DOI: https://doi.org/10.53350/pjmhs22168161

ORIGINAL ARTICLE

Efficacy of Methotrexate Treatment; Nonsurgical Treatment of Ectopic Pregnancy (EP)

HUMAIRA BIBI[1], SHAMIM AKHTER[2], SABA NASIR[3], BUSHRA SADIA[4]
[1]*Consultant Gynae/Obs Abha Maternity and Children Hospital Aseer Region Saudi Arabia*
[2]*Assistant Professor of Obstetrics & Gynaecology, Kuwait teaching hospital, Peshawar Medical College, Riphah International University*
[3]*District Specialist District Headquarters Hospital, Haripur*
[4]*Medical Officer District Headquarter Hospital Haripur*
Correspondence to Dr Humaira Bibi, email: drhumaira85@gmail.com, Cell: 0334-0901333

ABSTRACT

Background: Methotrexate treatment of ectopic pregnancies is not only effective but also safe and saves fallopian tube without major side effects related to surgery.
Aim: To determine the efficacy of Methotrexate for treatment of women with EP.
Study design and period: retrospective observational study 1 years from July 2021 till July 2022.
Setting: Department of Obstetrics & Gynaecology, Abha Maternity and Children hospital, Aseer Region Saudi Arabia.
Methods: This was a retrospective observational study, in which 52 women with EP were included and were given injection methotrexate 50 mg/m2 intramuscularly. The β-hCG level was measured before treatment and then on 7th day of treatment. If β-hCG was reduced by >15% of pre-treatment levels on day 7 then it was called as successful treatment.
Results: The overall success rate of this regimen was 73% of patients, including 6% of those who required second dose. 27% of patients underwent surgery and were designated as treatment failures. The mean β-hCG level before treatment was significantly lower in the treatment success group than in the treatment failure group (1491.79 ± 1094.69 vs 2701.50 ± 1417.28 IU/L, p= 0.0381). Sac size was considered statistically increased in the treatment failure group, ie, 3.75 ± 0.29 ($P < 0.05$).
Conclusion: Based on the findings of our study, it can be stated that methotrexate treatment is very effective in the treatment of patients with ectopic pregnancy and can be recommended as a first-line treatment in patients with a low initial β-hCG level and a small ectopic pregnancy sac size.
Keywords: ectopic pregnancy; methotrexate; operative laparoscopy; β-hCG; sac size

INTRODUCTION

A disaster in human reproduction is ectopic pregnancy in which fetus implants outside the uterine cavity and inevitably results in the death of the fetus.[1] Although ectopic pregnancy has been recognized for many years, it is a growing problem, affecting approximately 2% of all pregnancies.[2] There are also regional differences in its incidence, 18/1000 in India, 7.4/1000 births in Bangladesh, and 1:128 to 1:130 pregnancies in Pakistan.[3,4] Its incidence increased from 4.9/1000 pregnancies in 1970 to 9.6/1000 in 1992 .[5] This increasing incidence is due to greater prevalence of sexually transmitted diseases, tubal ligation and reversal, delayed conception, assisted reproductive technologies, and successful clinical detection.[6] Ectopic pregnancy not only causes maternal mortality, but also threatens a woman's future fertility if not diagnosed and treated promptly . Ectopic pregnancy accounts for 4–10% of all pregnancy-related deaths and is the second leading cause of maternal death after complications related to abortion in developing countries.[6,7] A study conducted in King Fahad University hospital, al Khobar shows prevalence of ectopic pregnancy is 1.19% out of which 61.1% were diagnosed in women with age less than 30years.[8]

Traditionally laparotomy has been the most commonly performed procedure, but since the last decade laparoscopy gained popularity in an attempt to decrease morbidity of patient but there are still only a small number of gynecologists trained in laparoscopic surgery in raising need for use of medical treatment.[9, 10] Medical management with methotrexate (MTX) not only avoids risks associated with surgery but also preserves tubes. However, it can only be given in selected patients in whom ectopic pregnancy is diagnosed early before tubal rupture. This early diagnosis is possible now a days with the use of high-resolution transvaginal ultrasonography and highly sensitive radioimmunoassay for beta subunit of human chorionic gonadotropin (β-hCG) measurement[11]. Other criteria for methotrexate therapy as recommended in China for hemodynamically stable patients is β-hCG levels <2000 IU/L and the size of adnexal mass size <4 cm in diameter[12].

Received on 02-07-2022
Accepted on 03-08-2022

Methotrexate (MTX) inhibits conversion of dihydrofolate to its active form, tetrahydrofolate which is necessary for DNA synthesis. It has been used for the treatment of diseases like neoplasia, severe psoriasis, and rheumatoid arthritis. Its main action is on rapidly proliferating cells which are fetal cells, cancer cells, bone marrow cells, and mucosal cells[13].

Both multi dose, single dose protocol of MTX can be used for treatment of EP. However single dose methotrexate is more readily accepted by patients because of low cost, less side effects with less monitoring of patients and also it does not require rescue therapy with leucovorin.[14] In single-dose protocol,50 mg/m^2 MTX is given intramuscularly then β-hCG is measured in serum on day1, day4, and day7 then weekly until the level <15IU/L. MTX treatment is said to be successful when between day4 and day 7 β-hCG levels declines by $\geq$15%.[15]. Approximately 20 percent of treated patients requires surgery due to pain, increase in size of EP and suboptimal β-hCG levels.[16] While 8.6% requires second injection of MTX.[17]

MTX treatment was found to be successful in 84.1% patients while 5.3% required surgery due to suspicion of rupture in one study[18]. Studies conducted on success of MTX treatment in EP may be biased by patient selection, as patients included in study are guided by a strictly established protocol with extensive follow-up of support staff, which can dramatically affect success rates and may not exist outside of these study populations. Therefore, this work retrospectively evaluated patients with ectopic pregnancy in our set up with the aim of determining the effectiveness of MTX treatment for ectopic pregnancy and its results, which will subsequently help reduce maternal morbidity and mortality.

The objective of the study was to determine the efficacy of methotrexate (MTX) for the treatment of women with EP.

MATERIAL AND METHODS

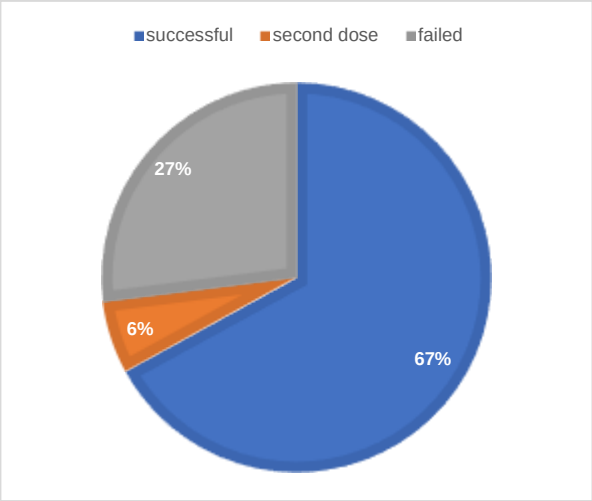
This retrospective observational study was conducted in Obstetrics & Gynaecology Department, Abha Maternity and Children Hospital, Aseer Region KSA. The duration of study was one years, from July, 2021 to July, 2022. After approval by the ethics board of the hospital, this study was initiated. A sample size of 52 cases was calculated with a 95% confidence level, a 10% margin of error, and

an expected success rate of 84.1% with methotrexate for the treatment of women with EP.[18] Hospital records of patients diagnosed with ectopic pregnancy and treated with injection methotrexate (MTX) (50mg/m2 intramuscular injection) were retrospectively reviewed. EP was defined as presence of pregnancy outside the uterine cavity on ultrasound with β-hCG level >2000IU/L. Deranged liver or kidney function, anemia, thrombocytopenia was considered as contraindications for MTX injection. Women fulfilling criteria stable hemodynamically, β-hCG levels of ≤2000 IU /L, EP mass ≤4 cm, absent cardiac activity and the absence of hemoperitoneum. Informed written consent was taken before starting the treatment. Treatment was successful if β-hCG levels decreased by >15% between day 1 and day 7 and second dose of 50mg/m^2 injection MTX was given in cases where β-hCG was same on day 7. Patients receiving second dose were not considered as failed treatment. Patients underwent surgery based on development of pelvic pain either de novo, persisting or worsening, increased or suboptimal levels of β-hCG and increased size of the adnexal mass measured by TVS. After that patients were followed up by weekly serum β-hCG until <15IU/L. Data collected included patient age, parity, size of mass and β-hCG levels before treatment and on day 7, as well as the number of patients requiring second dose. The patient demographics (e.g., age, parity), the EP sac size, pre-treatment β-hCG were compared between the successful and the failure group taking p-value of ≤0.05 as statistically significant. Computer program SPSS version 22 used for analyzing data. Quantitative variables like age, parity were presented as mean and SD. Frequencies and percentages were calculated for success, failure and requirement of second dose.

RESULTS

EP was resolved after the first dose of MTX in 67% (35/52) and after the second dose of MTX 6% (3/52) of patients. The remaining cases 14 (27%) required surgical intervention making success rate of MTX in this study 73% as second dose was also considered as treatment success and the failure rate to be 27%.

Figure: Success of methotrexate treatment in ectopic pregnancy



Mean age in successful treatment group was 27.8±4.3 years while in failed treatment group was 26.9 ± 3.9 years and mean parity was 2.1±1.5 and 2.7±1.2 in successful and failed treatment respectively. There was no statistical difference with regards to women's age and parity between the two groups as p value was >0.05. Sac size and initial β-hCG measurement considered to be statistically increased in the treatment failure group (P < 0.05). Initial β-hCG was significantly higher in failed treatment group than in successful group (2701.50±1417.28 Vs. 1491.79±1094.69, and P = 0.0381, respectively). There was a significant difference in sac size between successful and failed treatment group i.e. 2.52±0.80 and 3.75±0.29 respectively p value 0.0035.

Table: Demographic characteristics of patients with EP in relation to efficacy of methotrexate treatment

Characteristics	Successful treatment	Failed treatment	Significance
Total number	38	14	
Age (years)	27.8 ± 4.3	26.9 ± 3.9	P = 0.4
Parity	2.1 ± 1.5	2.7 ± 1.2	P = 0.45
Sac size(cm)	2.52 ± 0.80	3.75 ± 0.29	P = 0.0035
Pretreatment ß-hCG (IU/L)	1491.79 ± 1094.69	2701.50 ± 1417.28	P = 0.0381

DISCUSSION

In 1980 Tanaka et al. introduced methotrexate as a successful treatment option for EP first time.[19] Our study showed the success rate of the methotrexate treatment in EP 73% which is lower as compared to 89%, 90.2% as found in other studies[20,21]. One study focusing on the cases treated with MTX showed 12% failure rate of methotrexate treatment[22]. The reason for this lower success rates in our study could be early surgical intervention in our setup on an unruptured ectopic pregnancy that would otherwise resolve with medical treatment due to pain which is common after methotrexate injection and could be due to stretching of tube by hematoma and tubal abortion[23]. But it is difficult to differentiate between pain of tubal abortion and rupture. Therefore, it is necessary to consider other symptoms along with pain before taking decision of surgery and managing physician should expect pain after methotrexate administration. With more clinical experience of using methotrexate success rate will improve. Lashin ME et al. reported success rate of methotrexate 85% while 10% of patients (12 patients) required second dose of MTX. The requirement of second dose of methotrexate should be considered as treatment success, as surgical intervention was not needed.

In our study, no correlation was noted between age, parity and the outcome of medical management which is also noticed in other studies. Mean age was noted 30.23±5.16 years in successful group and 31.07 ±4.33 years in failed treatment group with p value 0.362 in a study conducted by Lee JH et al.[24] Another study by Keshta AS et al. showed that patients in successful group had parity 2 (0-9) and 1 (0-5) in failure group p value 0.73, not statistically significant comparable with our results.[25]

The most predictive variable of success of medical treatment is pretreatment β-hCG level. In our study, the difference between the mean pre-treatment serum β-hCG level in the success and failure groups was statistically significant i.e.,1491.79 ± 1094.69 vs. 2701.50 ± 1417.28 IU/L with p =0.038. Similar to our study mean pretreatment β-hCG level was significantly lower in treatment success than in treatment failure (2080 ± 2322 *vs*. 5707±3885 IU/L, *p* =0.001) in a study conducted by Tas EE etal[26]. Our study showed EP mass diameter of 2.52 ± 0.80cm in successfully treated patients vs. 3.75±0.29cm in failed treatment group which is statistically significant indicating that sac size is an important predictor of treatment failure. A study conducted by Alsammani MA also showed that greater sac is associated with high failure rate and found that sac size of ≥3.5 cm results in 3.73-folds increase in MTX treatment failure[27].

The success and failure rates of methotrexate treatment in our study were 73% and 27%, respectively and main predictors of this success of MTX were pretreatment quantitative β-hCG level and diameter of sac. However, the risk of fallopian tube rupture after medical treatment in combination with prolonged follow-up for the resolution of an ectopic pregnancy requires ambulatory rupture monitoring, which plays an important role in the selection of patients.

Limitation: The only limitation of this study was that we were not sure that we had not missed any important information as we had no way to verify that the medical records, we reviewed were complete. However, we collected data thoroughly to make the information as pure as possible

CONCLUSION

We concluded from this small study that medical treatment is safe and effective alternative to surgery in selective cases. Now a days new diagnostic and therapeutic modalities has changed the whole clinical scenario of ectopic pregnancy to one of potential success which was once considered a disaster. Therefore, we recommend to treat unruptured ectopic pregnancy with methotrexate but it needs further experience to clearly delineate the pain after methotrexate injection from pain of rupture as this influences the overall success rate and depends on the clinical decision to abandon medical therapy. We recommend to avoid surgery as long as the patient is hemodynamically stable with normal hemoglobin levels and β-hCG levels decrease adequately but with careful monitoring.

Author contributions: All contributed to study conception and design; data acquisition, analysis, and interpretation; and writing and revising the manuscript.

Funding: No financial assistance was received in the completion of this research.

Declarations of interest: None.

REFERENCES

1. Selvarajan S, Ramalingam J, Vijayaraghavan J, Bobby Z. Serum soluble FMS-like tyrosine kinase-1 in ectopic pregnancy. J Lab Physicians [Internet]. 2019;11(4):335–9.
2. Mitwally MF, Hozayen WG, Hassanin KM, Abdalla KA, Abdalla NK. Aromatase inhibitor letrozole: a novel treatment for ectopic pregnancy. Fertility and Sterility. 2020 Aug 1;114(2):361-6.
3. Shams G, Iqbal M, Habib S, Akhtar R, Kamran Q, Afridi S. Management options for ectopic pregnancy practiced in a tertiary care hospital of Peshawar. Kyber J Med Sci 2021;14(1):18-24.
4. Aftab A, Faiyaz M, Fahim U, Tabassum H, Rafique S, Hanif A. Variance in clinical presentation of ectopic pregnancy. Pak J Med Sci 2021;15(10):2845-47.
5. ES J, Varghese SA, Varghese MA, Yeldhos S, Baby A. World J Pharm Res 2020;9(5)400-415.
6. Wasim T. Proportionate morbidity & risk factors of Ectopic Pregnancy. Annals KEMU. 2017;10(3):298-300.
7. Priya N. Day 4 ß HCG dynamics as an early predictor of success in medically managed ectopic pregnancies: A retrospective cohort study. Int J Clin Obstet Gynaecol 2020;4(6):282-284.
8. Khalil A, Saber A, Aljohani K, Khan M. The Efficacy and Success Rate of Methotrexate in the Management of Ectopic Pregnancy. Cureus. 2022 Jul 11;14(7).
9. Tyagi S, Tyagi P. Retrospective study on laparoscopic management of ectopic pregnancy. International Journal of Clinical Obstetrics and Gynaecology. 2020;4(1):237-9.
10. Anjum F, Khan YL, Rahim A, Bashir R, Khan HL. Laparoscopic management of ectopic pregnancy. JFJMU 2018;10(3):42-45.
11. Sindiani AM, Alshdaifat E, Obeidat B, Obeidat R, Rawashdeh H, Yaseen H. The Use of Single Dose Methotrexate in the Management of Ectopic Pregnancy and Pregnancy of Unknown Location: 10 Years' Experience in a Tertiary Center. International Journal of Women's Health. 2020;12:1233.
12. Zhang J, Zhang Y, Gan L, Liu XY, Du SP. Predictors and clinical features of methotrexate (MTX) therapy for ectopic pregnancy. BMC Pregnancy and Childbirth. 2020 Dec;20(1):1-9.
13. Rawal S. Successful use of single dose of methotrexate for the treatment of unruptured ectopic pregnancy at Tribhuvan University Teaching Hospital, Kathmandu, Nepal. Nepal Journal of Obstetrics and Gynaecology. 2012;7(1):45-9.
14. Pulatoglu C, Dogan O, Basbug A, Kaya AE, Yildiz A, Temizkan O. Predictive factors of methotrexate treatment success in ectopic pregnancy: A single-center tertiary study. Northern clinics of Istanbul. 2018 Sep 1;5(3):227.
15. Ozyuncu O, Tanacan A, Duru SA, Beksac MS. Methotrexate therapy for ectopic pregnancies: a tertiary center experience. Revista Brasileira de Ginecologia e Obstetrícia. 2018;40:680-5.
16. Beguin C, Brichant G, De Landsheere L, Tebache L, Karampelas S, Seidel L, Nisolle M. Use of methotrexate in the treatment of ectopic pregnancies: a retrospective single center study. Facts, views & vision in ObGyn. 2019 Dec;11(4):329.
17. Baggio S, Garzon S, Russo A, Ianniciello CQ, Santi L, Laganà AS, Raffaelli R, Franchi M. Fertility and reproductive outcome after tubal ectopic pregnancy: comparison among methotrexate, surgery and expectant management. Archives of gynecology and obstetrics. 2021 Jan;303(1):259-68.
18. Hawrylyshyn K, McLeod SL, Thomas J, Varner C. Methotrexate for the treatment of unruptured tubal ectopic pregnancy. Canadian Journal of Emergency Medicine. 2019 May;21(3):391-4.
19. Lashin ME, Alabiad MA, Abdelsalam WA. Values and predictive factors for Success of Methotrexate Therapy in Medical Management of Ectopic Pregnancy. Zagazig University Medical Journal. 2020 Nov 1;26(6):990-6.
20. Khan FK, Iqbal R. Ectopic pregnancy: FMH experience of success rate of single dose of methotrexate for the medical management of ectopic pregnancy. The Professional Medical Journal. 2018 Aug 4;25(08):1164-7.
21. Verma ML, Singh U, Solanki V, Sachan R, Sankhwar PL. Spectrum of Ectopic Pregnancies at a Tertiary Care Center of Northern India: A Retrospective Cross-sectional Study. Gynecology and Minimally Invasive Therapy. 2022 Jan;11(1):36.
22. Levine Y, Yahav L, Schwarzman P, Yohai D, Hershkovitz R, Weintraub AY. The correlation between endometrial thickness and the criteria for MTX treatment for ectopic pregnancy. Journal of Obstetrics and Gynaecology. 2021 Nov 17;41(8):1230-3.
23. Dhar H, Hamdi I, Rathi B. Methotrexate treatment of ectopic pregnancy: experience at Nizwa hospital with literature review. Oman Medical Journal. 2011 Mar;26(2):94.
24. Lee JH, Kim S, Lee I, Yun J, Yun BH, Choi YS, Lee BS, Seo SK. A risk prediction model for medical treatment failure in tubal pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018 Jun 1;225:148-54.
25. Keshta AS, Alarabi D, Jeddy R, Almusalam MM, Albastaki N, Alsadoon A, Mustafa W, Albuainain H, Bushaqer N, Dayoub NM. The Use of Beta-Human Chorionic Gonadotropin (β-hCG) Levels as a Predictor of Successful Medical Management of Ectopic Pregnancy. Cureus. 2022 Feb 14;14(2).
26. Tas EE, Akcay GF, Avsar AF. Single-dose methotrexate for the treatment of ectopic pregnancy: Our experience from 2010 to 2015. Pakistan journal of medical sciences. 2017 Jan;33(1):13.
27. Alsammani MA, Moona NA. Predictors of success of a single-dose methotrexate in the treatment of ectopic pregnancy. The Journal of Obstetrics and Gynecology of India. 2016 Aug;66(4):233-8.