

The Effect of the Ultrasonographically Determined Tubal Implantation Site in Ectopic Pregnancy on the Success of Methotrexate Treatment and Subsequent Reproductive Outcome

Tamer MUNGAN, Evrim ERDEMOĞLU, Mehmet GÜNEY

Department of Obstetrics and Gynecology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey

Received 10 March 2007; received in revised form 28 June 2007; accepted 19 July 2007;

published online 21 November 2007

Abstract

Objective: To study the prognostic significance of tubal implantation site on success of methotrexate (MTX) treatment and reproductive outcome in ectopic pregnancies (EP).

Materials and Methods: Localization of ectopic pregnancies were determined and recorded by ultrasonography. Ninety-eight tubal EP cases meeting the conditions of haemodynamic stability and absence of fetal cardiac activity, were administered MTX (50 mg/m² intramuscularly). Main outcome measurements were as follows; positive result with methotrexate was regarded as decreasing β -hCG titer in blood until it was zero. The necessity of any invasive intervention was considered as failed MTX therapy. Recurrent EP and intrauterine pregnancy rate was recorded in patients who desired to become pregnant within one year after treatment for EP.

Results: Efficacy of MTX treatment was found to be 82.3%. It was successful in 91.6% of periampullar EP, but the success rate was 28.5% in periisthmic EP ($p<0.01$). Periisthmic EP was found to be a poor prognostic factor for the success of MTX treatment (OR: 27.5; 95% CI: 6.8-110.8; $p<0.001$). Fifty-nine patients desired pregnancy within one year after termination of EP. Although the overall cumulative pregnancy rates were similar, the rate of intrauterine pregnancy was significantly lower in periisthmic EP (25%) than in periampullar EP (87%) cases.

Discussion: Ultrasonographically determined implantation site of tubal EP is a significant factor affecting success with MTX and the subsequent reproductive outcome.

Keywords: ectopic pregnancy, methotrexate treatment, reproductive outcome, predictive factors, tubal localization

Özet

Tüp İçinde Ektopik Gebelikte Ultrasonografi ile Belirlenmiş Yerleşim Yerinin Metotreksat Tedavisinin Başarısına ve Sonraki Gebeliklere Etkisi

Amaç: Ektopik gebeliklerde tüp içinde yerleşim yerinin, metotreksat (MTX) tedavisinin başarısındaki ve sonraki üreme sonuçlarındaki öneminin araştırılmasıdır.

Materyal ve Metot: Ektopik gebeliklerin lokalizasyonu ultrasonografi ile saptandı ve kaydedildi. Tüp içinde ektopik gebelik durumunda doksan sekiz hastadan hemodinamisi düzenli olanlar ve fetüste kalp çalışması olmayanlara MTX (50 mg/m² i.m.) uygulandı. Ölçümlerin temel sonuçları; MTX ile kanda β -hCG düzeyinin sıfıra düşmesi, MTX tedavisi başarısız olduğunda invazif işlem gereksiniminin ortaya çıkması ve ektopik gebelikten sonraki 1 yıl içerisindeki rahim içinde veya tüp içinde tekrarlayan gebelik gelişimi idi.

Sonuçlar: MTX tedavisinin etkinliği %82.3'tü. MTX tedavisi periampuller ektopik gebeliklerin %91.6'sında, peri-istmik gebeliklerin %28.5'inde başarılı bulundu, $p<0.01$). Peri-istmik yerleşimli ektopik gebelik, MTX tedavisi başarısında önemli bir prognostik etkidir (OR: 27.5; %95 CI: 6.8-110.8; $p<0.001$). Ektopik gebelikten sonraki bir yıl içinde 59 hastanın gebelik istemi olmuştur. Her ne kadar genel toplam gebelik oranları peri-istmik ve periampuller yerleşimli ektopik gebeliklerde aynıysa da, rahim içinde gebelik oranları peri-istmik ektopik gebelik görülenlerde (%25) periampuller ektopik gebelik görülenlerden (%87) önemli derecede düşüktür.

Corresponding Author: Dr. Tamer Mungan

Süleyman Demirel Üniversitesi Tıp Fakültesi, Doğu Kampüsü,

Kadın Hastalıkları ve Doğum AD, Çünür, Isparta, Türkiye

Phone : +90 246 211 21 02

GSM : +90 505 706 71 71

E-mail : tdmungan@med.sdu.edu.tr

Tartışma: Tüp içinde ektopik gebeliğin yerleşim yeri, MTX uygulamasının başarısını ve gelecekteki gebeliği etkileyen önemli bir prognostik etkidir.

Anahtar sözcükler: ektopik gebelik, metotreksat, üretkenlikte sonuç, öngörüş etkenleri, tüp içinde yerleşim

Introduction

Conservative treatment of ectopic pregnancy (EP) such as by methotrexate (MTX) aims to reduce morbidity and preserve fertility (1). Effect of ultrasonographically determined localization of EP on success of the MTX treatment and the subsequent reproductive outcome has not yet been established. Factors affecting future reproductive outcome and performance after MTX treatment of EP are also not clear. In the present study, success of MTX treatment in association with periisthmic and periampullar localized EP is studied. Reproductive outcome after treatment of EP with MTX is also compared in periisthmic and periampullar localized EP.

Materials and Methods

Ninety-eight unruptured ectopic tubal pregnancies were included in the prospectively designed study between 1998 and 2007. EP was diagnosed when any of the following criteria were met: (a) abnormally rising human chorionic gonadotropine (β -hCG) levels in blood (<50% rise in 48 hours) and absence of chorionic villi in the curettage material; (b) absence of an intrauterine gestational sac upon transvaginal ultrasound with β -hCG levels of >2000 mIU/ml; (c) an extrauterine pregnancy measuring less than 5 cm (yolk sac /fetal pole) in the transvaginal ultrasound. All women who met these criteria were managed medically with informed consent. Hemodynamically unstable patients or women with fetal cardiac activity in EP were not given MTX treatment and excluded from study.

Transvaginal ultrasonographic examinations were performed by an experienced sonographer. Mean of the sum of two perpendicular diameters of gestational sac was recorded. Tubal localization of EPs by ultrasonography was subjectively categorized as proximal tubal (periisthmic) or distal tubal (periampullar). Baseline laboratory evaluation included complete blood count, serum aspartate transaminase levels and β -hCG levels. Surgery was performed if the hemoglobin level was <10 g/dl, platelet count was <50,000 mm³/L or the serum aspartate transaminase levels were more than twice the normal.

Medically managed patients were given a single dose of 50 mg/m² MTX intramuscularly without folate supplementation. β -hCG levels were evaluated on day 4 and 7 after the treatment, and then weekly. An additional dose of MTX was administered if fall of β -hCG level was less than 15% at day 4 and day 7. An additional dose of MTX was also given if β -hCG level plateaued or increased at weekly follow-ups. Cure with MTX was regarded as β -hCG value less than 5 mIU/ml.

Patients were followed up for one-year to evaluate reproductive outcome. β -hCG levels which were not falling,

and β -hCG levels which were increasing after consecutive MTX administration were regarded as failure of the MTX treatment. Worsening abdominal pain and hemodynamic instability requiring surgical exploration were indicative of MTX failure regardless of change in β -hCG levels. These EPs were managed by invasive interventions. Ultrasonographic localizations of EPs were compared with intra-operative findings in patients who had surgery. Patients were followed-up for one year in order to assess the reproductive outcome. During this period, main outcome measure of reproductive performance was development of an intrauterine pregnancy.

Statistical analysis

Student-*t* test and Mann-Whitney-U test were used to compare the continuous variables. χ^2 test was used for non-continuous data. Two-proportion tests were used to analyze the proportions of MTX success and reproductive performance (intrauterine and ectopic pregnancy rates in one-year). Logistic regression analyses were performed to identify any significant predictor on MTX treatment and reproductive performance. An alpha level of 0.05 was considered significant in all of the statistical analyses.

Results

Ninety-eight patients with unruptured tubal pregnancy were administered MTX. The mean age, gravida, parity and β -hCG values were 30 \pm 3.0 years, 3.2 \pm 0.8, 2.1 \pm 0.7 and 2157 \pm 1042 mIU/ml in periisthmic EPs, respectively. The mean age, gravida, parity and β -hCG values were similar 29 \pm 3.51 years, 3.0 \pm 0.8, 1.8 \pm 0.7 and 1859 \pm 871 mIU/ml in periampullar EPs, respectively ($p>0.05$). Age, gravida and parity were also similar in MTX-successful and MTX-failed groups ($p>0.05$). Twelve (12.2%) of 98 patients had history of previous ectopic pregnancy. Efficacy of MTX treatment was found to be 82.3% (81/98) and only 8.1% of cases required consecutive MTX administration. Seventeen patients had surgical intervention. The fall of β -hCG titer to zero was observed at the end of the first week of treatment in 6.2% (5/81) of patients, taking four weeks in the rest of patients.

Hemodynamic instability with suspicion of intraabdominal bleeding was the most common indication for surgery (70.5%). Increasing β -hCG levels was an indication for surgery in 17.7% of cases. Two of the patients (11.8%) were scheduled for operation, because of abdominal pain and refusal of MTX treatment despite decreasing β -hCG levels. Ultrasonographic localization of EP was in accordance with intraoperative findings in 88.3% (n=15/17) of cases. It was not possible to make a definitive diagnosis during the surgery due to mid-tubal localization of EP in the rest two of the cases which had been reported as periampullar at preoperative ultrasonographic examination.

Table 1. Ultrasonographic data on the patients

Gestational sac	Failure in MTX treatment (n)	Failure rate (%)
Diameter		
<20 mm	6/30	20% ^c
20-30 mm	4/38	10.5% ^c
30-40 mm	2/21	9.6% ^c
>40 mm	5/9	55.6% ^{a,c,d}
Tubal localization		
Periampullar	7/84	8.4% ^{b,c}
Periisthmic	10/14	71.4% ^{b,c,e}

^a Fischer's exact test, $p < 0.01$.
^b $\chi^2 = 6.8$, $p < 0.01$.
^c Two-proportions test, α level = 0.05.
^d Logistic regression test, OR: 8.02; 95% CI: 1.88-34.15; $p < 0.01$.
^e Logistic regression test, OR: 27.5; 95% CI: 6.8-110.8; $p < 0.001$.

Table 2. Tubal localization and pregnancy outcome in 59 women that actively attempted to become pregnant within 1 year after ectopic pregnancy

	n	Cure (%)	Pregnancy desired (n)	Cumulative pregnancy (n)	IUP	EP
Periampullar EP	84	77 (91.6%) ^a	55	52 (52/55) ^a	48 (92.3%) ^a	3 (5.7%) ^a
Periisthmic EP	14	4 (28.5%) ^a	4	3 (3/4) ^a	1 (33.3%) ^a	2 (66.6%) ^a
<i>P</i> value		$p < 0.001$		$p > 0.05$	$p < 0.05$	$p < 0.05$

^a Two-proportion tests with an α level of 0.05.

Periampullar and periisthmic EP was diagnosed in 85.7% (84/98) and 14.3% (14/98) of patients, respectively. MTX treatment was successful in 91.6% of periampullar EPs. However, success rate was 28.5% in periisthmic EPs ($p < 0.001$). Periisthmic EP was found to be a poor prognostic factor for the success of MTX treatment (Table 1, 2) in logistic regression analyses (OR: 27.5; 95% CI: 6.8-110.8; $p < 0.001$).

Others risk factors of failure of treatment were initial β -hCG level and size of gestational sac. Although the mean initial β -hCG levels were similar in both localizations, mean initial β -hCG levels were significantly different in MTX-successful as against the MTX-failed patients (1592 \pm 695 mIU/ml vs. 2370 \pm 970 mIU/ml, respectively).

The mean size of the gestational sac was 26.36 \pm 9.2 mm. MTX cure rate in patients with gestational sac of <20 mm, 20-30 mm, or 30-40 mm were similar (Table 1). However MTX failure rate was significantly higher in EP with a diameter of >40 mm ($p < 0.001$). Gestational sac of >40 mm was found to be a significant predictor of failure of MTX treatment in logistic regression analyses (OR: 8.02; 95% CI: 1.88-34.15; $p < 0.01$).

Fifty-nine patients attempted to become pregnant in one year after treatment of EP with MTX, and 91.5% (54/59) of them became pregnant in one-year. Nine percent of these pregnancies (5/54) were recurrent EP and 91% (49/54) were intrauterine pregnancies.

When the developed pregnancies were compared with respect to their previous EP implantation sites (Table 2), 87% of women with previous periampullar EP were seen to have achieved an intrauterine pregnancy, whilst only 25% of women with previous periisthmic EP had intrauterine pregnancy ($p < 0.05$). However, the overall cumulative pregnancy rate was similar in both groups. Patients with a previous EP localized in periisthmic region had a significantly increased rate of recurrent EP in one year (OR: 32; 95% CI: 2.2-471). Periisthmic EP was found to be an important risk factor for recurrent EP and was associated with lower rates of intrauterine pregnancy.

Discussion

New conservative treatments in EP have become popular in order to preserve the future fertility. However, there are a limited number of reports on the future fertility outcome in

EP treated with MTX in particular. Furthermore, the predictive factors affecting the success of treatment and factors affecting the future fertility are not clear (2-5). We studied the efficiency of MTX treatment in tubal pregnancies and analyzed the effect of tubal implantation site on the success of treatment and future fertility.

The most widely accepted MTX protocol is a single dose of intramuscular 50 mg/m² but MTX may also be used as an intravenous or oral agent in treatment of EP (6-7). We preferred intramuscular single dose injection because it is the most widely used protocol. In our study, MTX was effective in resolving EP in 82.3% of patients. This success rate is comparable with other reports (8-10). Adverse effects of MTX were rarely observed. The most common side effect is stomatitis. Lewis-Bliehall et al. reported laparoscopic treatment of EP was more successful than MTX treatment (90% vs. 79%) (11). Failure in surgical treatment of EP is rare. However, success rate of MTX treatment should not be underestimated. In these reports, the results of surgery and MTX treatment were not compared in terms of future fertility, complications and tubal patency. The main disadvantage of MTX treatment is prolonged hospitalization.

Initial β -hCG level and size of gestational sac are found to be statistically significant factors effecting success of MTX treatment; it is reported that single dose MTX treatment is appropriate for EP ≤ 4 cm in size (6) and it is reported that failure of MTX treatment increases by higher initial β -hCG levels (12). There are other reports of predictive scores based on initial levels of β -hCG, aspects of the image at ultrasound (hematosalpinx, tubal ring or live embryo), size of the mass and vascular flow in color Doppler examination (2,13,14). Fernandez et al. reported a pre-therapeutic scoring system which included the following criteria: gestational age, serum β -hCG level, serum progesteron level, abdominal pain, volume of hemoperitoneum, and haematosalpinx diameter (14). Our results indicate that periisthmic/periampullar localization of the EP is an important predictive factor on success rate of MTX treatment, and localization of tubal EP influences the reproductive outcome. Furthermore, the present study shows that ultrasonographic evaluation has a high success rate (88.3%) in revealing tubal localization of EP.

There are contradictory reports on the efficacy of medical treatment on preserving future fertility (15-17). In the present study, the reproductive performance of MTX-treated patients who attempted to become pregnant in one year was found to be satisfactory: 91% of patients had intrauterine pregnancy in one year. Ego et al. reported that age of >35 years, a history of infertility, and anterior tubal damage were important in determining future reproductive outcome in EP (15). They reported that fertility depends more on established patient characteristics than characteristics of ectopic pregnancy itself or treatment. However, value of the reproductive outcome without knowledge of the contralateral tube is one of the limiting factors in this and other studies.

Most of the patients with failed medical therapy required a radical surgical procedure such as salpingectomy. The radical approach may have the only benefit of avoiding recurrent EP on the unilateral site.

Periisthmic EP is a particular and difficult concern. Isthmic portion of the tube has the narrowest diameter and the EP invades the muscularis tuba early in the pregnancy. Isthmic EP ruptures in early gestational ages. MTX treatment of periisthmic EP is controversial (18,19). However, use of MTX in interstitial EP is increasing (20). Barnhart et al. reported that a disproportionate number of patients with interstitial pregnancy fail medical management and require emergency surgery compared with an isthmic or ampullary pregnancy (21).

As a conclusion, the diameter of gestational sac and initial levels of β -hCG are important factors in predicting MTX treatment failure in EP. We advocate that implantation site is another significant factor effecting MTX success and the future reproductive outcome. However, the number of isthmic EP in this study is one of the main limiting factors hindering to draw a conclusion. Isthmic localization of EP may be a significant predictor of MTX treatment failure and recurrent EP. However, further studies are needed to reproduce the ultrasonographic localization of EP and its impact on MTX treatment.

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