=186) çalışma dışı bırakıldı. Tek doz metotreksat ile tedavisi sağlanmış (n=128) ve ek doz uygulanmış (n=30) hastalara ait tıbbi özellikler, ultrasonografi bulguları ve laboratuvar değerleri karşılaştırıldı. $p < 0,05$ değeri anlamlı kabul edildi.

BULGULAR: Hasta özellikleri ve tıbbi özgeçmişler arasında anlamlı fark görülmedi. Ultrasonografide pelvik serbest sıvı miktarı fazla olanlarda ek doz ihtiyacı daha az olarak görüldü ($p < 0,001$). 4. gün/1. gün β -hCG oranı 0,8474 ve üzerinde olan hastalarda ek doz metotreksat ihtiyacının arttığı görüldü ($p < 0,001$).

SONUÇ: Ektopik gebeliğin etkin medikal tedavisinde hasta seçimi için farklı parametreler tanımlanmıştır. Bu çalışmada tanı anındaki ultrasonografi bulgularının ve takipteki β -hCG oranlarının hasta seçimine etkileri kantitatif olarak saptanmıştır. Ultrasonografi bulguları ve 4. gün/1. gün β -hCG oranının birlikte değerlendirilmesi ek doz metotreksat ihtiyacı olan hastaları belirlemeye yardımcı olabilir.

Anahtar kelimeler: Beta-human koryonik gonadotropin, ektopik gebelik, metotreksat

ABSTRACT

AIM: Dose regimens of methotrexate used in the medical treatment of ectopic pregnancy vary. In this study, factors determining single-dose and additional-dose methotrexate regimens were investigated.

MATERIAL AND METHOD: Patients diagnosed with ectopic pregnancy between 1 January 2012 and 31 August 2022 at a tertiary care center were reviewed, retrospectively (n=383). Those lost to follow-up (n=36) and those who underwent surgery (n=186) were excluded. Medical characteristics, ultrasonography findings, and laboratory values of patients treated with single-dose methotrexate (n=128) and patients treated with additional doses (n=30) were compared. $p < 0.05$ was considered significant.

RESULTS: There was no significant difference between the patient characteristics and medical history. The need for additional dose was less in patients with more pelvic fluid on ultrasonography ($p < 0.001$). Patients with a day 4/day 1 β -hCG ratio of 0,8474 and above required an additional dose of methotrexate ($p < 0.001$).

CONCLUSION: Different parameters have been defined for patient selection for effective medical treatment of ectopic pregnancy. In this study, the effects of ultrasonography findings and β -hCG levels at follow-up on patient selection were quantitatively determined. The combination of day 4/day 1 β -hCG ratio and ultrasonography findings may help to identify patients in need of additional doses of methotrexate.

Keywords: Beta-human chorionic gonadotropin, ectopic pregnancy, methotrexate

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INTRODUCTION

An ectopic pregnancy occurs when the developing blastocyst implants in a location outside the uterine cavity and this ectopic focus is the tuba uterina 96% of the time.¹ It is also rarely seen in the isthmus and ampulla.² The incidence of ectopic pregnancy varies between 0.6% and 2%.^{3,4} Among all causes of pregnancy requiring emergency surgery, ectopic pregnancy ranks first.⁵ Ectopic pregnancy accounts for 9% of all pregnancy-related mortality and more than 75% of first-trimester mortality.⁶ In hemodynamically stable patients, medical treatment with systemic methotrexate or follow-up-monitoring options are appropriate. There is insufficient data for the efficacy of the follow-up-monitoring approach.⁷ There are mainly single-dose, two-dose, and fixed multiple-dose regimens for patients to receive methotrexate.⁸ Although the treatment efficacy of single-dose and multiple-dose regimens is similar (90%), the single-dose regimen is usually chosen because multiple-dose regimens have more side effects.^{7,9} In single-dose regimens, 14% of patients eventually receive two or more doses, while in multi-dose regimens 10% of patients receive only a single dose.¹⁰ Criteria such as β -hCG level, ectopic focus size, and hemodynamic status have been defined to decide on the methotrexate option.¹¹ In this study, we investigated patients with ectopic pregnancy who were treated with methotrexate and planned to reveal the characteristics of those who needed an additional dose of methotrexate.

MATERIAL AND METHOD

The data of patients with a diagnosis of ectopic pregnancy were analyzed, retrospectively. Among these patients, those who received a single dose of methotrexate and achieved treatment success and those who needed an additional dose were compared. Methotrexate was administered 50 mg/m² body surface area (BSA), intramuscularly. Ectopic pregnancy was diagnosed with extrauterine focus and/or rupture findings or laboratory findings without intrauterine pregnancy findings on transvaginal ultrasonography. Obstetric history, age, previous operation, smoking status, complete blood count parameters (hemoglobin, hematocrit, leukocyte count), β -hCG levels (day 1, 4, and 7), ultrasonographic features (presence of ectopic focus, size, and localization of ectopic focus, endometrial thickness, presence of pelvic fluid) at the time of diagnosis were recorded and comparisons were made between groups. SPSS 22.0 program was used for data analysis. The Kolmogorov-Smirnov test was used to evaluate whether the data conformed to normal distribution. Student t-test and Mann-Whitney U test were used for numerical variables and Mc Nemar and Chi-square tests were used for categorical variables. $p < 0.05$ was considered significant. Approval was obtained from the Ethics Committee of the centre where the study was conducted, with decision dated 28/08/2022 and number E-22-1064.

RESULTS

Between January 01, 2012, and August 31, 2022, the records of patients hospitalized in the Gynecology and Obstetrics Clinic of Ankara Training and Research Hospital with the diagnosis of ectopic pregnancy were obtained from the electronic database. Patients who were treated surgically (n=186), whose follow-up information was not available, and who refused treatment (n=36) were excluded. Patients treated with a single dose of methotrexate with treatment success were selected as the control group (n=128). Thirty-three patients who could not be treated with a single dose were treated with an additional dose of methotrexate (n=30) or surgically (n=3). Patients who were treated with a single dose of methotrexate but did not have sufficient decrease in β -hCG levels and who were treated with an additional dose of methotrexate constituted the case group (n=30)

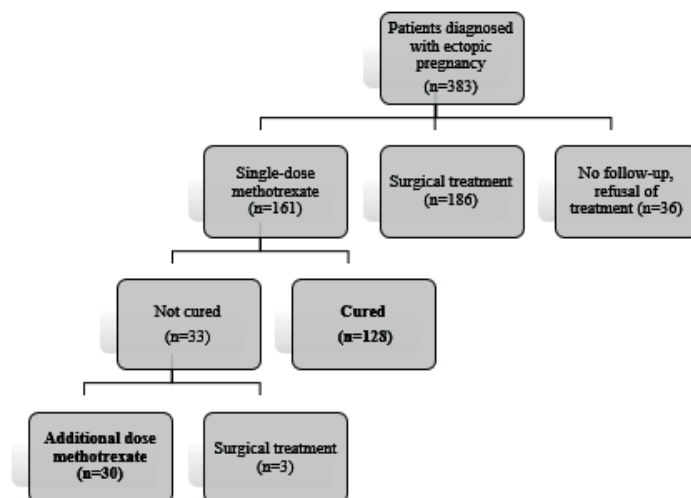


Figure 1. Distribution of patients diagnosed with ectopic pregnancy according to treatment modalities

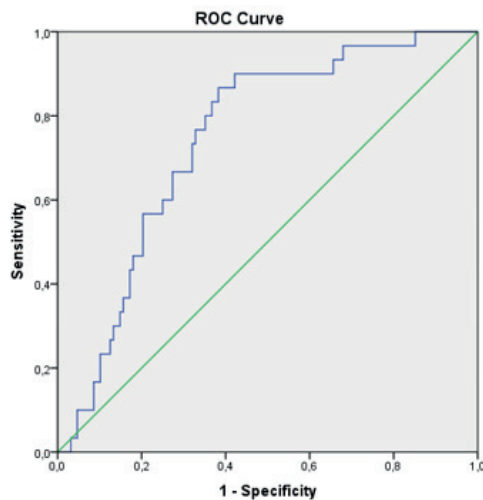
On the day of methotrexate administration (day 1), day 4, and day 7 β -hCG levels were analyzed. The patients who achieved treatment success with a single dose (n=128) and those who needed an additional dose (n=30) had similar mean ages (30.8 \pm 5.8 and 30.8 \pm 6.5, respectively). There was no statistically significant difference between the two groups in terms of demographic and medical characteristics. There was a statistically significant correlation between the patients who needed an additional dose of methotrexate and those who received a single dose in terms of the size of the free fluid detected by ultrasonography in the pelvis. Although there was no significant difference in terms of the location of free fluid in patients with free fluid, the need for additional doses was higher in patients with less fluid amounts ($p < 0.005$). β -hCG levels were higher in patients who received additional doses on days 1, 4 and 7 (2471.85 \pm 1004.59, 1874.00 \pm 613.27, 2442.91 \pm 802.42 vs 1268.21 \pm 143.0, 937.02 \pm 125.47, 300.26 \pm 42.33, respectively)

Table 1. Comparison of patients' demographic and clinical variables

	Single-dose methotrexate (n=128)	Repeated dose methotrexate (n=30)	p
Age (Mean \pm SE)	30.8 \pm 5.8	30.8 \pm 6.5	0.360
Gravida, n (median, min. - max.)	3 (1-10)	3 (1-8)	0.892
Parita, n (median, min. - max.)	1 (0-5)	1 (0-4)	0.307
D&C history, n (%)	20 (%15.6)	7 (%23.3)	0.313
IVF pregnancy (current pregnancy), n (%)	9 (%7)	2 (%6)	0.944
Using a contraceptive method, n (%)	58 (%45.3)	12 (%40)	0.350
Presence of chronic disease, n (%)	21 (%16)	0 (%0)	0.957
Chronic medication use, n (%)	11 (%8)	0 (%0)	0.735
Previous abdominal surgery, n (%)	41 (%32)	13 (%43)	0.240
Previous ectopic pregnancy, n (%)	16 (%12)	4 (%13)	0.902
Smoking, n (%)	42 (%32)	12 (%40)	0.455
Day 1 β -hcg (mean \pm SE) (mIU/ml)	1268.21 \pm 143.0	2471.85 \pm 1004.59	<0.001
Day 4 β -hcg (mean \pm SE) (mIU/ml)	937.02 \pm 125.47	1874.00 \pm 613.27	0.001
Day 7 β -hcg (mean \pm SE) (mIU/ml)	300.26 \pm 42.33	2442.91 \pm 802.42	<0.001
Hemoglobin (g/dL) (mean \pm SE)	11.9 \pm 1.61	12.2 \pm 1.27	0.453
Hematocrit (%) (mean \pm SE)	36.1 \pm 4.40	36.9 \pm 3.25	0.344
Leukocyte (10 ⁹ /L) (mean \pm SE)	8306 \pm 2273.26	7994 \pm 1725.07	0.178
Endometrial thickness (mm) (mean \pm SE)	7.8 \pm 4.2	7.7 \pm 3.3	0.333
Presence of free fluid (%)	44 (%34)	5 (%16)	0.059
Size of free fluid (mm) (mean \pm SE)	8.4 \pm 13.6	3.6 \pm 9.8	0.001
Presence of ectopic focus (%)	86 (%67)	16 (%53)	0.153
Ectopic foci size (mm2) (mean \pm SE)	396 \pm 552.32	264 \pm 441.3	0.253
Initial dose of MTX (mg) (mean \pm SE)	82.37 \pm 12.51	82.33 \pm 9.5	0.279

D&C: dilation & curettage, IVF: in-vitro fertilization, MTX: Methotrexate, SE: Standard Error

Patients with β -hCG levels below the diagnostic threshold had signs of extrauterine pregnancy or rupture. Day 4/day 1 β -hCG ratios were analyzed in both groups and the threshold value was obtained by creating a ROC curve. Accordingly, it was observed that the need for additional dose increased at ratios of 0.8474 and above ($p < 0.001$) (Sensitivity=66.7 %, Specificity=68.0%, % 95 CI)



AUC: 0.744 (0.658-0.831 % 95 CI), $p < 0.005$, Cut-off: 0.8474, Sensitivity=66,7 %, Specificity=68.0%

Figure 2. ROC curve analysis for Day 4/Day 1 β -hCG ratio

DISCUSSION

There are two cornerstones in the medical management of ectopic pregnancy: the success rate and the incidence of adverse events. Treatment focuses on lower doses of methotrexate to treat the patient. Completing the treatment in a short time reduces the length of hospital stay and costs. On the other hand, lower doses may result in lower success rates. Clinicians therefore need more specific information to manage the patient. All attempts to define specific criteria are a result of these needs.

According to a meta-analysis, the treatment success of two doses of methotrexate is higher than single dose. In the presence of high β -hCG levels and large adnexal mass, the success of two doses increases even more. There is no statistically significant difference between the two methods in terms of the need for surgical procedures and follow-up period. On the other hand, single-dose methotrexate has a lower incidence of side effects.¹²

According to the guidelines on the treatment of ectopic pregnancy, it is known that surgical treatment should be considered primarily in cases that will cause hemodynamic instability, but there is no consensus on medical treatment approaches.¹³

In a study in which single-dose, two-dose, surgical, and follow-up methods were examined, it was observed that baseline β -hCG level and ectopic focus size were significant in determining treatment success, but patient characteristics were not significant.¹⁴ Similarly, in our study, it was observed that demographic and medical characteristics of the patients (age, gravida, history of infertility or abortion, previous pelvic surgery, infection, location of ectopic focus, etc.) did not make a significant difference in terms of single dose and additional dose administration.

Single-dose and multi-dose methotrexate efficacy and characteristics between patient groups were compared in unruptured ectopic pregnancies and it was found that β -hCG level, progesterone level, presence of cardiac activity, presence of yolk sac, endometrial thickness and ectopic focus size were not different between treatment groups.¹⁵

There was a significant difference between the patient groups in our study in terms of the amount of pelvic free fluid ($p < 0.001$). It was observed that the need for additional doses was less in patients with more fluid. This may be associated with the fact that pelvic free fluid may occur as a result of spontaneous tubal abortion.

In a study aiming to predict methotrexate treatment success, basal progesterone level and the ratio of day 4/day 1 β -hCG levels were

examined and it was found that medical treatment success may be higher in patients with a β -hCG day 4/day 1 ratio lower than 0.7, but progesterone level was not effective in prediction.¹⁶ Another study concluded that in patients started on a single dose of methotrexate, a more than 22% decrease in β -hCG levels between days 1 and 4 may help predict the need for additional doses.¹⁷ In our study, patients with a β -hCG day 4/day 1 ratio of 0.8474 and above required more additional doses (sensitivity 66.7%, specificity 68.0%, $p < 0.005$).

There are similar studies in the literature. In a study encompassing 439 women, methotrexate success rates were notably influenced by initial β -hCG levels and the ratio of β -hCG levels between day 4 and day 1, with success rates dropping to 50% for β -hCG levels exceeding 5000 mIU/mL. Additionally, a crucial β -hCG cutoff of 2255 mIU/mL and a day 4 to day 1 β -hCG ratio were identified as predictive markers for methotrexate success.¹⁸ In another study involving 406 patients, a decline in Neutrophil-to-Lymphocyte Ratio (NLR) of less than 23% on day 4, as well as specific changes in human chorionic gonadotropin levels, were significantly associated with single-dose methotrexate treatment failure. Notably, an NLR decrease of less than 23% on day 4, plateau or increase in serum hCG on day 4, and an hCG value greater than 1000 mIU/mL on day 0 were identified as predictors of single-dose methotrexate treatment failure.¹⁹ These findings collectively provide valuable insights for clinicians in predicting methotrexate treatment outcomes and optimizing management strategies for ectopic pregnancy patients.

The limitations of this retrospective study include the fact that only β -hCG and complete blood count were analyzed among the laboratory parameters and the lack of height and weight information of the patients.

CONCLUSION

According to the findings of this study, the day 4/day 1 β -hCG ratio may be useful in predicting the need for additional doses.

Conflict of interest

The authors declare no conflict of interest.

Ethical statement: Approval was obtained from the Ethics Committee of the centre where the study was conducted, with decision dated 28/08/2022 and number E-22-1064.

Author contributions:

SK: Writing-Original Draft, Writing-Review & Editing, Visualization, Supervision, Project administration, Formal analysis, Investigation

GDY: Resources, Data Curation, Software, Validation

MG: Supervision, Conceptualization, Methodology, Formal analysis, Investigation,

YÜ: Conceptualization, Methodology, Supervision

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