

## IDENTIFYING PROGNOSTIC FACTORS WHICH AFFECT THE SUCCESS OF ECTOPIC PREGNANCY TREATMENT WITH A SINGLE DOSE METHOTREXATE

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### SUMMARY

**Objective:** To identify prognostic factors which affect the success of ectopic pregnancy treatment with a single dose methotrexate

**Material and methods:** 99 patients whom applied to Cerrahpaşa Medical Faculty Obstetrics and Gynecology Department, between year 2000 and 2010 treated with single-dose methotrexate were divided into two subgroups; successful and unsuccessful. Likely to affect the success of the demographic clinical and laboratory findings were compared retrospectively.

**Results:** Single-dose methotrexate therapy has been successful in 67 patients (67.6%). In the unsuccessful group, serum  $\beta$ -hCG values were significantly higher than successful group. (successful group median  $\beta$ -hCG value: 819 (122-3822) mIU/ml, Unsuccessful group median  $\beta$ -hCG value: 3562 (642-18000) mIU/ml,  $p < 0.001$ ).

**Conclusion:** Single-dose methotrexate therapy is effective in the initial treatment of ectopic pregnancy. It is observed that the main prognostic factor affecting the failure is elevated levels of  $\beta$ -hCG.

**Key words:** ectopic pregnancy, single-dose methotrexate therapy,  $\beta$ -hCG

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### TEK DOZ METOTREKSAT İLE EKTOPIK GEBELİK TEDAVİSİNİN BAŞARISINI ETKİLEYEN PROGNOSTİK FAKTÖRLERİN BELİRLENMESİ

#### ÖZET

**Amaç:** Tek doz metotreksat ile ektopik gebelik tedavisinin başarısını etkileyen prognostik faktörleri belirlemek.

**Gereç ve yöntemler:** 2000 ile 2010 yılları arasında Cerrahpaşa Tıp Fakültesine başvurup tek doz metotreksat tedavisi alan 99 hasta başarılı olan ve olmayan diye iki alt gruba ayrıldı. Başarıyı etkileyebilecek olası demografik, klinik ve laboratuvar bulguları retrospektif olarak karşılaştırıldı.

**Bulgular:** Tek doz metotreksat tedavisi 67 (% 67.6) hastada başarılı olmuştur. Başarısız olan grupta serum  $\beta$ -hCG değerleri başarılı olan gruba göre anlamlı olarak yüksek bulunmuştur (başarılı olan grup medyan  $\beta$ -hCG değeri: 819 (122-3822 mIU/ml, başarısız olan grup medyan  $\beta$ -hCG değeri: 3562 (642-18000) mIU/ml,  $p < 0,001$ ).

**Sonuç:** Tek doz metotreksat tedavisi ektopik gebeliğin başlangıç tedavisinde etkili bir yöntemdir. Tedavinin başarısızlığını etkileyen ana prognostik faktör olarak  $\beta$ -hCG değerinin yüksekliği gözükmemektedir.

**Anahtar kelimeler:** ektopik gebelik, tek doz metotreksat tedavisi,  $\beta$ -hCG

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## INTRODUCTION

The incidence of ectopic pregnancy has been increasing in developed countries<sup>(1)</sup>. However, the possibility of early detection has significantly decreased disease related morbidity and mortality. In the treatment of disease process, there has been a shift from surgery to medical therapy<sup>(2)</sup>. Medical treatment of ectopic pregnancy with methotrexate was applied first time in 1982 by Tanaka et al. and in the following period, medical treatment in the treatment of ectopic pregnancy without the risks associated with surgery was safe and effective<sup>(3)</sup>. Although there is a very high treatment failure, it may be tubal rupture after a few days of treatment. Despite the effectiveness of treatment, success rates ranged from 64.0% to 94.2%. This situation makes it important to determine factors affecting the success of medical treatment of ectopic pregnancy<sup>(4-6)</sup>.

The purpose of this study is to investigate the prognostic factors affecting the success on patients diagnosed ectopic pregnancy and treated medically single-dose methotrexate during a ten-year period in our clinic.

## MATERIALS AND METHODS

In Istanbul University Cerrahpaşa Medical Faculty Obstetrics and Gynecology Department, retrospectively, between January 2000 - January 2010, a total of 222 patients diagnosed and treated ectopic pregnancy were subjected to evaluation. Such cases; age, gravida, pariete, abortus and curettage number, method of contraception, previous ectopic pregnancy, tubal sterilization history, initial  $\beta$ -hCG value, ultrasonographic findings and treatment regimens were recorded by examination of patient files and operative reports. 121 patients who preferred surgery as initial treatment were excluded from the study. Scheduled to receive a single dose methotrexate therapy, hemodynamically stable, without evidence of rupture and transvaginal ultrasonography of fetal cardiac activity 101 patients with ectopic pregnancies were included in the study.

Methotrexate was performed in the absence of methotrexate allergy, liver, lung, kidney, hematological diseases. In order to determine this, blood groups, complete blood count, liver function tests, blood urea nitrogen and creatinine levels were measured for all

patients. Patients with a history of lung disease was assessed by chest X-ray due to the risk of methotrexate interstitial pneumonitis. For failing to adhere to this criterion, one of two patients, methotrexate were not applied, had liver enzyme elevation, while the number of platelets was below 100,000 in the other patient. For the Methotrexate treatment, patients acknowledged the informed consent form. Patients suitable for methotrexate treatment were treated 50mg / m<sup>2</sup> single dose of methotrexate IM. Rh immunoglobulin was performed to patients with Rh incompatibility. The day Methotrexate dose applied was considered as day 1. Between day 4 and day 7 of treatment,  $\beta$ -hCG falling more than 15% in value, patients were followed up three times until  $<5\text{mIU/ml}$  and these patients were considered patients with adequate single dose methotrexate. However, between day 4 and day 7 of treatment,  $\beta$ -hCG falling less than 15% in value and hemodynamic instability in developing patients were considered patients with inadequate single dose methotrexate. Hemodynamic instability; following-up after single-dose methotrexate therapy, suggestive of intrabdominal rupture and hemorrhage, chronic decline in hematocrit follow-up series accompanying tachycardia and hypotension were considered the development of acute abdominal findings. Repeated doses of methotrexate or surgery was performed to patients single-dose methotrexate therapy was failed.

As initial therapy, 99 patients with hemodynamically stable methotrexate therapy area were divided into two groups.

Group 1: Initially taking methotrexate therapy and medical treatment was successful.

Group 2: Initially taking methotrexate therapy and medical treatment was failed.

For these groups, age, gravidity, parity, abortion, curretage, ectopic pregnancy, conceive shape, Intrauterine device presence, pelvic inflammatory disease, previous history of surgery admission  $\beta$ -hCG level, and ectopic pregnancy ultrasound findings were compared retrospectively.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Software, version 18.0. The Shapiro Wilk test and Kolmogorov-Smirnov test of normality were performed to choose the appropriate statistical test. Continuous variables were be given as mean  $\pm$  standard deviation if normally distributed, and as median (interquartile range) if not

normally distributed. If the normality assumption for the comparison of means between two groups was satisfied, Student's t-test was used for the comparisons of means. Alternatively, if there was evidence of non-normality the Mann-Whitney U test was used. Comparisons between proportions were performed with a Pearson's chi-squared test or Fisher's exact test. Differences among groups were considered to be significant if the P value was < 0.05.

### RESULTS

A total of 222 patients diagnosed and treated ectopic pregnancy were subjected to evaluation between January 2000 - January 2010. As initial therapy, 99 patients were treated with a single dose of methotrexate. The average age of patients was 30.72 ± 5.76, at the time of diagnosis of gestational week was 6.7 ± 1.0 weeks, ectopic pregnancy size was 22.07 ± 13.32 mm, serum β-hCG level was 2196 ± 2603 mIU/ml (Table I). While single-dose methotrexate therapy was successful in 67 (% 67.6) patients, it was unsuccessful 32 in (32.3%) patients. Single-dose methotrexate for patients' (with and without success) demographic, clinical and laboratory features are shown in Table II. Between the groups, no difference was observed in terms of age, parity, abortion, hospital admission weeks of pregnancy, ectopic pregnancy size. However, in the second group, serum β-hCG values were significantly higher than the first group (The first group of median β-hCG value: 819 (122-3822) mIU / mL, the second group of median β-hCG value 3562 (642-18000) mIU / mL, p < 0.001), also median gravidity and curettage

values were significantly higher than the first group. The risk factors for ectopic pregnancy were compared for first and second groups at Table III. There was no difference in terms of the parameters measured.

**Table I:** Single-dose methotrexate-treated patients' demographic, clinical and laboratory features.

	Single-dose methotrexate-treated patients (n=99)
Age (years)	30.72±5.76
Gravidity (n)	1.8±1.9
Parity (n)	0.8±1.01
Abortion (n)	0.38±0.84
Curettage (n)	0.56±1.27
Hospital admission weeks of pregnancy (weeks)	6.7±1.0
β-hCG(mIU/ml)	2196±2603
ectopic pregnancy size before treatment (mm)	22.07±13.32

**Table III:** Single-dose methotrexate therapy in patients' (with and without success) risk factors for ectopic pregnancy.

	Group 1	Group 2	p
Ectopic pregnancy history (n/N,%)	2/67(%0.2)	4/32(%12.5)	0.063
Use of intrauterine devices (n/N,%)	2/67(%0.2)	1/32(%0.3)	0.97
PID history (n/N,%)	2/67(%0.2)	1/32(0.3)	0.97
Ovulation Induction (n/N,%)	9/67(%13.4)	3/32(%0.9)	0.563
Abdominal surgery history (n/N,%)	23/67(%34)	12/32(%37)	0.617

P<0.05: significant

**Table II:** Single-dose methotrexate for patients' (with and without success) demographic, clinical and laboratory features.

	Group 1 (n:67)		Group 2 (n:32)		p
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age (years)	31.1±5.9	31 (19-44)	29.8±5.2	29.5 (20-40)	0.300
Gravidity (n)	1.6±1.9	1 (0-10)	2.3±1.8	2 (0-8)	<b>0.021</b>
Parity (n)	0.7±0.9	0 (0-4)	1±1.1	1 (0-4)	0.194
Abortion (n)	0.4±0.8	0 (0-5)	0.3±0.8	0 (0-4)	0.605
Curettage (n)	0.4±1.3	0 (0-9)	0.8±1.0	0.5 (0-3)	<b>0.002</b>
Hospital admission weeks of pregnancy (weeks)	6.5±3.1	7.5 (0-11)	6.9±3.2	7.8 (0-11)	0.224
β-hCG(mIU/ml)	1180±953	819 (122-3822)	4394±3552	3562 (642-18000)	<b>&lt;0.001</b>
Ectopic pregnancy size before treatment (mm)	21.01±12.6	18 (4-70)	24.1±14.5	20 (0-60)	0.201

P<0.05: significant

## DISCUSSION

Ectopic pregnancy is the leading cause of the first trimester maternal mortality and morbidity. Effective and safe medical treatment with Methotrexate decreased the incidence of surgical treatment<sup>(7)</sup>. However, medical treatment was not hundred percent successful and prognostic factors affecting the success is not clear. In our study,  $\beta$ -hCG values for failure of a single dose of methotrexate use are higher than successful ones. Including ectopic foci size and the weeks of pregnancy, majority of the other parameters were not significantly different between the groups.

The use of single-dose methotrexate for ectopic pregnancy are in clinical use since the 1990s<sup>(8,9)</sup>. Success rates ranged from 64% to 94.2%<sup>(4,10-15)</sup>. In our study, the success rate was consistent with success rates of different studies in the literature (67.7%). Initial  $\beta$ -hCG level was found  $2196 \pm 2603$  mIU/ml. 9 of 32 patients who failed were treated second dose methotrexate and 23 patients were treated surgically. In the study by Adalı et al, single-dose methotrexate therapy was found to be successful 14 in 18 patients (% 77.7). Initial  $\beta$ -hCG level was determined as  $2615 \pm 2064$  mIU/ml. 4 patients underwent surgery after a failed single dose methotrexate therapy<sup>(16)</sup>. In the study by Turhan et al, same treatment was found to be successful 9 in 11 patients (81.8%). Initial  $\beta$ -hCG level was determined as  $1664 \pm 1571$  mIU/ml. The second dose methotrexate treatment was needed for 2 patients (18.2%) who failed<sup>(17)</sup>. In the study by Alkış et al, same treatment was found to be successful 81 in 98 patients (82.7%) and rest of the failed 17 patients (%17.3) underwent surgery. Initial  $\beta$ -hCG level was determined as  $1592 \pm 2613$  mIU/ml<sup>(18)</sup>.

In patients with ectopic pregnancy, reports on prognostic factors to successful response to single-dose methotrexate therapy are limited. In two previous studies in a manner similar to ours, high serum  $\beta$ -hCG levels has been identified as a single prognostic factor<sup>(6,19)</sup>. while in the study by Kimiaei et al, on top of initial  $\beta$ -hCG values, ectopic focus size was determined to be significant in determining the effectiveness of single-dose methotrexate therapy<sup>(20)</sup>. Also in some studies, in addition to the height of initial  $\beta$ -hCG values, initial and after methotrexate, fourth day, value of the decline at the  $\beta$ -hCG level was the most important indicators in predicting success<sup>(21,22)</sup>. Moreover, in

the study by Mungan et al, ectopic pregnancy implantation at tubo-uterine has been shown to be important to determine the success of single-dose methotrexate therapy in ectopic pregnancy. In 73 of the 98 patients (%74.4), single-dose methotrexate therapy were found to be successful while patients were divided by periampullary and peri-isthmic implantation and a dramatic difference was observed. According to this, 77 of 84 (%91.6) periampullary located ectopic pregnancy were succeed while 4 of 14 (28.5) ectopic pregnancy localized in the peri-isthmic were succeed<sup>(23)</sup>.

As a result, single-dose methotrexate therapy are effectively used in the initial treatment of ectopic pregnancy. The main prognostic factor that affect the success of treatment appears to be the height of  $\beta$ -hCG values. In terms of other potential prognostic factors such as maternal age, gestational week and focus size of ectopic pregnancy, more studies are needed.

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