Original Article

Comparison of The Success of Single Dose Versus Multiple Dose Methotrexate in Ectopic Pregnancy with β-HCG Level 2000-5000 MIU/Ml

Mobashara Ghulam Muhammad[1], Sobia Luqman[2], Kausar Masoom[3], Gul Amber Benish[4], Shumaila Naeem[5]

[1]Assistant Professor Mohtarma Benazir Bhutto Shaheed Medical College Mirpur AJK
[2]Assistant Professor, MCH Center, PIMS, Islamabad, [3,5]Associate Professor, MCH Center, PIMS, Islamabad
[4]Senior Registrar in Akber Niazi teaching hospital, Islamabad

Correspondence: Dr Sobia Luqman
Assistant Professor
Dept of Obs and Gynae, Pakistan Institute of Medical Sciences, Islamabad
sobialuqman8@gmail.com

Abstract

Objectives: To compare the success of single dose versus multiple dose methotrexate in ectopic pregnancy with β-HCG level 2000-5000 mIU/mL.
Methodology: This randomized controlled trial. Obstetrics and Gynecology unit, PIMS Hospital, Islamabad from15th December 2016 to 14th June 2017. A total of 100 patients with ectopic pregnancy, 18 to 40 years of age were included. Patients with ruptured ectopic pregnancy, viable intrauterine pregnancy, renal failure, CLD and hypersensitivity to methotrexate were excluded. All patients were divided into two groups i.e. group A and B by random number tables. Group A patients were given single intramuscular injection of methotrexate in a dose of 50mg/m2 on presentation. Group B patients were given intramuscular injection of methotrexate in a dose of 50mg/m2 on presentation and 2nd dose was given on day 4. Success was measured after one week.
Results: Mean age was 30.93 ± 6.04 years. Mean gestational age was 7.39 ± 2.36 weeks. The mean baseline β-hcg levels in group A was 3045.63 ± 688.64 mIU/L and in group B was 3032.13 ± 666.28 mIU/L. Success (> 15% lowering of β-hcg levels from baseline at the end of one week) was seen in 90.0% in group A (single dose methotrexate) and 74.0% in group B (multiple dose methotrexate) with p-value of 0.037.
Conclusion: This study concluded that success rate of single dose of methotrexate in ectopic pregnancy with β-HCG level 2000-5000 is higher compared to multiple dose methotrexate.
Keywords: Ectopic pregnancy, methotrexate, single dose, multiple dose.

Cite this article as: Muhammad MG, Luqman S, Masoom K, Benish GA, Naeem S. Comparison of The Success of Single Dose Versus Multiple Dose Methotrexate in Ectopic Pregnancy with B-HCG Level 2000-5000 MIU/Ml. J Soc Obstet Gynaecol Pak. 2023; 13(2):181-185

Introduction

A pregnancy in which the fertilized ovum implants outside the uterine cavity is known as ectopic pregnancy (EP).[1] Over the past decades, the occurrence of ectopic pregnancy (EP) has been noted all over the world; at present, the rate is nearly 2% of all pregnancies.[2] It is reported to be the major cause of early pregnancy maternal deaths. EP is an important cause of maternal morbidity and occasional mortality. An overall 1.5-2% of all reported pregnancies are extrauterine.[3] Despite major advances, early diagnosis of EP is still a challenge for clinicians.[4] In the past 20 years, the use of sensitive βhCG tests, high-resolution transvaginal ultrasound, and advances in laparoscopy (LS) have enabled the detection of EP without tubal rupture. In the case of early detection, the possibility and success of noninvasive medical treatment as an alternative to surgical treatment increase.[5]

Early pregnancy units (EPUs) with their access to high resolution transvaginal ultrasonography (TVS) and the rapid immunoassay of serum hCG allow early diagnosis of pregnancy location. Currently over 90% of ectopic pregnancies can be visualized on TVS.[6] As a consequence, the clinical presentation of ectopic pregnancy has changed from a life-threatening disease,

Authorship Contribution: [1-3]Substantial contributions to the conception or design of the work, acquisition, analysis, or interpretation of data for the work, [4-5]Drafting the work or revising it critically for important intellectual content, Final approval of the version to be published.

Funding Source: none
Conflict of Interest: none

Received: Dec 27, 2022
Accepted: July 18, 2023

necessitating emergency surgery, to a benign condition in frequently asymptomatic women for whom nonsurgical treatment options are available.[7] However, there is a group of women with ectopic pregnancy who can be managed non-surgically. One of the potential advantages of non-surgical treatment of ectopic pregnancy is the avoidance of any iatrogenic injury to the Fallopian tubes, which may decrease the risk of recurrent ectopic pregnancy and improve the chance of successful intrauterine conception.[8]

Until recently, ectopic pregnancy was considered an exclusively surgical condition. In 1989, Stovall et al showed that outpatient medical management of women with an ectopic pregnancy who were clinically stable, using methotrexate, was safe and acceptable, and by 1991 had developed the single-dose outpatient regimen commonly used today.[9] Methotrexate is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase and reduces the supplies of tetrahydrofolate, which is a cofactor in the synthesis of DNA and RNA and necessary for cell division.[10] The single dose of methotrexate (compared to the double dose) is effective in cases of EP with primary low level of β-HCG.[11]

However in cases with higher level of β-HCG or probability of tube rupture, administration of double dose is recommended.[12] Erdem et al[13] in a study on 34 patients who received single dose of MTX, noticed the higher rate of success compared to two dose methotrexate (96.0% versus 80.0%). They concluded that the mean of β-HCG is an important factor in response to treatment.[13]

On searching the literature, I have found no local randomized controlled trial on evaluating the success of single dose versus two dose methotrexate in ectopic pregnancy. So, this study was planned to determine the success of single dose versus multiple dose methotrexate in ectopic pregnancy with β-HCG level 2000-5000 mIU/mL. Furthermore, for the management of women with un-ruptured tubal ectopic pregnancy having higher β-hcg levels, evidence for selection of medical versus surgical management is scarce and no local data available on this in our general population, so this study will also give better management plan for our population in order to avoid tubal injury and improve fertility outcome.

Methodology

After permission from Local Ethical Committee, 100 pregnant women with ectopic pregnancy as per-operational definition was included**.** Patients with ruptured ectopic pregnancy assessed on ultrasound. Hemodynamically unstable patients, coexistent viable intrauterine pregnancy (heterotropic pregnancy), patients with renal failure (s/creatinine >1.1 mg/dl), patients with chronic liver disease (s/bilirubin >1 mg/dl), known hypersensitivity to methotrexate were excluded from the study. After taking informed, written consent from each patient for participation in the study, all patients were divided into two groups i.e. group A and B by random number tables. Group A patients were given single intramuscular injection of methotrexate in a dose of 50mg/m^2 on presentation. Group B patients were given intramuscular injection of methotrexate in a dose of 50mg/m^2 on presentation and 2nd dose was given on day 4. Success was measured after one week as per-operational definition. All the information was entered in specially designed Performa attached at the end. Statistical analysis was conducted by SPSS version 20.0. Age, gestational age, weight and β-hcg levels were presented by mean ± SD. Success (yes/no) was presented by frequency and percentages. Comparison between the groups with respect to success was analyzed by Chi-square. P value ≤0.05 was considered as statistically significant. Control of confounding variables were done by making cross matched stratified tables for age of patients, gestational age and baseline β-hcg levels. Chi-square test was applied to see the effect of these on success.

Results

There were total 125 patients who underwent transvaginal scan for various symptoms and were enrolled in this study after taking an informed consent. The mean age of these patients was (31.47 ± 2.67) years of which the minimum age was 25 year and maximum of 37 years. Female patients who presented with the symptoms of pain in lower abdomen, secondary amenorrhea or infertility (either primary or secondary), the mean duration of symptoms among these females was calculated to be(17.72 +9.95) months with minimum of 0 month and maximum of 36 months duration. A total of 90 females (72%) were found in primary infertility group whereas in the secondary infertility maximum had parity 1 i.e. 27 (21.6%) followed by parity 2 (4.0%) and 3 women were conceived in their history but had 0 parity shared (2.4%) burden of the total percentage. The minimum parity was noted as 0 and the maximum was 2. All the patients undergone transvaginal ultrasonography for the diagnosis of ovarian endometriosis and revealed positive by TVS in 99 (79.2%) patients and it was diagnosed negative in 26

Table I: Distribution of patients according to baseline β-hcg levels.						
Baseline B-hcg levels (mIU/mL)	Group A (n=50)		Group B (n=50)		Total (n=100)	
	Frequency	%age	Frequency	%age	Frequency	%age
2000-3500	40	80.0	40	80.0	80	80.0
35001-5000	10	20.0	10	20.0	20	20.0
Mean ± SD	3045.63 ± 688.64		3032.13 ± 666.28		3038.83 ± 674.15	

(20.8%) patients. Correspondingly, taking Laparoscopy results as the gold standard the positive cases demonstrated with ovarian endometriosis were 106 (84.8%) and negative diagnosis was perceived in 19 (15.2%) females. (Table I)

The true positive cases were verified97 and the true negative cases were confirmed 17 on both diagnostic modalities, whereas 2 false positive cases on TVS were professed and 9 cases were declared false negative. A contingency table was generated to calculate the sensitivity of transvaginal ultrasound and reported to be 91.5% sensitivity, followed by specificity 89.5%, Positive predictive value (PPV) 98.0%, Negative predictive value 65.4% and accuracy 91.2% in the diagnosis of ovarian endometriosis. (Table II)

Table II: Comparison of Success between both Groups (n=100).					
		Group A (n=50)		Group B (n=50)	
		No. of Patients	%age	No. of Patients	%age
SUCCESS	Yes	45	90.0	37	74.0
	No	05	10.0	13	26.0
P value is 0.037 which is statistically significant.					

Data was stratified for the age groups it was noticed that maximum number of patients present with the various symptoms of endometriosis belongs to age group (20-34) years i.e. 106/125 (84.8%), followed by the age group (34-45) years 19 (15.2%). But on comparison it was noticed that TVS was more sensitive for age (35-45) years as compared to (20-34) years i.e. (100.0% vs 90.0%), and more specific in age (20-34) years as compared to (35-45) years (93.8% vs 66.7%), PPV (98.8% vs 94.1%), NPV (62.5% vs 100.0%) respectively. And statistically significant difference was validating between both groups. (Table III)

Similarly, stratification with respect to duration of symptoms; most of the patients presented in the hospital with the duration less than 12 months i.e. 71/125 (56.8%) but the sensitivity was higher and specificity of TVS was less in the patients with the duration of more than 12 months i.e. sensitivity (87.0% vs 96.5%), specificity (94.1% vs 50.0%), PPV (97.9% vs 98.0%), NPV (69.6% vs 33.3%) and the accuracy (88.7% vs 94.4%) respectively. The difference among the groups was found to be significant. (Table IV)

Discussion

Women with a visible ectopic pregnancy and pregnancy of unknown location (PUL) have been offered medical treatment with methotrexate.5 Methotrexate can be administered systemically as a single dose regimen (MTX 1.0 mg/kg or 50 mg/m2 i.m without folinic acid) or as multiple dose regimen (MTX 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). A single dose regimen was introduced to

Table III: Stratification of success with respect to age groups.					
Age of patients (years)	Group A (n=50)		Group B (n=50)		p-value
	Success		Success		
	Yes	No	Yes	No	
18-30	20 (90.91%)	02 (9.09%)	17 (89.47%)	02 (10.53%)	0.877
31-40	25 (89.29%)	03 (10.71%)	20 (64.52%)	11 (35.48%)	0.026

Table IV: Stratification of success with respect to gestational age.					
Gestational age (in weeks)	Group A (n=50)		Group B (n=50)		p-value
	Success		Success		
	Yes	No	Yes	No	
≤6 weeks	23 (95.83%)	01 (4.17%)	19 (86.36%)	03 (13.64%)	0.255
>6 weeks	22 (84.62%)	04 (15.38%)	18 (64.29%)	10 (35.71%)	0.089

Table V: Stratification of success with respect to baseline β-hcg levels.					
Baseline B-hcg levels	Group A (n=50)		Group B (n=50)		P-value
	Success		Success		
	Yes	No	Yes	No	
2000-3500	37 (92.50%)	03 (7.50%)	30 (75.0%)	10 (25.0%)	0.034
35001-5000	08 (80.0%)	02 (20.0%)	07 (70.0%)	03 (30.0%)	0.606

minimize side effects, to improve patient compliance and to reduce the overall costs. Methotrexate has been shown to be safe with virtually no adverse effects reported on reproductive outcome. Careful follow-up and assessment are required for all women presenting with pain in the few days following methotrexate therapy before assuming that the treatment has failed and if there is need for surgical intervention.[15] I have conducted this study to compare the success of single dose versus multiple dose methotrexate in ectopic pregnancy with β-HCG level 2000-5000 mIU/mL.

Age range in my study was from 18 to 40 years with mean age of 30.93 ± 6.04 years. Majority of the patients 59 (59.0%) were between 31 to 40 years of age. Mean gestational age was 7.39 ± 2.36 weeks. The mean baseline β-hcg levels in group A was 3045.63 ± 688.64 mIU/L and in group B was 3032.13 ± 666.28 mIU/L as shown in Table III. Mean weight of the patients is 72.44 ± 8.39 kg. Success (> 15% lowering of β-hcg levels from baseline at the end of one week) was seen in 90.0% in group A (single dose methotrexate) and 74.0% in group B (multiple dose methotrexate) with p-value of 0.037. Erdem et al[13] in a study on 34 patients who received single dose of MTX, noticed the higher rate of success compared to two dose methotrexate (96.0% versus 80.0%). They concluded that the mean of β-HCG is an important factor in response to treatment.[14,15]

In a study, the success rates between the single-dose and multiple-dose groups did not show a significant difference [82.6 versus 87.0%; relative risk (RR) 0.95; 95% confidence interval (CI) 0.80-1.13]. However, the success rate in a subgroup of participants with a pretreatment β-hCG level of >5000 mIU/ml appeared to be higher in the multiple-dose group than in the single-dose group (80.0 versus 58.8%), although the difference was not statistically significant. No significant differences in methotrexate-associated side effects, cost or treatment satisfaction were observed between the groups. The multiple -dose group required a lower number of days for the β-hCG level to decrease to <5 mIU/ml than the single-dose group (25.7 ± 13.6 versus 31.9 ± 14.1 days; P = 0.025).[16]

Srivichai et al. reported a success rate of 90.6% in 96 out of 106 patients were successfully treated with methotrexate though four required a second dose.[15] Success reached 90% (n=10) in patients out of 11 with single dose treatment in Merisio's series. Literature published so far shows a success rate ranging from 67% to100% in single versus multidose treatment for ectopic pregnancies.[16] Mahboob reported a success rate of 80% by treating 12 out of 15 women with single dose MTX with initial β-hcg levels equal to 5000mIU/ml.[17]

In a randomized controlled trial conducted by Hamed et al[18], the success rate was 82.0% in the single-dose group and 88.6% in the multiple-dose protocol group, with no significant differences between the groups. Moreover, there were no significant differences in the adverse events between the groups (25.6% in the single-dose group versus 30.4% in the two-dose group). In a retrospective study including 87 ectopic pregnancy patients[19], the success rates (87.0% versus 90.2%) and adverse events (45.7 versus 58.7%) were comparable between the single-dose and multiple-dose groups.

There is a meta-analysis, including 26 article and 1327 cases, recently published by Barnhart[8] 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.[20] In one of the recent studies by van Mello[21], it has been demonstrated that, when the serum β-hCG concentrations were lower than 3,000 mIU/ml, systemic MTX in a multipledose regimen can be recommended. But if the serum β-hCG concentrations were lower than 1,500 mIU/ml, this time single- dose methotrexate regimen can be administrated. In another study[22,23], 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%.

Conclusion

This study concluded that success rate of single dose of methotrexate in ectopic pregnancy with β-HCG level 2000-5000 is higher compared to multiple dose methotrexate. So, we recommend that single dose of methotrexate should be preferred in ectopic pregnancy with β-HCG level 2000-5000 in order to avoid tubal injury and improve fertility outcome.

References

1. Helmey S, Sawyer E, Ofili-Yebovi D, Yazbek J, Nagi JB, Jurkovic J. Fertility outcomes following expectant management of tubal ectopic pregnancy. Ultrasound Obstet Gynecol. 2007;30:988–93.

2. Skubisz M, Lee J, Wallace E, Tong S. Decline in bhCG levels between days 0 and 4 after a single dose of methotrexate for ectopic pregnancy predicts treatment success: a retrospective cohort study. Br J Obstet Gynecol. 2011;118:1665–668.
3. Yuk JS, Park WI, Ahn HS, Kim HJ. Comparison of single-dose and multi-dose administration of methotrexate in treatment of ectopic pregnancy: a systematic review and meta-analysis. Prospero. 2016;2016:CRD42016032951.
4. Saadati N, Najafian M, Masihi S, Safiary S, Abedi P. Comparison of two different protocols of methotrexate therapy in medical management of ectopic pregnancy. Iran Red Crescent Med J. 2015;17(12):e20147.
5. Song T, Kim MK, Kim ML, Jung YW, Yun BS, Seong SJ. Single-dose versus two-dose administration of methotrexate for the treatment of ectopic pregnancy: a randomized controlled trial. *Hum Reprod.* 2016;31(2):332-38.
6. Kasum M, Oreskovic S, Simunic V, Jezek D, Tomic V, Tomic J, et al. Treatment of ectopic pregnancy with methotrexate. Acta Clin Croat. 2012;51:543-48.
7. Helmey S, Sawyer E, Ofili-Yebovi D, Yazbek J, Nagi JB, Jurkovic J. Fertility outcomes following expectant management of tubal ectopic pregnancy. Ultrasound Obstet Gynecol. 2007;30:988–93.
8. Skubisz M, Lee J, Wallace E, Tong S. Decline in bhCG levels between days 0 and 4 after a single dose of methotrexate for ectopic pregnancy predicts treatment success: a retrospective cohort study. Br J Obstet Gynecol. 2011;118:1665–668.
9. Yuk JS, Park WI, Ahn HS, Kim HJ. Comparison of single-dose and multi-dose administration of methotrexate in treatment of ectopic pregnancy: a systematic review and meta-analysis. Prospero. 2016;2016:CRD42016032951.
10. Song T, Kim MK, Kim ML, Jung YW, Yun BS, Seong SJ. Single-dose versus two-dose administration of methotrexate for the treatment of ectopic pregnancy: a randomized controlled trial. *Hum Reprod.* 2016;31(2):332-38.
11. Kasum M, Oreskovic S, Simunic V, Jezek D, Tomic V, Tomic J, et al. Treatment of ectopic pregnancy with methotrexate. Acta Clin Croat. 2012;51:543-48.
12. Pandya MJ, Ninama NV, Thummar CV, Patel MK. Role of methotrexate in ectopic pregnancy. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2021 Jan 1;10(1):84-8.
13. Song T, Kim MK2, Kim ML2, Jung YW2, Yun BS2, Seong SJ. Single-dose versus two-dose administration of methotrexate for the treatment of ectopic pregnancy: a randomized controlled trial. Hum Reprod. 2016 Feb;31(2):33.
14. Tas EE, Akcay GF, Avsar AF. Single-dose methotrexate for the treatment of ectopic pregnancy: Our experience from 2010 to 2015. Pak J Med Sci. 2017 Jan-Feb;33(1):13-17.
15. Saadati N, Najafian M, Masihi S, Safiary S, Abedi P. Comparison of two different protocols of methotrexate therapy in medical management of ectopic pregnancy. Iranian Red Crescent Medical Journal. 2015 Dec;17(12).
16. Mahboob U, Mazhar SB. Management of ectopic pregnancy: a two-year study. J Ayub Med Coll Abbottabad 2006. Oct-Dec;18(4):34-37.
17. Hamed HO, Ahmed SR, Alghasham AA. Comparison of double- and single-dose methotrexate protocols for treatment of ectopic pregnancy. Int J Gynaecol Obstet 2012;116:67–71.
18. Gungorduk K, Asicioglu O, Yildirim G, Gungorduk OC, Besimoglu B, Ark C. Comparison of single-dose and two-dose methotrexate protocols for the treatment of unruptured ectopic pregnancy. J Obstet Gynaecol 2011;31:330–334.
19. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing “single dose” and “multidose” regimens. Obstet Gynecol 2003;101:778-84.
20. Lipscomb GH, Stovall TG, Ling FW. Nonsurgical treatment of ectopic pregnancy. New Eng J Med. 2000;343:1325-9.
21. van Mello NM, Mol F, Mol BW, Hajenius PJ. Conservative management of tubal ectopic pregnancy. Best Pract Res Clin Obstet Gynaecol. 2009;23:509-18.
22. Aybatlı A, Kaplan PB, Alicik M, Sayın NC, Yüce MA. Single Dose Methotrexate in Treatment of Ectopic Pregnancy: Review of 32 Case. Balkan Med J. 2011; 28: 10-13.
23. Shatkin Hamish N, Wolf M, Tendler R, Sharon A, Bornstein J, Odeh M. Early prediction of methotrexate treatment outcome in tubal ectopic pregnancy based on days 0 and 4 human chorionic gonadotropin levels. Journal of Obstetrics and Gynaecology Research. 2020 Jul;46(7):1104-9.