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Outpatient methotrexate treatment strategies for unruptured tubal ectopic pregnancy

Anrüptüre tubal ektopik gebeliklerde ayaktan metotreksat tedavi stratejileri

Alper Başbuğ [1], Aşkı Ellibeş Kaya [1], Mete Çağlar [2], Ali Yavuzcan [1]

Abstract

Aim: To evaluate the selection criteria for outpatient treatment of unruptured ectopic pregnancy.
Methods: A total of 124 unruptured ectopic pregnancies that had been treated with single-dose intramuscular methotrexate injections during the period from 2012 to 2017 at Duzce University Faculty of Medicine, Training and Research Hospital were evaluated.
Results: Success rate of the medical treatment with single dose methotraxate was 76.61% (n = 95) of 124 patient. The mean duration of hospital stay was shorter in successful medical treatment group (p=0.030). Combining β-hCG level at the first day of methotrexate treatment with size of ectopic focus and/or the presence of fluid in the abdomen significantly increased the sensitivity, specificity and positive predictivity for successfully treated with methotrexate (sensitivity = 70.3%, specificity =86.3%, positive predictive value =80%).
Conclusions: We can choose patients that will be good responder to methotrexate treatment of ectopic pregnancy without hospitalization by initial serum β-hCG values, size of ectopic focus and the presence of fluid in the abdomen.

Key Words: Ectopic pregnancy, methotrexate, outpatient treatment.

Öz

Amaç: Rüptüre olmamış ektopik gebeliğin ayaktan tedavisi için seçim kriterlerini değerlendirmek.
Yöntemler: Düzce Üniversitesi Tıp Fakültesi, Eğitim ve Araştırma Hastanesi'nde 2012-2017 yılları arasında tek doz intramusküler metotreksat enjeksiyonları ile tedavi edilen toplam 124 rüptüre olmamış ektopik gebelik retrospektif olarak değerlendirildi.
Bulgular: Tek doz metotreksat ile medikal tedavi 124 hastanın % 76,61'inde (n = 95) başarılı bulundu. Başarılı olarak tedavi edilen grupta ortalama hastanede kalış süreleri daha kısa idi (p=0,030). Metotreksat enjeksiyonunun 1.günü β-hCG düzeyinin ektopik odak büyüklüğü ve / veya batın içinde sıvı varlığı ile birleşmesi metotreksat ile başarılı bir şekilde tedavi edilmek üzere duyarlılık, özgüllük ve pozitif öngörüyü anlamlı olarak arttırmıştır (duyarlılık= %70,3, özgüllük= %86,3, pozitif kestirim değeri= %80).
Sonuç: Başlangıç serum β-hCG seviyeleri, ektopik odak büyüklüğü ve batında sıvı varlığı ile metotreksat tedavisine iyi yanıt verecek hastaları, hastane yatışı gerektirmeden seçebiliriz.

Anahtar Sözcükler: Ektopik gebelik, metotreksat, ayaktan tedavi.

[1] **Department of Obstetrics and Gynecology, Duzce University, Faculty of Medicine, Duzce, Turkey**

[2] **Department of Obstetrics and Gynecology, Faculty of Medicine, Akdeniz University, Antalya , Turkey**

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Sorumlu yazar / Corresponding author:
Alper Başbuğ
Adres/Address: Düzce Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Kliniği, Orhangazi Mah., Konuralp 500. Cd, No: 125/7, 81450, Düzce, Türkiye.
e-posta: dralper23@gmail.com
Tel: +90 505 824 06 66

Introduction

Ectopic pregnancy (EP) occurs when developing blastocyst becomes implanted at a site other than the endometrium of the uterine cavity and EP is a significant cause of morbidity and mortality in the first trimester of pregnancy [1, 2]. It is managed expectantly, medically (with methotrexate (MTX) or surgically. While surgical approaches are the mainstay of treatment, advances in early diagnosis have facilitated the introduction of medical therapy with MTX [3].

As a single or multiple intramuscular injections, MTX is used in the treatment of EP [4-6]. A number of accepted protocols with injected MTX exist for the treatment of EP. Specifically, treatment with a systemic single dose of MTX has become a safe and effective management with promising results [7].

Further clinical experience with MTX and the increasing use of guideline-based protocols have increased the success of medical treatment of EP [8]. Medical management of ectopic pregnancy is generally considered to be less expensive than surgery [9, 10]. A major reason of low cost of medical treatment of EP is the reduced length of hospital stay. Outpatient medical treatment of unruptured EP results in low consumption of the resources [11]. In our country, no study has been done regarding to cost of the medical treatment of EP but some studies that have previously reported the mean length of hospital stay after medical treatment of EP and this time ranged between 4 and 10 days [12, 13].

The aim of this study was to determine factors associated with the success or failure of response to treatment with single dose MTX protocol in women with tubal EP and to determine the criteria for outpatient treatment of unruptured EP.

Material and methods

The study was approved by the local ethics committee (2017/12) and the study protocol adhered to the tenets of the Declaration at Helsinki. Written consent could not be taken due to the retrospective design of the study.

In our study, all consecutive cases of EP treated with an intramuscular single dose of 50 mg/m^2 MTX therapy from January 2012 to January 2017 in the Department of Obstetrics and Gynecology at Duzce University Faculty of Medicine were enrolled.

The EP diagnosis was based on atypical trends of β-hCG (human chorionic gonadotropin) levels and the absence of intrauterine pregnancy according to transvaginal ultrasound (TVUS).

Inclusion criteria were: female patients whose age are 18 years or older with diagnoses of unruptured tubal EP, absence of hepatic, hematologic, or renal diseases, hemodynamically stable patients, who were treated with a single dose 50 mg/m^2 intramuscular MTX.

Exclusion criteria were: female patients younger than 18 years, hemodynamically unstable patients, other locations of EP (abdominal, ovarian, cervical, cesarean scar), women who treated without a single dose 50 mg/m^2 intramuscular MTX, patients with renal and hepatic disease, immunodeficiency, active pulmonary disease and peptic ulcer. In addition, patients with MTX toxicity after treatment such as macular rush on the scalp, the neck, and the chest regions were excluded from the study.

After considering the inclusion and exclusion criteria, A total of 124 women with EP were included in the study and these patients were divided into 2 groups: those treated successfully with systemic MTX intramuscular administration (Group 1, n= 95) and those have failure after systemic MTX intramuscular administration (Group 2, n=29).

Demographic data such as age, body mass index (BMI), parity, last menstrual period date , current pregnancy history, previous history of infertility treatment, previous history of EP, use of intrauterine contraceptive device (IUCD) and clinical presentation such as abdominal pain, vaginal bleeding, and amenorrhea, serum β-hCG levels on days 1, 4, and 7, number of MTX doses; and the need for surgical therapy were recorded. BMI (kg/m^2) was calculated using the following formula: weight in kilograms divided by the square of height in meters.

Study Protocol

The patients received intramuscular MTX at a dose of 50 mg/m^2 of body-surface area, which was calculated with a calculator that uses height and actual body weight has been described in detail as MTX treatment protocol for tubal EP [14, 15]. If the decrease in β-hCG levels between the days 4 and 7 was more than 15 percent, the concentration of β-hCG was monitored weekly until β-hCG was undetectable. If the decrease in β-hCG between the days 4 and 7 was less than 15 percent, a second intramuscular dose of MTX 50 mg/m^2 was administered and if the decrease in β-hCG between the days 7 and 14 was more than 15 percent, the concentration of β-hCG was monitored weekly until the β-hCG was undetectable. If the β-hCG level did not decline as described in the study protocol for tubal EP, or if the cardiac activity was still present, patient presents with abdominal pain and have obvious signs of hemoperitoneum, the medical treatment was considered to have failed and surgical procedures were performed.

Statistical Analysis

The descriptive statistics for continuous variables were expressed in mean ± standard deviation or median (minimum-maximum), while nominal variables were expressed in the number and percentage (%). The significance of the difference between the mean values of the groups was evaluated using the Student's t-test, while the significance of the difference in the median values was evaluated using the Mann-Whitney U test. Categorical data was compared by Chi-square distribution. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows version 22 software (SPSS Inc., Chicago, IL, USA).

Results

A total of 124 women were enrolled in this trial. Considering the all 124 patients, in 95 patients (% 76.6) EP was completely resolved with MTX administration and in 29 patients (% 23.4) there was a need for subsequent operations because of rupture of tubal EP or failure of MTX treatment. Therefore, the success rate of the single-dose MTX therapy for EP was 76.1% (95/124).

In the success group, 83 patients (%87.4) were cured with a single dose of MTX, and the remaining 12 patients (%12.6) were cured with a second/repeated dose of MTX. 29 patients (%23.4) underwent surgical treatment after an average of 4.5 ± 2.9 days (range 2-8 days). The second doses of MTX were administered after a mean of 7.6 ± 0.7 days when needed. Four of the patients (33.3%) who had received the second dose of MTX required surgical treatment.

There were no significant differences between two groups regarding maternal age (p=0.061), gravidity (p= 0.703), parity (p= 0.830), BMI (p=0.311) and gestational age (p=0.570) (Table 1).

The mean pretherapeutic β-hCG level for successfully treated with MTX (Group 1) was 2073.7± 751.5 mIU/mL. The doses of MTX used ranged from 75 mg to 95 mg with a mean of 82.2 ± 7.6 mg. In patients in whom medical treatment failed, the

β-hCG level at the first day of the injection was 3167 ± 316.7 mIU/mL, 3362.3 ± 378.0 mIU/mL at day 4 and 3002.5 ± 368.2 mIU/mL at day 7. β-hCG levels were statistically higher in Group 2 at day 1, day 4 and day 7 (p=0.012). Size of ectopic focus was greater in Group 2 as 38.4±23.7 mm vs 29.9 ± 14.8 mm (p= 0.033). There was also statistically significant difference between the two groups in terms of the presence or absence of fluid in the abdomen by TVUS (p=0.041). The rate of failure of medical treatment in patients with fluid detected during TVUS was 37.9% as seen in 11 patients, while 23.1% in the non-fluid group as seen in 22 patients (p = 0.041).

Table 1: Characteristics of the patients.

Characteristics	Group 1 (success group) n=95	Group 2 (failure group) n=29	p
Age (year) [μ]	34.6±4.9	30.8±5.4	0.061
BMI ((kg/m2) [μ]	29.4±4.3	28.2±8.2	0.311
Gravidity (n) [¥]	2 (1-5)	2 (1-5)	0.703
Parity (n) [¥]	1 (0-3)	1 (0-4)	0.830
Gestational ages (weeks) [μ]	6.0±1.7	6.5±1.2	0.570
D1 β-hCG level (mIU/mL) [μ]	2073.7±751.5	3167±316.7	0.012
D4 β-hCG level (mIU/mL) [μ]	2136.2±336.7	3362.3±377.9	0.012
D7 β-hCG level (mIU/mL) [μ]	1637.6±348.5	3002.5±368.2	0.012
Size of ectopic focus (mm) [μ]	29.9±14.8	38.4±23.7	0.033
Presence of fluid in the abdomen [α]	22 (23.1)	11(37.9)	0.041
Duration of hospital stay (day) [μ]	4.0±2.2	7.1±2.4	0.030

[μ]: mean ± standard deviation, [¥]: n (range), [α]: n (%), D1: 1st day of first MTX injection, D4: 4th day after MTX injection, D7: 7th day after MTX injection.

The mean duration of the hospital stay was 4.2 ± 1.9 days and 6.9 ± 2.1 days in Group 1 and Group 2, respectively (p= 0.030).

Cut-off values discriminating treated with MTX successfully from failure of MTX treatment by using Receiver Operating Characteristics (ROC) curve analysis of β-hCG levels at the first day of MTX treatment and size of ectopic focus were 2034 mIU/mL (AUC=0.628) and 25.5 mm (AUC=0.560), respectively (Figure 1).

Figure 1: ROC curves for the prognostic value of initial hCG level (mIU/mL) and size of ectopic focus (mm).

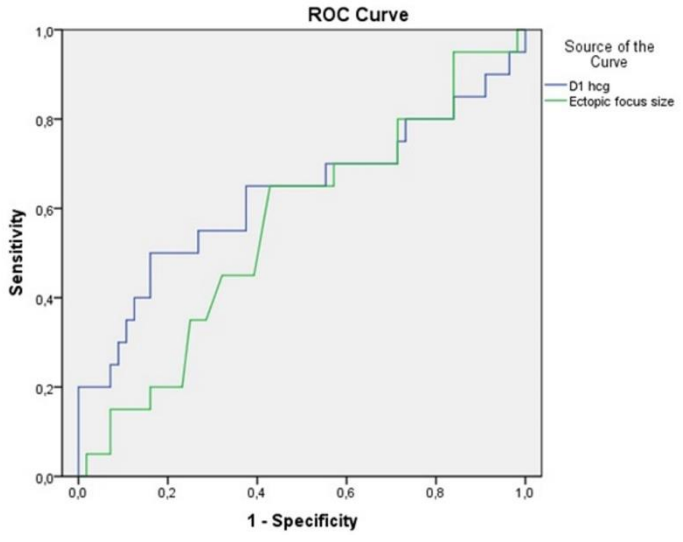

Table 2 represents sensitivity, specificity and the performance of β-hCG levels at the first day of MTX treatment, size of ectopic focus and the presence of fluid in the abdomen for assessing the diagnostic efficiency alone and joint screening of the three variables for discriminating successful MTX treatment and failure of MTX treatment. β-hCG levels at the first day of MTX treatment showed a moderate sensitivity with 56.9% and specificity of 59.1% while testing the size of ectopic focus alone indicated a moderate sensitivity with 43% and specificity of 68.1% and the presence of fluid in the abdomen showed a moderate sensitivity with 43.5% and specificity of 56.5%. Combining β-hCG levels at the first day of MTX treatment with size of ectopic focus and/or presence of fluid in the abdomen significantly increased the sensitivity, specificity and positive predictive values up to 70.3%, 86.3% and 80.0%, respectively (Table 2).

Table 2. Diagnostic performance of β-hCG level at the first of the treatment when combined with size of ectopic focus and presence of fluid in the abdomen discriminating successful MTX treatment.

Characteristics	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
D1 β-hCG level	56.9	59.1	53.4
Size of ectopic focus	43.0	68.1	59.4
Presence of fluid in the abdomen	43.5	56.5	51.5
D1 β-hCG level + Size of ectopic focus	66.1	77.2	71.1
D1 β-hCG level + Size of ectopic focus + Presence of fluid in the abdomen	70.3	86.3	80

D1: 1st day of first MTX injection.

Discussion

Medical treatment of EP with MTX has been performed since 1980 [16]. Success rates and factors affecting the success of medical treatment and have been shown by previous studies [17-19]. The overall success rate of single-dose MTX therapy in this study was 76.1%, which is comparable with the success rates reported in other studies. We found that initial serum β-hCG levels, size of ectopic focus and the presence of fluid in the abdomen were the most important predictors of successful medical treatment. Unlike other studies, we also evaluated the duration of hospital stay of patients, in which medical treatment was successful 4.03 day and 7.08 day for which MTX treatment failed. The long duration of hospital stay of patients associated with failure of medical management and subsequent surgical treatment.

Today, there is no consensus on the threshold of β-hCG above which MTX is contraindicated. Several studies found that initial β-hCG levels of 1000-5000 IU / ml are associated with treatment failure [5, 20, 21]. In our study, we found that the initial levels of β-hCG above 2000 mIU / ml were associated with failure of single dose MTX treatment. As with β-hCG, there is no consensus on the size of the ectopic focus that affects success rate of medical treatment [22, 23]. Some authors use the 25 mm ectopic focus size as the threshold while others use 35 mm to predict the success rate of medical treatment with single dose of MTX. In our study, we found that the size of ectopic focus greater than 25 mm related with failure of single dose MTX treatment.

Although there have been many studies evaluating the efficacy of the expectant, medical or surgical management options, there are only a small number of studies that have evaluated the cost of treatments for EP [24]. The ambulatory and hospital costs of care for ectopic pregnancy ranged from 1,700

euros to 1900 euros when the first-line treatment was surgical whereas these costs amounted to about 700 euros for subacute EP treated with MTX [9]. The cost of treating ectopic pregnancy depends on length of hospital stay. MTX resulted in a low rate of hospitalization and a short hospital stay and cost-effective [11].Some studies published in our country showed that the length of hospital stay varies between 4 and 10 days [12, 13]. Similarly in our study we found that the mean length of hospital stay was long for patients treated with MTX. Lecuru et al [11] followed 55 women treated with MTX and they found that management has naturally been significantly different for the medical and sugical treatment options, with a high rate of outpatient and ambulatory care in medically traeted group. Hospital stay was significantly shorter (0.6 ± 1.7/day) in medically treated group.

There is no established true cut-off initial β-hCG levels and size of ectopic focus for suitable candidate for outpatient medical management of ectopic pregnancies. The decision to proceed with medical or surgical management depends on the clinician's discussion with the patient [25]. In this study, we aimed to define the selection criteria to determine which patients can be treated as outpatient and shorten the length of hospital stay of hospitalized patients. We think that the combination of cut off values of the initial serum β-hCG levels, size of the ectopic focus and the absence of the abdominal fluid use for the prediction of successfully outpatient treatment for EP and represented study showed that; initial serum β-hCG ≤ 2000 mIU/mL, size of the ectopic focus ≤ 25 mm and if absence of the abdominal fluid successfully outpatient treatment of EP was feasible.

Retrospective nature and small sample size were the weaknesses of the study. We decided to focus on hospital stay in terms of cost in this study but it is important to know that there are other factors that may also affect the cost such as patient travel and time off work. There will be a need for prospective studies with larger populations to support our findings.

Conclusion

MTX therapy is simple and if initial β-hCG value less than 2000 mIU/mL, size of ectopic focus smaller than 25 mm and absence of abdominal fluid it does not require hospitalization. We can choose patients that will be good responder to MTX treatment of EP by initial serum β-hCG values, size of ectopic focus and presence of fluid in the abdomen. Better results can be expected from these patients and the outpatient MTX option may result in low consumption of resources.

References

1. Yıldız A, Doğan O. Ektopik Gebelik Olgularının Yönetimi ve FertiliteDurumları: BeşYıllık Tek Merkezli Çalışma. Turkiye Klinikleri J Gynecol Obst. 2016;26:93-7.
2. Berg CJ, Chang J, Callaghan WM, Whitehead SJ. Pregnancy-related mortality in the United States, 1991–1997. Obstet Gynecol. 2003;101:289-96.
3. Pulatoglu Ç, Doğan O, Basbug A, Ellibes Kaya A, Yildiz A, Temizkan O. Predictive Factors of Methotrexate Treatment Success in Ectopic Pregnancy: A Single Tertiary Center Study. North Clin Istanb. 2017. DOI:10.14744/nci.2017.04900.
4. Yıldız A, Doğan O. Evaluation of Medical Treatment Success in Ectopic Pregnancy with Single Dose Methotrexate: 5 years Single Center Experience. Kafkas J Med Sci. 2017;7:188-92.
5. Rodi IA, Sauer MV, Gorrill MJ. The medical treatment of unruptured ectopic pregnancy with methotrexate and citrovorum rescue: preliminary experience. Fertil Steril. 1986;46:811-3.
6. Hoover KW, Tao G, Kent CK. Trends in the diagnosis and treatment of ectopic pregnancy in the United States. Obstet Gynecol. 2010;115:495-502.
7. Capmas P, Bouyer J, Fernandez H. Treatment of ectopic pregnancies in 2014: new answers to some old questions. Fertil Steril. 2014;101:615-20.
8. Jurkovic D, Wilkinson H. Diagnosis and management of ectopic pregnancy. BMJ. 2011; 342: d3397.
9. Seror V, Gelfucci F, Gerbaud L, Pouly JL, Fernandez H, Job-Spira N, et al. Care pathways for ectopic pregnancy: a population-based cost-effectiveness analysis. Fertil Steril. 2007;87:737- 48.
10. Mol F, Mol BW, Ankum WM, van der Veen F, Hajenius PJ. Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: a systematic review and metaanalysis. Hum Reprod Update. 2008;14:309-19.
11. Lecuru F, Camatte S, Viens-Bitker C, Chasset S, Leonard F, Taurelle R. Hospital Resources Used for Ectopic Pregnancy Treatment by Laparoscopy and Methotrexate. JSLS. 2001;5:117-22.
12. Uğurlucan FG, İyibozkurt AC, Çetin C, Nehir A, Akhan S. Methotrexate treatment for ectopic pregnancy: Factors affecting treatment outcome. Ege J Med. 2013;52:199-204.
13. Yenicesu C, İmir G, Çetin M, Küçüközkan T. Evaluation Of The Treatment Modalities And Hospitalization Period In Patients With Acute Pelvic Pain Related To Adnexal Pathologies. C.Ü. Tıp Fakültesi Dergisi. 2008;30:1-7.
14. Barnhart KT. Clinical practice. Ectopic pregnancy. N Engl J Med. 2009;361:379-87.
15. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 94: Medical management of ectopic pregnancy. Obstet Gynecol. 2008;111:1479-85.
16. Ory SJ, Villanueva AL, Sand PK, Tamura RK. Conservative treatment of ectopic pregnancy with methotrexate. Am J Obstet Gynecol. 1986;154:1299-306.
17. Corsan GH, Karacan M, Qasim S, Bohrer MK, Ransom MX, Kemmann E. Identification of hormonal parameters for successful systemic single-dose methotrexate therapy in ectopic pregnancy, Hum Reprod. 1995;10:2719-22.
18. Nazac A, Gervaise A, Bouyer J, de Tayrac R, Capella-Allouc S, Fernandez H. Predictors of success in methotrexate treatment of women with unruptured tubal pregnancies, Ultrasound Obstet Gynecol. 2003;21:181-5.
19. Cohen A, Zakar L, Gil Y, Amer-Alshiek J, Bibi G, Almog B, et al. Methotrexate success rates in progressing ectopic pregnancies: a reappraisal. Am J Obstet Gynecol. 2014;211:128.e1-5.
20. Sagiv R, Debby A, Feit H, Cohen-Sacher B, Keidar R, Golan A. The optimal cutoff serum level of human chorionic gonadotropin for efficacy of methotrexate treatment in women with extrauterine pregnancy. Int J Gynaecol Obstet. 2012;116:101-4.
21. Nazac A, Gervaise A, Bouyer J, de Tayrac R, Capella-Allouc S, Fernandez H. Predictors of success in methotrexate treatment of women with unruptured tubal pregnancies. Ultrasound Obstet Gynecol. 2003;21:181-5.
22. Sowter MC, Farquhar CM, Petrie KJ, Gudex G. A randomised trial comparing single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured tubal pregnancy. BJOG. 2001;108:192-203.
23. Var A, Özyurt R, Şık BA, Kumbasar S, Sever E, Deveci M, et al. Retrospective analysis of factors that affect the success of single-dose methotrexate treatment in ectopic pregnancy. Turk J Obstet Gynecol. 2015;12:215-9.
24. Westaby DT, Wu O, Duncan WC, Critchley HO, Tong S, Horne AW. Has increased clinical experience with methotrexate reduced the direct costs of medical management of ectopic pregnancy compared to surgery? BMC Pregnancy Childbirth. 2012;12:98.
25. Bachman EA, Barnhart K. Medical Management of Ectopic Pregnancy: A Comparison of Regimens. Clin Obstet Gynecol. 2012;55:440-7.