

## Methotrixate for nonsurgical management of ectopic pregnancy

Ariana Kh. Jawad\*

### الخلاصة

عقار الميثوتريكسات استخدم بصورة واسعة لعلاج حالات الحمل خارج الرحم تهدف الدراسة لتقييم مدى سلامة وفعالية استخدام عقار الميثوتريكسات لعلاج حالات الحمل خارج الرحم المبكر وغير المنفجر. دراسة مستقبلية سريرية تضمنت ستون امرأة في مستشفى الولادة في اربيل للفترة من الاول من كانون الثاني 2007 ولغاية الاول من كانون الثاني 2009 وتم التشخيص باستخدام السونار المهبطي وقياس مستوى  $\beta$ -HCG في الدم . اعطي الميثوتريكسات بالعضله 50 ملغم /متر مربع في اليوم الاول وتم قياس مستوى  $\beta$ -HCG في الدم في اليوم الرابع والسابع وتم اعتبار العلاج ناجح اذا قل المستوى بنسبة 15% وتم المتابعه اسبوعيا الى ان يصل مستوى سالب. تم اعطاء جرعه ثانيه من العقار في اليوم السابع اذا كان مستوى  $\beta$ -HCG اعلى او يساوي او لم يقل عن 15% عن مستوى اليوم الرابع. نسبة النجاح لجرعه واحده من الميثوتريكسات كانت 75% و 16.6% احتاجوا الى جرعه متعدده و 8.3% لم يستجيبوا عولجوا جراحيا عقار الميثوتريكسات بالعضله يعد سليم و فعال ويمثل بديل عن التداخل الجراحي لحالات الحمل الخارج الرحم المبكر

### Abstract

Systemic Methotrexate has been widely used to treat ectopic pregnancy. The aim of current study were to evaluate the safety and efficacy of single dose intramuscular methotrexate as a treatment option for early unruptured ectopic pregnancies.

From 1<sup>st</sup> of January 2007 to 1<sup>st</sup> of January 2009 at Maternity teaching Hospital-Erbil, a case cohort prospective study was conducted on 60 patients with small unruptured ectopic pregnancies treated as in-patients with single dose of Methotrexate therapy.

\*Specialist in obstetrics and gynaecology; Maternity teaching Hospital-Erbil

Ectopic pregnancy was diagnosed by both transvaginal ultrasound for the size and volume of the gestational mass and  $\beta$ -HCG measurement. Intramuscular methotrexate 50 mg/m<sup>2</sup> was administered on days 1 and Serial  $\beta$ -hcg was repeated on days 4 and 7, If the  $\beta$ -HCG on day 7 was at least 15% lower than that on day 4, the patient was regarded as treatment success, and Follow-up serum  $\beta$ -HCG was performed weekly until become negative (value of <15 mIU/ml). while additional doses(second dose) of methotrexate were given on day 7 If the  $\beta$ -HCG level on day 7 was the same or higher or less than 15% lower than that on day 4.

The success rate of systemic methotrexate (single dose) was 75%(n=45), 25%(n=15) exposed to 2 or more doses of methotrexate ,16.6%(n=10) of patients exposed to multidose methotrexate respond to treatment, remain only 8.3%(n=5) not respond to multidose treatment they were treated surgically ,in which 2 cases of them operation done for them on their request after one dose of methotrexate, and other 3 cases were failed to respond to medical treatment after receiving 3 dose of methotrexate. The over all success rate of treatment in our study(medical treatment) was 91%(n=55).Success rate was higher in patients whom with  $\beta$ -HCG was  $\leq$  1500 mIU .Treatment was well-tolerated; most side effects were reported as mild and transient.

All cases respond to methotrexate reported satisfaction with this regimen. Within two years follow up visit 38 cases become pregnant , 2 of them developed recurrent ectopic pregnancy.

**Key Words:** Ectopic pregnancy, methotrexate, medical management, safety

## Introduction

Ectopic pregnancy is an acute emergency in the first trimester where surgery is the mainstay of treatment. With the advent of improved diagnostic techniques like high-resolution transvaginal ultrasonography and expedient serum human chorionic gonadotrophin (HCG) assay, ectopic pregnancy is now diagnosed early. Systemic methotrexate treatment of unruptured ectopic

pregnancy has emerged as a safe and effective alternative to surgical procedures(1,2).

Reports of the incidence is showing rise from 0.5-1-2% .There has been a rise of 3-5% in ectopic pregnancies following assisted reproductive techniques (3,4).

Methotrexate is an antimetabolite chemotherapeutic agent Although the exact mechanism of action is unknown, methotrexate is believed to cause either resorption or tubal abortion of the conceptus. Methotrexate can be administered systemically as a single dose regimen (methotrexate 1.0 mg/kg or 50 mg/m<sup>2</sup> i.m without folinic acid) or as multiple dose regimen (methotrexate 1.0 mg/kg i.m daily 0,2,4,6 alternated with folinic acid 0.1 mg/kg orally on days 1,3,5,7). Methotrexate has been shown to be safe with virtually no adverse effects reported on reproductive outcome. Women most likely to respond to methotrexate therapy are thought to be those with small gestational masses, lower serum concentrations of human chorionic gonadotropin and progesterone, and the absence of blood in the peritoneal cavity(5-7 ).

### **Objective**

The aim of this study were to investigate the efficacy, the safety ,the adverse event and acceptability of a single dose of methotrexate to treat ectopic pregnancy,and also to assess pregnancy outcome during a 2 -year follow-up period.

### **Pateints and method**

This study was conducted as a case cohort study From 1<sup>st</sup> of January 2007 to 1<sup>st</sup> of January 2009 at Maternity teaching Hospital in Erbil city/ Kurdistan region/North of Iraq. Amoge patients who attended the emergency department of Hospital, 60 pateints with small unruptured ectopic pregnancies treated as in-patients with single dose of methotrexat therapy.

The diagnosis of ectopic pregnancy was made using both transvaginal ultrasound and measurement of  $\beta$ -HCG. All cases selected for medical management gave their informed written consent before starting the treatment.

The scientific committee in Maternity teaching Hospital approved the study, the committee responsible on ethical approval confirming the study.

Pretreatment serum concentrations of human chorionic gonadotropin, The ultrasound examination was performed, the size and volume of the gestational mass was recorded and confirmed absence of hemoperitoneum.

Selection criteria included hemodynamically stable women with  $\beta$ -HCG level of  $\leq 3000$  mIU/ml, adnexal mass  $\leq 5$  cm, absent cardiac activity and hemoperitoneum less than 100 ml. Patients who were hemodynamically unstable with hemoperitoneum, those with adnexal mass  $>5$  cm, the presence of cardiac activity on ultrasonography and  $\beta$ -HCG  $>3000$  mIU/ml and patient with abnormal liver functions tests were excluded from the study.

Baseline investigations such as full blood count,  $\beta$ -HCG, renal and liver functions tests, and blood group RH factor were done. Intramuscular methotrexate 50 mg/m<sup>2</sup> was administered on days 1, repeated measurement of  $\beta$ -HCG done on day 4 and 7, If the  $\beta$ -HCG on day 7 was at least 15% lower than that on day 4, the patient was regarded as treatment success, In case of success follow-up serum  $\beta$ -HCG was performed weekly until with a value of  $<15$  mIU/ml. Success rate was defined as ectopic resolution without the need for further dose of methotrexate or surgical interference.

On day 7, Cases with persistent plateauing or rising serum hcg concentration or fall less than 15% in serum hcg concentrations in compare with day 4, received additional dose of methotrexate, if patient didn't respond to 3 dose of methotrexate they were regarded as treatment failure and surgical intervention were considered. Also for patients with hemodynamically unstable and signs of tubal rupture undergone emergency laparotomy.

The side effect of methotrexate treatment was evaluated by noticing lower abdominal pain, vaginal bleeding, mouth ulcers, sore throat, gastrointestinal side effects and rashes.



Patient satisfaction to therapy also assessed by asking a direct question to the patient. Future pregnancy outcome for all cases were followed for two years.

Non-sensitized Rhesus negative women received anti-D immunoglobulins 250 µg .Women treated with methotrexate were advised to avoid sexual intercourse until serum hcg was negative, and not to conceive within three months of treatment.

Data were presented as mean ± SD. Statistical analysis was conducted using SPSS version 18. Proportions were compared by using the Chi-square test. The Pearson correlation statistic was used to investigate correlations between variables. Statistical significance was set at P <0.05.

**Result**

In this study the success rate of systemic methotrexate (single dose) was 75%(n=45), 25%(n=15) exposed to 2 or more doses of methotrexate ,16.6%(n=10) of patients exposed to multidose methotrexate respond to treatment, remain only 8.3%(n=5) not respond to multidose treatment they were treated surgically ,in which 2 cases of them operation done for them on their request after one dose of methotrexate. And other 3 cases were failed to respond to medical treatment after receiving 3 dose of methotrexate. The over all success rate of treatment in our study(medical treatment) was 91%(n=55)

In this study, the mean age was 24.73±6.78 years ranging between 15-45 years The success rate of methotrexate in first age group (15-30) years was 46.7% (n =28) while for the second age group(31-45)years was 28.3%(n=17), the success rate increase with decrease maternal age (Table-1).

**Table 1 – Maternal age in years**

No.	Ag in year	Cases		Successful		p-value
		NO.	%	NO.	%	
1	15-30	38	63.3	30	46.7	0.757
2	31-45	22	36.6	17	28.3	

The success rate of methotrexate in multigravid lady(p1-p5) was 43.3% (n=26) and in primipara was 31.1% (n=19). The success rate was higher in smaller gravid lady (**Table-2**) although the difference was statistically not significant .

**Table 2 –Distribution of cases according to parity**

						p-value
NO.	parity	Cases		Successful		0.764
		No.	%	No	%	
1	0	34	56	26	43.3	
2	1-5	26	43	19	31.7	

The mean gestation age at diagnosis was  $5.06 \pm 1.12$  weeks .The success rate of methotrexate in gestational age 4-5 weeks was 46.7% (n=25) and of gestational age group 6-7 weeks was 33.3% (n=20), success rate was higher in gestational age of 6-7 weeks (Table 3).

**Table 3 – Gestational age at diagnosis**

		Cases		Successful		p- value
No.	weeks	N0.	%	N0.	%	0.296
1	4-5	31	51	25	46.7	
2	6-7	29	48	20	33.3	

The mean adenexial mass was  $3.58 \pm 1.27$  cm , Adnexal mass ranged from 1.5-5 cm.The success rate of methotrexate in Adnexal mass  $\leq 3$  was 48.3%(n=29) and of Adnexal mass  $\leq 5$  cm was 26.7% (n=16.) ,success rate was higher in smaller Adnexal mass  $\leq 3$ cm, which was statistically significant (Table 4).

**Table 4 – Adenexial mass size**

		Cases		Successfull		p-value
N0.	Adnexal mass(cm)	N0.	%	N0.	%	0.011
1	1.5-3	33	55	29	48.3	
2	4-5	27	45	16	26.7	

56.7%(n=34) with  $\beta$ -HCG <1500 respond to treatment and 18%(n=11) with bhcg  $\leq$ 3000iu was respond to treatment, success is higher with smaller  $\beta$ -hcg level (Table-5).

**Table 5 -  $\beta$ -HCG level**

B-HCG mIU	Cases		Successfull		p- value
	N0.	%	N0	%	
$\leq$ 1500	39	65	34	56.7	0.03
$\leq$ 3000	21	35	11	18.3	

15cases were in need for additional methotrexate dose ,majority of them were cases with higher  $\beta$ -HCG level( $\leq$ 3000 iu) and cases with larger adnexal size( $\leq$  3cm)-Table-6.

**Table 6 – Additional methotrexate dose in relation to  $\beta$ -hcg level & adnexal size**

Additional methotrexate dose	$\beta$ -hcg iu		adnexal size cm	
	$\leq$ 1500	$\leq$ 3000	$\leq$ 3	$\leq$ 5
▶ Cases (N0.=15	4	11	4	11
▶ cases Resolute with additional methotrexate dose (2 or more doses)	4(26.7%)	6(40%)	3(20)	7(46.7%)

Time of resolution for ectopic pregnancy was defined as the total number of days from the beginning of treatment until  $\beta$ -HCG level became negative (<15mIU/ml).

Time frame for normalization was longer for patient group with  $\beta$ -HCG  $\leq$ 3000iu. Pateints with bhcg  $\leq$ 1500iu ,46.6%(n=28) resolution occure between the period of 3-4weeks and 16%(n=10) of patients resolution occur between the period of 5-6weeks period, for cases with bhcg  $\leq$ 3000 mIU, resolution occure 8.3%(n=5),20%(n=12) respectively Table-7.

**Table 7 – Time frame for normalization in relation to basic  $\beta$ -HCG level & adnexal size**

Time frame for normalization(weeks or days)	$\beta$ -HCG iu		adnexal size cm	
	$\leq$ 1500 N0.=38	$\leq$ 3000 N0.=17	$\leq$ 3n0.=32	$\leq$ 5 (n0=23
▶ 4-5 wks(18-22 days)	28(46.6%)	5(8.3%)	18(30%)	14(23%)
▶ 6-7wks (23-30 days)	10(16%)	12(20%)	14(23%)	9(15%)

Surgical intervention was required for only 5 patients .43 patients complained of lower abdominal pain between days 2-7,they respond to simple analgesia ,10 pateints complained from vaginal bleeding which was mild . 10 cases complained from nausea all of them were cases received third methotrexate dose. only 4 cases have vomiting during the treatment coarse.

The incidence of risk factor in the studied group were, infertility in 7.2% (n=8), six women had conceived by ovulation induction and the rest with assisted reproductive technique. There were 1.8% (n=5) women with history of previous ectopic pregnancy and 14.4% (n=16) with past surgical history. 30.6%(n=34) of cases with no identifiable risk factors.

On the other hand, 34.2%% (n=38) women reported successful pregnancy outcome after 2 year , two cases developed recurrent ectopic pregnancy ,Moreover, 19.8% (n= 22) of cases suffered secondary infertility .

## **Discussion**

Ectopic pregnancy occurs in around 1% of pregnant women and may seriously compromise women's health and future fertility. Ectopic pregnancy can be diagnosed before the patient's condition has deteriorated and cornerstone of diagnosis is the use of transvaginal ultrasound and serum human chorionic gonadotrophin measurement(8,9).

Historically, the treatment of ectopic pregnancy was limited to surgery. With evolving experience with methotrexate, the treatment of selected ectopic pregnancies has been revolutionized. Medical therapy of ectopic pregnancy is appealing over surgical options for a number of reasons, including eliminating morbidity from surgery and general anesthesia, potentially less tubal damage, and less cost and need for hospitalization. Measures of current trends in the management of ectopic pregnancy in the United States from 2002-2007 indicate that the percentage of patients treated with methotrexate increased from 11.1% to 35.1%(10).

Dhar et al reported the success rate of single dose methotrexate therapy was 65% (n=39) and 35% (n=21) required surgical

intervention(11).The over all success rate of treatment in our study (medical treatment) was 91%(n=55),which was higher than study done by Dhar et al, most probably higher the success rate in our study related to basic  $\beta$ -HCG level involved in study which was  $\leq 3000$  mIU to be included in the study because higher success rate observed in group with lower  $\beta$ -HCG ( $\leq 1500$  mIU), while in Dhar`s study basic  $\beta$ -HCG level involved in study was  $\leq 5000$  mIU, all patients who failed to respond to medical treatment were cases with  $\beta$ -HCG more than 5000 mIU/ml

Study done by Gary H et al,1999 (12) reported success rate of 91%(n=230) for the total 350 women in the study, 283 (81 percent) received one dose of methotrexate, in which most caes failed to respond to medical treatment were cases with higher initial mean serum chorionic gonadotropin level , its goes with our study ,although sample size of Gary H`s study was so larger than our study. Regression analysis revealed the pretreatment serum chorionic gonadotropin concentration to be the only factor that contributed to the failure rate(12).

Astudy conducted by Thia EW et al,2009 success rate was (84.5 %), 16 patients eventually required surgery and only one patient defaulted on follow-up (2). Success rate was slightly lower than our study.

In study done by Lipscomb GH et al,1998 Overall 287 patients were successfully treated with methotrexate, success rate was 90.1%, Reported a success rate of 96% with  $\beta$ -HCG less than 6000 mIU/ml and 58% when  $\beta$ -hcg is greater than 6000 mIU/ml. He noted that initial  $\beta$ -HCG is the only predictor of success for repeated injection of methotrexate in single dose regimen(13). Although Lipscomb GH start with higher initial  $\beta$ -hcg but agree with our study in which response was higher in smaller  $\beta$ -HCG group( $\leq 1500$  mIU),all other parameter involved in the study(age and parity) were nearly similar to our study apart from sample size. In Cho GJ et al, 2006 study the success rate was (73.3%), Only 22 women of a total 30 women were successfully treated with a single dose of methotrexate. Five women required a second injection, and one woman required a third dose. The combined

success rate for medical management of ectopic pregnancy with 1-3 doses of methotrexate was 86.7% (26 women)(14).The success rate slightly lower than our study,this might be related to half sample size of Cho GJ et al, 2006 study.

In Cho GJ study pretreatment  $\beta$ -hCG levels were significantly lower in women who responded to single dose therapy than in those who required either multiple doses or who had failure of medical management ( $p < 0.001$ ),which goes with our study in which success rate were higher in patients with lower  $\beta$ -HCG ( $\leq 1500$  mIU),In both the initial  $\beta$ -hCG level is the only factor that has significant meaning as predictor of success of repeated injections of methotrexate in the single-dose regimen.

In our study where success rate of methotrexate treatment decreased as maternal age increase , 10 patient ( 16.6%) were not respond to single dose methotrexate there age were higher than 30 years, although the difference was statistically not significant Which goes with study done by Dhar H et al, 2011 , but didn't go with study done by Gary H et al,1999 in which The women treated successfully and unsuccessfully did not differ significantly with regard to age,

In our study where success rate of methotrexate treatment didn't differ significantly with regard to parity which goes with study done by Dhar,Although the size of an ectopic gestational mass is frequently used as an exclusion criterion for methotrexate therapy, few data are available about the effect of this factor on success rates.

In the current study adnexal mass ranged from 1.5-5 cm .in patient with adenaxial mass between 1.2-3cm associated with higher success rate, which goes with study done by Dhar et al, 2011, in which Adnexal mass ranged from 2-4 cm. In patients with adnexal mass more than 4 cm, the success rate was less,but didn't goes with study done by Gamzu R et al,2002 in which the initial size of the ectopic mass was not related to the success of the treatment nor to serum HCG levels(15).

In all comparative studies fetal cardiac activity and , the presence of free peritoneal fluid has been used for comparison in success

rate between the groups, but in our study we didn't use it, the reason being that the methotrexate regimen is the first time to be used in our institution. In addition, the presence of fetal cardiac activity has also been considered a relative contraindication to methotrexate therapy. Most reports have indicated an increase in failure rates when cardiac activity was present. Also the presence of free peritoneal fluid, presumably blood, is considered by many to be a contraindication to methotrexate therapy, because it may indicate ongoing tubal rupture(4),(16-19).

In our study time frame for normalization was longer for patient group with  $\beta$ -HCG  $\leq 3000$  mIU. Also time for normalization is longer for cases received additional methotrexate dose, agree with study done by Dhar t al,2011, The average time of resolution for ectopic pregnancy was 32 days for single dose of methotrexate and 58 days for those receiving two doses or more in Dhar's study. also agree with study done by Erdem M et al,2004, in which the mean time to resolution of  $\beta$ -HCG was 26.5 days (10 to 37 days) with methotrexate. All 3 patients who failed medical therapy had beta-hCG level  $>4,000$  mIU/ml and 2 of them had positive fetal cardiac activity. (20).

There was no major side effect detected in our study. The minor side effects reported included vaginal bleeding (19.1 percent) and abdominal pain (28.2 percent), which goes with majority of study done like Cho GJ et al, 2006 study Lipscomb GH et al,1998. study.,also goes with study done by Thia EW et al,2009, There was no major side effect detected in this cohort. The minor side effects reported included mucositis (19.1 %) and abdominal pain (28.2 %). Incidence of ectopic pregnancy as a risk factor in Zargar M et al,2006 was 30% which was higher than our study it accounted for 7.2% (n=8)(21), but agree with Dhar H et al, 2011 study in accounted for 15(n=9).

In our study 34.2%% (n=38) women reported successful pregnancy outcome after 2 years. relatively higher in our study in comparison to Dhar study in which 30% (n=18) women reported successful pregnancy outcome after one year and 13.3% (n= 8) cases after 2 years. probably due to shorter period of follow up in our study

which was 2 years and for Dhar study was between 3-5 years. Moreover, 19.8% (n= 22) cases in our study suffered secondary infertility successful pregnancy while 11.6% (n= 7) cases in Dhar`s study suffered secondary infertility and the rate of repeat ectopic pregnancy in Dhar`s study was 1.6% (n= 1), while in our study 2 cases developed repeat ectopic pregnancy.

### **Conclusion**

1. Intramuscular methotrexate is a safe and cost effective alternative to the surgical intervention in the unruptured ectopic pregnancies that were diagnosed at early gestational age.
2. 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. These results can be used to counsel women with ectopic pregnancies regarding the likelihood of successful treatment with systemic methotrexate.

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