



CODEN [USA]: IAJPBB

ISSN: 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<http://doi.org/10.5281/zenodo.3958753>Available online at: <http://www.iajps.com>

Research Article

**EVALUATION OF SYSTEMIC SINGLE DOSE
METHOTREXATE TREATMENT IN PATIENTS PRESENT
WITH ECTOPIC PREGNANCY****¹Dr Hina Tariq, ¹Dr Iqra Nisar, ²Dr Arooj Imtiaz**¹Madina Teaching Hospital Faisalabad²Allama Iqbal Medical College Lahore**Article Received:** May 2020**Accepted:** June 2020**Published:** July 2020**Abstract:**

Objective: To assess the success rate of single dose MTX (Methotrexate) treatment among patients present with EP (Ectopic Pregnancy) and to examine the various factors associated with the treatment.

Methodology: This retrograde research work carried out in the Madina Teaching Hospital Faisalabad from March 2015 to December 2020. In this research work, we retrieved the characteristics of demography, clinical condition, findings of ultrasonography, pre-treatment serum β -hCG (β -Human Chorionic Gonadotropin) and levels of progesterone of 50 patients present with ectopic pregnancy. The grouping of the patients carried out in accordance with the success of the Methotrexate treatment.

Results: Treatment with single dose Methotrexate was successful in 72.40% (n: 32) patients. There was low average pre-treatment level of β -hCG in the group of responders as compared to the group of failures (2080.0 \pm 2322.0 vs 5707.0 \pm 3885.0 IU/L, $P = 0.0010$) and 2678.0 IU/L was suitable cut off for the prediction of success (75.0% sensitivity, 73.80% specificity). Furthermore, the rate of failure was 8.450 times greater in the patients whose values of β -hCG were determined greater than cutoff. The availability of the cardiac activity of fetal adversely influenced the success of the treatment (Odds Ratio= 12.0, $P = 0.0040$). There was no influence of past history of Ectopic Pregnancy, endometrium's thickness, value of progesterone and free pelvic fluid on the success of treatment.

Conclusion: The rate of success of single-dose Methotrexate in current research work was 72.80%, and we discovered that the rate of failure of treatment of Methotrexate was 8.450 times higher in the patients who were present with initial values of serum β -hCG above 2678.0 IU/L and twelve times greater in the patients present with the fetal cardiac activity.

KEYWORDS: B-Hcg, Sensitivity, Serum, Success Rate, Endometrium, Cardiac Ectopic Pregnancy, Methotrexate, Pregnancy.

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Please cite this article in press Hina Tariq et al, Evaluation Of Systemic Single Dose Methotrexate Treatment In Patients Present With Ectopic Pregnancy ., *Indo Am. J. P. Sci*, 2020; 07(07).

INTRODUCTION:

Ectopic Pregnancy (EP) is the implantation of the blastocyst outside the cavity of uterine. According to the findings of different centers of disease control and prevention, there are two percent ectopic pregnancies in USA [1]. There is about 57.0% decrease in the rate of maternal mortality from 1980 to 2010 with the advancement in the field of treatment. Ectopic Pregnancy is the most important cause of maternal mortality especially in first three months of pregnancy. There are surgical and non-surgical options for the treatment of Ectopic Pregnancy [2]. Advancements in the techniques of early diagnosis have facilitated much the elaboration of the treatment through MTX (Methotrexate). Methotrexate treatment is much cost efficient and it is able to achieve the same outcome with multi-dose Methotrexate treatment in terms of rate of success and fertility in future [3]. Drug-based treatments circumvents the inherent risks of surgery as well as anesthesia [4]. The range of the success rates for the Methotrexate treatment is from 76.0% to 100.0% [5-8]. Preliminary research reports have explained many factors potentially related with the failure of Methotrexate treatment, notably level of pretreatment β -hCG (β -human chorionic gonadotropin) and availability of cardiac activity of fetal [4-6]. Main objective of this research work was to experience the impact of utilization of single dose Methotrexate in the patients suffering from Ectopic Pregnancy and to examine the pretreatment β -hCG, levels of progesterone and availability of the fetal cardiac activity as we found much limited information particularly about the association among success of treatment and these mentioned factors.

METHODOLOGY:

In this research work, we retrospectively reviewed the data of 98 patients diagnosed with suffering from Ectopic Pregnancy from March 2015 to December 2020 in Madina Teaching Hospital Faisalabad. All these patients underwent systemic Methotrexate treatment or surgery. The ethical committee of our institute gave the permission to conduct this research work. The diagnosis of Ectopic Pregnancy was carried out by unsuitable increase in the level of serum β -hCG and presence of adnexal mass or extra-uterine tubal gestational sac in the absence of intrauterine gestation, as identified with the utilization of TUV (Transvaginal Ultrasonography). First option of treatment for the patients present with the excessive free pelvic fluid or instability of the hemodynamic with symptoms of acute abdomen. We treated the remaining patients with the systemic

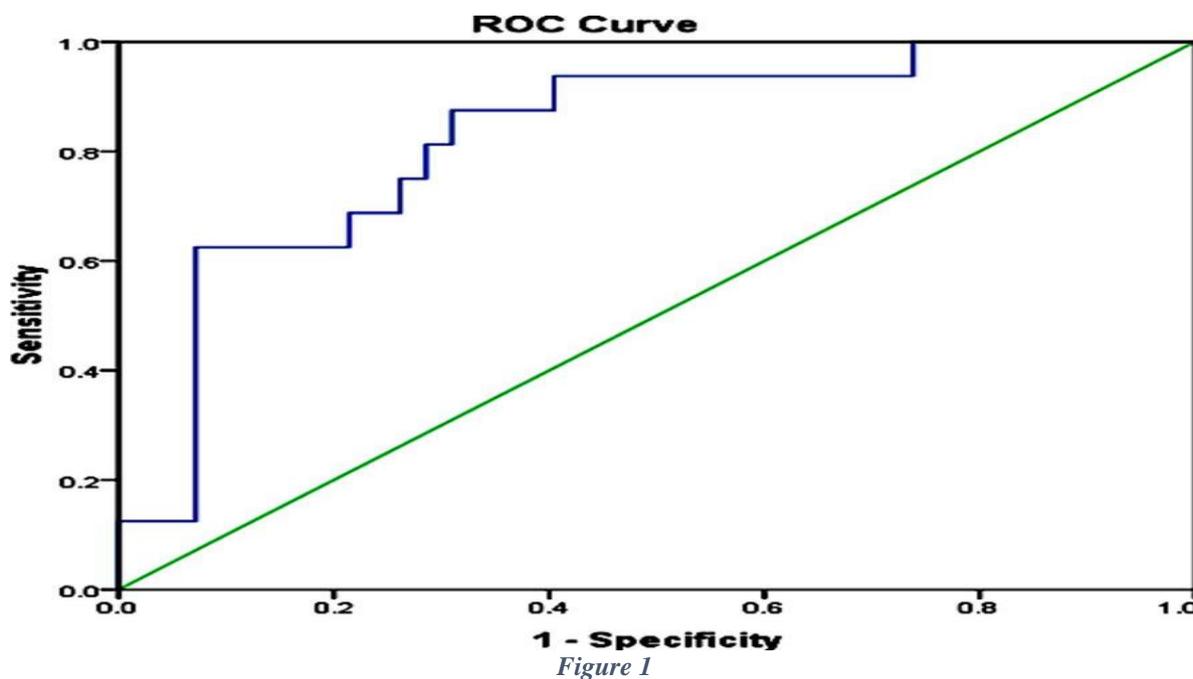
single dose MTX (50.0 mg/m²), no patient got exclusion from Methotrexate treatment because of baseline serum level of β -hCG or ultrasonic identification of the fetal cardiac activity.

We measured the concentration of serum β -hCG on days 4 and 7 after injection and on weekly basis thereafter until a decrease of $\geq 15.0\%$ and concentration of less than 15.0 IU/L, showing the success of treatment, were achieved. Data about the characteristics of demography as well as clinical traits, findings of TVU and pretreatment levels of serum β -hCG & levels of progesterone were retrieved from the records of hospitals. We grouped the patients according to the success of Methotrexate treatment.

SPSS V. 23 was in use for the statistical analysis of the collected information. We used the Kolmogorov-Smirnov test to evaluate normality of data. We expressed the normally distributed data in averages and standard deviations. We expressed the non-parametric data in median. We also used the T test and Mann-Whitney U test for the comparison of the parametric as well as non-parametric data correspondingly, between all groups. The comparison of the categorical variables was carried out with the utilization of the Chi-square test. We used the logistic regression analyses to evaluate the influencing factors on the success of treatment. P value of less than 0.050 was considered as significance.

RESULTS:

We administered the single-dose Methotrexate treatment in 50 out of 98 patients suffering from Ectopic Pregnancy and success of this treatment was 72.40% (n: 32) patients. We gave the second dose of MTX in the three patients in failure group and 13.30% (n: 11) patients had to undergo surgical intervention. Thus, surgery was performed in total 54.10% (n: 50) patients. There was significant difference in the pretreatment level of β -hCG between failure and treatment response groups (5707.0 versus 2080 mIU/dL; P= 0.0010). Most suitable cutoff for the β -hCG value of 2678.0 IU/L for the prediction of success of treatment (75.0% sensitivity & 73.80% specificity). Only the occurrence of fetal cardiac activity influenced adversely the success of treatment, which was obtained in 25.0% (2 out of 8) patients describing this kind of activity (OR= 12.0, P= 0.0040) (Figure-1).



The summary of the characteristics of all the patients administered with single dose Methotrexate treatment, according to the success of treatment and overall are present in Table-1.

Table-I: Characteristics of Patients Treated with Single-Dose Methotrexate, Overall and According to Treatment Success

Characteristic		Single-dose MTX (n = 50)	Treatment success (n = 32)	Treatment failures (n = 18)	p ^p	ORs
Demographical Properties	Age (years)	30.9 ± 4.9 (21-44)	31.5 ± 5.2 (21-44)	29.2 ± 3.9 (22-39)	0.13	0.884
	Gravidity	3 (2) (1-8)	3 (3) (1-8)	3 (2) (1-5)	0.28	1.18
	Parity	1 (2) (0-3)	1 (2) (0-2)	2 (2) (0-3)	0.15	2.6
	Previous ectopic	9 (15.5%)	8 (19%)	1 (6.3%)	0.42	0.94
	Gestational age (weeks)	6 (2) (3-12)	6 (2) (3-12)	6 (1) (3-8)	0.5	1.64
Pretreatment Signs and symptoms	None	6 (10.3%)	3 (5.2%)	3 (5.2%)	0.33	0.6
	Pelvic pain	52 (89.7%)	39 (67.2%)	13 (22.5%)		
	Pelvic pain only	20 (34.5%)	16 (27.6%)	4 (6.9%)		
	Vaginal bleeding	17 (29.3%)	12 (20.7%)	5 (8.6%)		
	Pelvic pain with	15 (25.9%)	11 (19%)	4 (6.9%)		
Laboratory Values and TVU Findings	β-hCG level (IU/L)	3080 ± 3244 (151-16,200)	2080 ± 2322 (151-10,360)	5707 ± 3885 (676-16,200)	0.001	8.45
	Progesterone level (mg/dL)	4.45 (5.35) (0.98-21.1)	6 (7.1) (0.9-14.3)	4.2 (3.6) (1.2-21.1)	0.22	0.99
	Endometrial	7 (2) (3-16)	7 (2) (3-13)	7.5 (5.5) (4-)	0.63	1.52
	Pseudo sac	9 (15.5%)	7 (16.7%)	2 (12.5%)	0.52	0.71
	Fetal cardiac	8 (13.8%)	2 (4.7%)	6 (37.5%)	0.004	12
	Free pelvic fluid	25 (43.1%)	20 (47.6%)	5 (31.3%)	0.37	0.5

Data are presented as mean ± standard deviation (range), median (interquartile range) (range), or n (%).

MTX: Methotrexate; β-hCG: β-human chorionic gonadotropin.

ORs: Odds Ratios TVU: Transvaginal ultrasound

“Successful treatment required multiple MTX doses or surgical intervention.

^p Treatment success vs. failure.

DISCUSSION:

Methotrexate is a folic-acid antagonist that has the ability to restrict the activity of cellular DNAs de novo synthesis [9]. This drug is widely in use for the treatment of Ectopic Pregnancy since utilized by Tanaka [10] for the very first time in year of 1982. It is standard option of treatment for majority of the patients. There is most common use of the single as well as multi dose systemic methotrexate protocols with not much difference in the rates of success [3, 11]. In the whole world, single dose protocol is much widely in use because of its simplicity and low rate of complications [12]. In associate literature, level of β -hCG exceeding 5000-6000 IU/L and availability of the fetal cardiac activity were identified as the relative contraindications to systemic treatment by methotrexate by one research work [13, 14]. There is much variation in the reported rates of success of methotrexate regimes, because of many factors. Pretreatment value of β -hCG is most important factor. There is decrease in the shown rate of success with the increase in the pretreatment level of β -hCG [6, 15]. There are many proposed cutoff values with different rates of specificities and sensitivities in reports of past but there is lack in prediction of the cutoff value for success of treatment.

But in this current research work, we identified a cutoff value of 2678.0 IU/L, with 75.0% sensitivity rate and 73.80% specificity rate; however, in his research work, Mir bolouk [14] stated a rate of success by a single dose treatment of methotrexate much similar to the results of this current research work (77.10%), established much low value of β -hCG cutoff (1375.0 IU/L) with same rate of specificity as well as sensitivity. The disparities may be because of the choosing traits of the selected patients or may be because of the indeterminate factor which have not been yet established.

Another most important adverse factor is fetal cardiac activity's presence as presented in this current research work. Erdem in his research report stated no success of treatment in the patients present with fetal cardiac activity. Opposite to it, Lipscomb stated a 87.50% rate of success although pretreatment levels of serum β -hCG were 3 times greater than the results of this research study (87.50% versus 25.0%.) [16]. Zargar in his research study stated there was much response of cardiac activity to the single-dose treatment [17]. Because of the wide range in the rate of success [7, 14, 16], particularly in the patients with presence of fetal cardiac activity, we are suggesting the methotrexate treatment in clinics which have the facilities of emergency surgery conditions especially laparoscopy after getting the written consent from the patients and after the preparation of different blood components before the surgery. The rate of

success of treatment by systemic MTX may reduce with the increase in endometrial thickness, but the importance of this particular impact is much controversial. Some research reports have stated the important impacts, attributing them to high levels of β -hCG reflected by high endometrial thickness [18, 19], while this current research work as well as some other studies showed no important association ($P=0.63$, OR: 1.52) [14].

One research work conducted examined the association between presence of pseudo-sac and treatment success with systemic Methotrexate, and authors discovered that pseudo sacs enhanced the risk of treatment failure about twenty-four times [20]. Conversely, there was high prevalence of pseudo sacs in our treatment group although this variable was not associated with the success of treatment ($P=0.520$, OR= 0.710). levels of progesterone, age and reproductive profile do not have impacts on the success of Methotrexate treatment as presented in the findings of this research work as well as results of the research works conducted in past. Many professionals have regarded the availability of the pelvic fluid on ultrasonography to contraindicate the medical treatment due to the concern that it may predict the ongoing Ectopic Pregnancy rupture. Systemic-methotrexate is much secure in the patients who are stable hemodynamically with no excessive clotting, and the presence of the fluid has not the ability to influence the success of the treatment as prescribed by this current research work as well as others [20]. One of the promising agents to treat the incidence of Ectopic Pregnancy is Methotrexate but for majority of the patients, the main treatment option is still surgery. Greater than half amount of the patients suffering from Ectopic Pregnancy is in requirement of surgery. The most frequent advocated approach in these patients is laparoscopy but many clinical institutes have not utilized it much effectively. In our institute, there was application of laparoscopy on 77.30% of patients suffering from Ectopic Pregnancy.

CONCLUSION:

The rate of success with the use of single dose Methotrexate in this current research work was 72.80%. We found that the rate of failure of Methotrexate therapy was 8.450 times higher in the patients group whose initial values of serum β -hCG were more than 2678.0 IU/L and twelve times greater in the patients present with presence of cardiac activity. We suggest the Methotrexate therapy for the patients especially present with presence of fetal cardiac activity.

REFERENCES:

1. Marion LL, Meeks GR. Ectopic pregnancy: History, incidence, epidemiology and risk

- factors. *Clin Obstet Gynecol.* 2012;55(2):376-386. doi: 10.1097/GFR.0b013e3182516d7b.
2. Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980-2007. *Obstet Gynecol.* 2011;117(4):837-843. doi: 10.1097/AOG.0b013e3182113c10.
 3. 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(4):778-784.
 4. Lermann J, Segl P, Jud SM, Beckmann MW, Oppelt P, Thiel FC, et al. Low-dose methotrexate treatment in ectopic pregnancy: a retrospective analysis of 164 ectopic pregnancies treated between 2000 and 2008. *Arch Gynecol Obstet.* 2014;289(2):329-335. doi: 10.1007/s00404-013-2982-x.
 5. Lipscomb GH, McCord ML, Stovall TG, Huff G, Portera SG, Ling FW. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *N Engl J Med.* 1999;341(26):1974-1978.
 6. Stika CS, Anderson L, Frederiksen MC. Single-dose methotrexate for the treatment of ectopic pregnancy: Northwestern Memorial Hospital three-year experience. *Am J Obstet Gynecol.* 1996;174(6):1840-1846.
 7. Erdem M, Erdem A, Arslan M, Oc A, Biberoglu K, Gursoy R. Single-dose methotrexate for the treatment of unruptured ectopic pregnancy. *Arch Gynecol Obstet.* 2004;270(4):201-204. doi: 10.1007/s00404-003-0543-4
 8. Nguyen Q, Kapitz M, Downes K, Silva C. Are early human chorionic gonadotropin levels after methotrexate therapy a predictor of response in ectopic pregnancy? *Am J Obstet Gynecol.* 2010;202(6):630.e1-5. doi: 10.1016/j.ajog.2010.03.022
 9. Barnhart K, Coutifaris C, Esposito M The pharmacology of methotrexate. *Expert Opin Pharmacother.* 2001;2(3):409-417. doi: 10.1517/14656566.2.3.409
 10. Tanaka T, Hayashi H, Kutsuzawa T, Fujimoto S, Ichinoe K. Treatment of interstitial ectopic pregnancy with methotrexate: report of a successful case. *Fertil Steril.* 1982;37(6):851-852.
 11. Barnhart K, Esposito M, Coutifaris C. An update on the medical treatment of ectopic pregnancy. *Obstet Gynecol North Am.* 2000;27(3):653-667.
 12. Lipscomb GH. Medical management of ectopic pregnancy. *Clin Obstet Gynecol.* 2012;55(2):424-432. doi: 10.1097/GRF.0b013e3182510a48.
 13. Bachman EA, Barnhart K. Medical management of ectopic pregnancy: a comparison of regimens. *Clin Obstet Gynecol.* 2012;55(2):440-447. doi: 10.1097/GRF.0b013e3182510a73.
 14. Mirbolouk F, Yousefnezhad A, Ghanbari A. Predicting factors of medical treatment success with single dose methotrexate in tubal ectopic pregnancy: a retrospective study. *Iran J Reprod Med.* 2015;13(6):351-354.
 15. Ustunyurt E, Duran M, Coskun E, Ustunyurt ÖB, Şimsek H. Role of initial and day 4 human chorionic gonadotropin levels in predicting the outcome of single-dose methotrexate treatment in women with tubal ectopic pregnancy. *Arch Gynecol Obstet.* 2013;288(5):1149-1152. doi: 10.1007/s00404-013-2879-8
 16. Lipscomb GH, Bran D, McCord ML, Portera JC, Ling FW. Analysis of three hundred fifteen ectopic pregnancies treated with single-dose methotrexate. *Am J Obstet Gynecol.* 1998;178(6):1354-1350.
 17. Zargar M, Razi T, Barati M. Comparison of single and multidose of methotrexate in medical treatment of ectopic pregnancy. *Pak J Med Sci* 2008; 24:506-509.
 18. Da Costa Soares R, Elito J Jr, Han KK, Camano L. Endometrial thickness as an orienting factor for the medical treatment of unruptured tubal pregnancy. *Acta Obstet Gynecol Scand.* 2004;83(3):289-292.
 19. Takacs P, Chaktoura N, De Santis T, Verma U. Evaluation of the relationship between endometrial thickness and failure of single-dose methotrexate in ectopic pregnancy. *Arch Gynecol Obstet.* 2005;272(4):269-272. doi: 10.1007/s00404-005-0009-y.
 20. Lim JE, Kim T, Lee NW, Oh MJ, Seol HJ, Jung NH, et al. Ultrasonographic endometrial features in tubal pregnancy: are they predictive factors of successful medical treatment? *Ultrasound Med Biol.* 2007;33(5):714-719. doi: 10.1016/j.ultrasmedbio.2006.10.018.