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Comparison of Two Different Protocols of Methotrexate Therapy in Medical Management of Ectopic Pregnancy

Najmieh Saadati,[1] Mahin Najafian,[1,*] Sara Masihi,[1] Sara Safiary,[1] and Parvin Abedi[2]

[1]Obstetrics and Gynecology Department, Fertility Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran
[2]Midwifery Department, Reproductive Health Promotion Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran

*Corresponding Author: Mahin Najafian, Obstetrics and Gynecology Department, Fertility Infertility and Perinatology Research Center, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran. Tel: +98-9161188801, Fax: +98-6113738333, E-mail: nil2f@yahoo.com; parvinabedi@ymail.com

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Abstract

Background: Ectopic pregnancy (EP) is one of the most dangerous complications of pregnancy and without prompt diagnosis and treatment, it could become a major cause of maternal morbidity and mortality.

Objectives: In this randomized controlled study, we compared single and double dose of methotrexate (MTX) therapy in the treatment of ectopic pregnancy.

Patients and Methods: This study was performed on 76 patients who were admitted to Obstetrics Ward with primary diagnosis of ectopic pregnancy based on their medical history, physical examination, beta subunit (β-HCG) level, and transvaginal ultrasonography. Using random block allocation, the patients were classified in two groups of single dose and double dose administration of MTX. In single dose group, 50 mg/m^2 of MTX was given at day 0 and in double dose group, the patients received two doses of MTX at day 0 and 4. The level of β-HCG was measured at day 0, 4, 7 in both groups. The successful treatment was defined as 15% reduction in β-HCG level between day 4 and 7. The two groups were compared with each other with regard to their need for operation, or extra dose of MTX; duration of hospitalization; and MTX complications.

Results: Results showed that the rate of success in double dose method was more than single dose one (79% versus 69%) but the difference was not significant (P = 0.29). Although the need for operation and extra dose of MTX were lower in the double dose group (15.8% vs. 18.8% and 5.26% vs. 13.2%, respectively), these differences were not significant too. Duration of hospitalization was significantly lower in double dose compared to the single dose (11.55 d vs. 14.76 d, P < 0.001).

Conclusions: Single dose therapy of MTX has sufficient power and efficacy in the treatment of ectopic pregnancy, however in patients with higher serum level of β-HCG, the successful treatment increases by using double dose method. Using double dose also could decrease the necessity of operation, re-administration of MTX, and duration of hospitalization.

Keywords: Pregnancy Ectopic, Methotrexate, Beta Subunit

1. Background

Ectopic pregnancy (EP) is a term used for implantation of blastocyst outside the natural cavity of uterus (1, 2). The prevalence of EP has been doubled since 1960 and comprises 2% of pregnancies diagnosed at the first trimester (3). In the developing countries like Iran, 10% of women diagnosed with EP, cannot survive, as they refer to the hospital very late (4). The prevalence of EP has increased owning to high occurrence of prior damage to the fallopian tubes, due to the abdominal operation (5), infertility (6), using artificial reproductive technology (7), infections like *Chlamydia trachomatis* (8), and using contraception devices, which contains only progesterone (9). Considering high prevalence of EP, finding efficient and safe methods of treatment has gained top priority. Treatment of EP can be postponed in special cases under the restrict observation. If the patient's hemodynamic condition is stable, with no significant symptoms, and low free intraperitoneal fluid detected on ultrasound (10), medical treatment is preferable in which the single dose of methotrexate (MTX) is prescribed in 34% - 69% of cases (11). There is no general census on medical or surgical treatment of EP. However, when the fallopian tubes remained unruptured, the medical treatment is preferable for preserving fertility (12). Also, medical treatment is more feasible, affordable, and accepted by patients. But it is not clear that which medical protocol (single, double, or multiple doses) is preferable. However, the success of multidose therapy is more than single dose in most of the studies (13). Some studies have found that double dose is preferable due to its few side effects (14).

2. Objectives

There are few studies on comparing the effectiveness of single dose with double dose administration of MTX, therefore this study was designed to compare the effectiveness of single and double dose of MTX in treatment of EP.

3. Patients and Methods

This research is a randomized controlled trial study conducted on 76 patients with ectopic pregnancy referring to Imam Khomeini hospital of Ahvaz city, Iran during 2012 - 2013. The design of this study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Reference number: Ajums.REC. 1392.19, Date: 22/April/2013). Imam Khomeini hospital is specialty teaching hospital affiliated to the Ahvaz Jundishapur University of Medical Sciences and is the referral hospital in the Khuzestan province. Inclusion criteria were as follows: healthy women with stable hemodynamic condition and β-HCG value of less than 15000 mIU/mL. Women who had a history of liver and kidney disease, blood dyscrasia or breastfed were excluded from the study (14). The informed written consent was obtained from every participant prior to the intervention.

The diagnosis was performed by transvaginal sonogram and β-HCG tests (4). Patients were randomly assigned in two groups of single and double dose by the method of enclosed envelope include block randomization (with ratio 1:1). According to similar studies, the lowest success rate for single dose and double dose have been reported 55% and 77%, respectively (14). Considering 95% confidence interval the sample size was calculated as 76 patients (38 in each single or double dose group) according to the following equation:

$$(1) \qquad \frac{\left(S_1^2+S_2^2\right)\left(Z_{1-\frac{\alpha}{2}}+Z_{\beta}\right)^2}{(M_1-M_2)^2}$$

Where $\alpha = 0.05$ and $\beta = 2\%$.

3.1. Intervention

In the single dose group, 50 mg/m^2 MTX was administered at day 0, while in the double dose group; patients received two doses of 50 mg/m^2 at days 0 and 4. The values of β-HCG in both groups were measured on the fourth and seventh day of hospitalization. About 15% decrease in β-HCG level was considered as a successful treatment. In case of treatment's failure, elective surgery or administration of extra dose of MTX was used. If the rupture of fallopian tube occurred, patient would undergo immediate operation. The necessity of extra doses of MTX or operation was determined in both groups. Patients remained hospitalized during the intervention period and were checked for the level of β-HCG every 48 hours.

3.2. Measures

Before prescribing MTX, blood tests, kidney and liver transaminase levels, creatinine and urea levels were measured and if the patients showed any problem, they were excluded from the study. During the intervention, the following signs were compared between two groups and considered as drug complications; if liver transaminase increased 1.5 times more than normal, or creatinine increased to 1.5 mg/dL, WBC count decreased to 2000, or platelets declined fewer than 100,000 (11).

In order to compare the effectiveness of MTX doses in different β-HCG levels or mass sizes; patients were classified in 3 groups of lower than 2000 mIU/mL, 2000 - 4000 mIU/mL, and more than 4000 mIU/mL based on β-HCG levels and in 3 groups of lower than 2 cm, 2-4 cm and more than 4 cm based on mass size. The value of β-HCG was measured using passive latex agglutination inhibition test.

Every woman remained hospitalized under the precise observation until their β-HCG value reached 200 mIU/mL. The duration of hospitalization was also recorded for single dose and double dose groups. The side effects of MTX, as well as function of liver and kidney were checked in each participant one week after completion of treatment and patients were asked for complications such as nausea, vomiting, and gastrointestinal symptoms.

Data were assessed statistically by SPSS software version 19. The Chi-square, independent t test, and logistic regression were used for analyzing data. The normality of data was checked using Kolmogorov-Smirnov test and as a result, all continuous variables were normal.

4. Results

The recruitment and retention of participants in the study are illustrated in Figure 1. Sociodemographic characteristics of the patients such as age, parity, and history of abortion are listed in Table 1. As it is evident in Table 1, demographic characteristics and the mean of β-HCG level in two groups did not show any significant difference. As demonstrated in Table 2, the success rate of single dose was 69% and in double dose group, it was 79%. However these differences were not statistically significant (P = 0.29). The rate of operation was 19% and 16% in single and double dose groups, respectively (P = 0.76). The necessity of extra dose of MTX in the single dose grope was 14% and in the double dose group, it was 6% (P = 0.23).

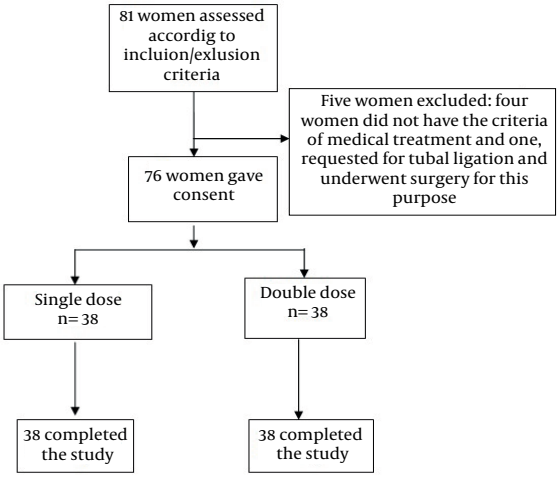

Figure 1. Flow Diagram of Recruitment and Retention of Participants in the Study

The two therapeutic methods were compared with regard to 3 different levels of β-HCG and mass size. The results of logistic regression showed that there were no any significant differences between two groups in the rate of success considering the level of β-HCG and mass size (P > 0.05, Table 3).

Table 1. Sociodemographic Characteristics of Women in Single and Double Dose Groups[a,b,c]

Variables	Single Dose	Double Dose	P Value
Age, y	28 ± 7	27 ± 6	0.69
BMI, kg/m^2	23 ± 3	24 ± 4	0.28
Parity			0.77
0	7 (19)	9 (24)	
1	15 (40)	11 (29)	
2	10 (27)	15 (40)	
> 3	6 (16)	3 (8)	
History of abortion	9 (24)	11 (29)	0.44
Gestational age, d	50 ± 10	53 ± 10.8	0.75
β-HCG, mIU/mL	3249 ± 1427	3311 ± 1250	0.97

[a]Abbreviation: BMI, body mass index.
[b]N = 38.
[c]Data are presented as No. (%) or mean ± SD.

Table 2. Distribution of Participants According to Their Need to Extra Dose of MTX and Rate of Operation[a,b]

Variables	Single Dose	Double Dose	P Value
Need to extra doses of MTX	7 (19)	2 (6)	0.23
Need to extra dose of MTX according to the level of β-HCG mIU/mL			0.06
< 2000	1 (3)	2 (6)	
2000 - 4000	3 (8)	0	
> 4000	1 (3)	0	
Need to extra dose of MTX according to the mass size, cm			0.23
2 - 4	3 (8)	1 (3)	
> 4	3 (8)	0	
The rate of operation based on the level of β-HCG, mIU/mL			0.32
< 2000	0	1 (3)	
2000 - 4000	3 (8)	3 (8)	
> 4000	4 (11)	2 (6)	
The rate of operation based on mass size, cm			0.13
< 2	0	3 (8)	
2 - 4	2 (6)	1 (3)	
> 4	3 (8)	2 (6)	

[a]Data are presented as No. (%).
[b]N = 38.

Table 3. The Rate of Success, Duration of Follow-up and Side Effects in two Groups of Single and Double Dose[a,b]

Variables	Single Dose	Double Dose	Odds Ratio, 95% Confidence Interval	P Value
The overall success	26 (69)	30 (79)	1.73 (0.61 - 4.88)	0.29
Success based on the level of β-HCG, mIU/mL				
< 2000	11 (29)	10 (27)	0.3 (0.027 - 3.4)	0.3
2000 - 4000	12 (32)	16 (43)	2.66 (0.55 - 12.8)	0.2
> 4000	3 (8)	4 (11)	3.33 (0.36 - 30.7)	0.5
Rate of success based on mass size, cm				
< 2	9 (24)	11 (29)	0.30 (0.02 - 3.2)	0.3
2 - 4	11 (29)	14 (37)	3.18 (0.51 - 19.6)	0.3
> 4	6 (16)	5 (14)	2.5 (0.34 - 18.3)	0.3
Duration of follow-up period, d	14.8 ± 3.2	11.5 ± 3.3	-	< 0.001
Side effects of MTX	4 (11)	7 (19)		0.32

[a]Data are presented as No. (%) or mean ± SD.
[b]N = 38.

Results showed that only the rate of operation at the β-HCG level of 2000 - 4000 mIU/mL was lower in the double dose compared to the single dose group (P = 0.05).

Duration of hospitalization in double dose group was significantly lower than that of the single dose group (11.55 vs. 14.76 d, P < 0.001). The rate of complications in double dose group was more than single dose group, but no significant difference was observed (P = 0.32).

Complications included vomiting and gastrointestinal symptoms and no blood or urine disorders were reported after prescription of MTX among patients.

5. Discussion

This study designed to compare the effectiveness of single and double doses of MTX in patients with EP. Our research showed that double dose method might induce better response with regard to necessity of operation and extra doses of MTX compared to single dose method. Therapeutic success of double dose method in our research was 79%, which was lower than Hamed et al. study result (82% and 88% in the single and double dose, respectively) (13). This discrepancy may be due to the level of β-HCG in our patients that was more than that of the Hamed et al. study (13). They also did not notice any significant relation between therapeutic method and response to the treatment in their research. In a study by Barnhart et al. in which they administered 50 mg/m^2 MTX on days 0 and 4, results showed that the success rate was 87% and the fallopian tubes ruptured in 3% of patients. The reported side effects were mild and transient and most women were satisfied with the treatment (14). The rate of success in our study in the double dose group was less than that observed by Barnhart et al. study (14) that may be due the overall level of β-HCG in their study which was lower than that of our study.

Erdem et al. (15) in a study on 34 patients who received single dose of MTX, noticed the higher rate of success in the group with β-HCG level lower than 2000 mIU/mL compared to the group with β-HCG level more than 4000 mIU/mL (78% versus 33.33%). They concluded that the mean of β-HCG is an important factor in response to treatment (15). In our study, the rate of success was also higher in the group with β-HCG level lower than 2000 mIU/mL (91.7% and 77%, respectively) and the mean of β-HCG was also lower in patients responded to the treatment than cases who did not.

In a study by Alleyassin et al., they compared the effect of single dose with multiple doses of MTX in selected women. The results showed that the rate of success in the single dose was 88.9%, while in the multiple doses, it was 92.6% (P > 0.05). The researchers concluded that single dose can be considered as the first choice of treatment in selected patients (16). The success rate in Alleyasin et al. study in the single dose group was more than our success rate. The higher level of initial β-HCG in the single dose group in our study may be a reason for this dissimilarity (3249 ± 1427 vs. 3146.9 ± 2389).

According to our findings, the single dose of methotrexate (compared to the double dose) is effective in cases of EP with primary low level of β-HCG. However in cases with higher level of β-HCG or probability of tube rupture, administration of double dose is recommended. Also the duration of hospitalization in the double dose group was significantly lower compared to this time in the single dose group.

This is the first time in Iran that we compared the single dose versus double dose of MTX for treatment of ectopic pregnancy. Results of this study have been considered as a part of treatment regimens in the Imam Khomeini Hospital after completion of this study.

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Footnotes

Authors' Contribution: Najmieh Saadati, Mahin Najafian, Sara Masihi and Sara Safiary were involved in study design and concept. Sara Safiary was responsible for data collection, data analyzing and writing the manuscript in Persian. Parvin Abedi was responsible in data interpretation, writing, and finalizing the manuscript in English.

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