

# Single Dose Methotrexate in Treatment of Ectopic Pregnancy: Review of 32 Case

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## ABSTRACT

**Objective:** To evaluate the efficacy of single dose intramuscular methotrexate in the treatment of ectopic pregnancy.

**Material and Methods:** 32 patients who matched the inclusion criteria were enrolled. Success of treatment was defined as a resolution of ectopic pregnancy without performing surgical intervention. The cases in whom the treatment was successful and those that were not were compared for  $\beta$ -hCG values and clinical features.

**Results:**  $\beta$ -hCG at diagnosis averaged 1293.9 mIU/ml. Of the 32 patients who received methotrexate, 26 were successfully treated. 23 patients (71.8%) received a single dose of methotrexate, 3 patients (9.3%) received an additional dose of methotrexate, 6 patients (18.7%) who had failed methotrexate required surgery for cure. The success rate of single-dose methotrexate was 79.3%.

**Conclusion:** Our study shows that single dose systemic methotrexate treatment can be used as an option in unruptured pregnancies.

**Key Words:** Ectopic pregnancy, methotrexate,  $\beta$ -hCG, single dose

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## Introduction

Ectopic pregnancy (EP) causes major maternal morbidity and mortality with pregnancy loss, and its incidence is increasing worldwide (1). Despite the continued increase in incidence, the rate of death from ectopic pregnancy declined as a result of earlier diagnosis before tubal rupture (2).

EP management basically follows a three-pronged approach: expectant management awaiting spontaneous resolution, medical treatment, and surgical treatment by laparoscopy or laparotomy. The wide availability of transvaginal ultrasound and the rapid immunoassay of serum  $\beta$ -hCG in early pregnancy also means that early ectopic pregnancies are being diagnosed in asymptomatic women. Surgical management in these women is not always necessary or appropriate. In these situations the medical treatment is now considered a good alternative to surgery.

Several drugs have been suggested in literature for medical treatment. Among them, methotrexate (MTX) systematically administered seems to offer the greatest benefits in terms of efficacy and tolerability. It has proved to be a good alternative to surgery in selected cases (3). The first single-dose MTX protocol was developed in 1991 (4).

In particular, a single-dose of 50 mg/m<sup>2</sup> of MTX given intramuscularly has been associated with a 94% success rate (4).

In the present study we did a retrospective evaluation of the efficiency of a single dose of MTX in 32 women with ectopic pregnancy.

## Materials and Methods

All patients admitted to Department of Gynecology and Obstetrics of Trakya University with EP were included in the study, provided that they matched all of the following inclusion criteria: 1) baseline  $\beta$ -hCG levels of or below 5,000 mIU/ml, 2) increase in  $\beta$ -hCG levels of less than 50% in two values 48 hours apart, 3) hemodynamic stability, 4) count blood cells, platelets, renal function, and liver enzymes in the normal range and 5) absence of fetal cardiac activity.

The patients received a regimen which included the following tests and administration schedules: Day 0, blood tests ( $\beta$ -hCG, count blood cells, serum transaminase activity, uremia, blood creatinine, blood group and RH factor) and administration of MTX i.m. in a single dose of 50 mg/m<sup>2</sup>; Days 4 and 7,  $\beta$ -hCG tests.

If the  $\beta$ -hCG level on Day 7 was at least 15% lower than that on Day 4, the patients were singled out for biochemical follow-up. If the  $\beta$ -hCG level on Day 7 was the same as or higher than that on Day 4, the patients received a second 50 mg/m<sup>2</sup> dose of MTX. Repeated MTX administration at the starting dose was considered also for patients whose  $\beta$ -hCG levels remained steady or increased during the follow-up period. Follow-up  $\beta$ -hCG tests were performed weekly until they were negative (with a value of  $\leq 6$  mIU/ml).

Single-dose MTX treatment was considered successful when  $\beta$ -hCG levels decreased until they became negative

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without further administration of MTX doses and without surgery. Moreover, the medical management of EP was considered successful when  $\beta$ -hCG levels became negative following the administration of one or more MTX doses.

Finally,  $\beta$ -hCG levels, previous ectopic pregnancy histories and clinical features were compared in responders and non-responders.

## Results

All patients admitted to our center with EP diagnosis between 2006 and 2007 were included in the study, provided that they matched inclusion criteria for treatment of MTX.

Characteristics of women were as follows: Mean age: 29,0 years, parity:1 (0-4). 56.2% of the patients were using a contraceptive method. The most common contraceptive method was coitus interruptus (25%) and three patients were using IUD (12.5%). Previous ectopic pregnancy rate was 9% (Table 1).

$\beta$ -hCG levels at diagnosis averaged 1293,9 mIU/ml (range, 81-4769 mIU/ml), (Table 1).  $\beta$ -hCG levels, measured on Day 4 and on Day 7, averaged 1129.6 mIU/ml (range, 37-5460 mIU/ml) and 594.5 mIU/ml (range, 6-4075 mIU/ml), respectively.

Out of the 32 treated patients, 29 (90.6%) received a single dose of MTX and the remaining 3 patients (9%) in which single dose MTX therapy failed received an additional dose of MTX equal to the starting dose. In these patients,  $\beta$ -hCG levels at diagnosis were higher than the mean levels in patients receiving

a single MTX dose, (Table 2). In 6 patients (18.7%), surgery became the definitive treatment after single dose MTX treatment failure. In surgically treated group, four patients developed signs and symptoms of acute abdomen two days later of single dose MTX and in remaining two ones,  $\beta$ -hCG levels measured on Day 4 were markedly increased with compared with on Day 0  $\beta$ -hCG levels.

The medical treatment with a single-dose of MTX was successful in 23 patients (79.3%). If we redefined successful medical management of EP as  $\beta$ -hCG levels becoming negative after administration of one or more MTX doses, total success rate was 81.2%.

## Discussion

Pharmacologic management of ectopic pregnancy has been the topic of many studies (5, 6). The medical management by MTX seems to offer several benefits over surgical treatment: it is less invasive, less expensive and can be given on an out-patient basis.

Different features of ectopic pregnancy (serum hCG, progesterone, folic acid level, endometrial thickness, the presence of yolk sac or embryo) have been taken into consideration when deciding MTX treatment success. In the last couple of years, most of the studies on ectopic pregnancies treated with single-dose methotrexate have concentrated on identifying prognostic factors in these patients (Table 3).

In the published literatures the initial serum hCG is probably the single most important factor in predicting the likely success of methotrexate, with significantly higher failure rates when the hCG level is above 1000 mIU/ml (7). Likewise Nowak-Markwitz et al. (13) reported in their retrospective study that, when the  $\beta$ -hCG level is >1790 mIU/ml, the MTX treatment of ectopic pregnancy is at risk of failure. In our study, the average  $\beta$ -hCG level in the successfully treated with single-dose MTX group was 1085 mIU/ml whereas in surgically cured patients mean  $\beta$ -hCG level was 1558 mIU/ml. Lipscomb et al. (5) evaluated in another study the predictors of success of methotrexate treatment in 350 women with tubal ectopic pregnancies who were treated with methotrexate intramuscularly according to a single-dose protocol. They concluded that the initial serum chorionic gonadotropin concentration is the best prognostic indicator of treatment success in women with ectopic pregnancies who are treated according to a single-dose methotrexate protocol.

Besides initial  $\beta$ -hCG level, the increment in  $\beta$ -hCG levels (%) in the 48-h interval has been demonstrated to be another important predicting factor of MTX therapy (14). In this

**Table 1. Characteristics of the patients**

	Successful single dose mtx (n=23)	Second dose mtx (n=3)	Surgically cured (n=6)
Age <sup>a</sup>	28.4	31	29
Parity b	1.1 (0-4)	0	1.6 (0-4)
Previous EP rate	2/32 (%6.2)	0	1/32 (%3.1)
Contraception rate			
Contraception type	11	1	2
CI	7/32 (%9.2)	1/32 (%3.1)	0
OC	1/32 (%3.1)	0	1/32 (%3.1)
IUD	3/32 (%9.3)	0	1/32 (%3.1)
Beginning $\beta$ -hCG level <sup>a</sup>	1085 (81-4620)	2372 (141-4769)	1558 (238-2928)

<sup>a</sup>: mean, b: median (min.-max.)

**Table 2. Treatment's features**

	n	Number of MTX doses	$\beta$ -hCG levels at diagnosis	4 <sup>th</sup> day $\beta$ -hCG level	7 <sup>th</sup> day $\beta$ -hCG level
Treatment successful with a single dose mtx	23	1	1085 (81-4620) (n=23)	748 (37-5460) (n=23)	414 (6-4075) (n=20)
Treatment unsuccessful with the need of second mtx dose	3	2	2372 (141-4769) (n=3)	2355 (607-4671) (n=3)	1500 (333-2772) (n=3)
Treatment unsuccessful with the need of surgical intervention	6	1	1558 (238-2928) (n=6)	2144 (196-3995) (n=5)	1037 (510-1565) (n=2)

**Table 3. Published studies on predictors of success and failure for management with single-dose methotrexate**

Year	First author	Predictor of success/failure	Value & Comments
2004	Dudley (7)	Serum hCG Serum hCG incremental rate	Failure rate was significantly higher when the serum hCG was >1000 IU/l Serum hCG values prior to ectopic diagnosis that increased >66% over 48 h and rising hCG values after treatment with methotrexate were independent predictors of tubal rupture
2004	Lipscomb (8)	Serum hCG level Previous ectopic pregnancy	Logistic regression analysis showed that only hCG and a history of previous methotrexate remained significant risk factors
2005	Takacs (9)	Folic acid levels.	A serum folate level >50 nmol/l (22 ng/ml) was found to be associated with failure of methotrexate treatment
2005	Takacs (10)	Endometrial thickness.	An endometrial thickness of >12mm was found to increase the risk for treatment failure with single-dose methotrexate
2005	Bixby (11)	Presence of a yolk sac.	The presence of a yolk sac was always associated with treatment failure
2006	Gabbur (12)	Day 7 serum hCG levels	Day 7 serum hCG levels were associated with successful single-dose methotrexate therapy

recent study, it has been shown that the lower  $\beta$ -hCG increment in the 48-h interval prior to treatment, the greater the likelihood that treatment of ectopic pregnancy with MTX will be successful. In our study, although increase in  $\beta$ -hCG levels measured on Day 4 and Day 0 were seemed to be significant between surgically treated group and second-dose MTX administered group, we had only three patients in the later group, and we couldnot compare them statistically. Ultrasonographic features at the time of MTX treatment were also investigated and as an example, the presence of yolk sac has not been shown to be an indicator of MTX treatment success (17). Likewise Moon et al. (18) concluded that the presence of tubal ring on transvaginal ultrasound can be considered as a predictor of MTX failure. In our study, we do not have enough ultrasonographic data for comparing cases in the success of MTX in responders and nonresponders.

There is a meta-analysis, including 26 article and 1327 cases, recently published by Barnhart (15) compared the success rates of single vs multidose MTX treatment. And they reported 92.7% and 88.1% success rates of multidose and single dose MTX treatment, respectively. In another study by Lipscomb et al, rates of success of systemic methotrexate were 96% with a multiple-dose protocol and 91.5% with a single dose protocol (2). In one of the recent studies by van Mello (16), it has been demonstrated that, when the serum  $\beta$ -hCG concentrations were lower than 3,000 mIU/ml, systemic MTX in a multiple-dose regimen can be recommended. But if the serum  $\beta$ -hCG concentrations were lower than 1,500 mIU/ml, this time single-dose methotrexate regimen can be administrated. In our study, 29 of the patients received single dose MTX and 23 responded. The success rate of single-dose methotrexate was 79.3%. Three patients required second dose MTX. The overall success rate of MTX regimen was found to be 81.2%.

To conclude, this study presents further evidence of the efficacy of single-dose MTX in EP treatment, the success being

higher with lower pretreatment  $\beta$ -hCG levels, in our case mean  $\beta$ -hCG levels in responders was 1085 mIU/ml. The results of our study also seem to suggest that further studies on larger case series might lead to identification of a  $\beta$ -hCG cut-off value at diagnosis and prediction of success.

#### Conflict of Interest

No conflict of interest was declared by the authors.

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