Outcome of Medical Management of Unruptured Ectopic Pregnancy by Methotrexate in Chittagong Medical College Hospital

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Abstract

Background: For Unruptured Ectopic Pregnancy (UEP) medical treatment with Methotrexate (MTX) is a safe and efficient alternative that carries none of the dangers of surgery.The aim of this study was to evaluate the outcome of medical management of ectopic pregnancy by methotrexate.

Materials and methods: This cohort study was conducted in the Department of Obstetrics and Gynaecology of Chittagong Medical College Hospital (CMCH) Chattogram, Bangladesh from January 2022 to June 2022. A total of 48 admitted women with ectopic pregnancy were included in this study.The percentage of drop in β-hCG readings between days 4 and 7 was used to assess the effectiveness of medical care with methotrexate; these values had to be > 15% negative without the need for additional surgery. Collected data were classified, coded and entered into the computer for statistical analysis by using SPSS version 23.

Results: The overall success rate of treatment with MTX was 97.9% and failure was 2.1%. Mean β-hCG was significantly decrease (p=0.001) when compared on admission with day 7.H/O PID was significantly higher in failed show than successful one.The successful treatment group had a considerably lower mean -hcg level in several follow-up measurements compared to the failure group (p<0.05).

Conclusion: In conclusion, women with ectopic pregnancies have a safer, more successful and better option in Methotrexate (MTX) medication.

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Introduction

A common acute disease in obstetrics and gynecology is Ectopic Pregnancy (EP). The reported incidence ranges from 1% to 2%.[1] One of the biggest health risks to women's lives and fertility is ectopic pregnancy.[2] 10% of maternal deaths are attributed to this common cause of mortality.[3]

The most typical clinical signs of an ectopic pregnancy include vaginal bleeding, abdominal-pelvic pain, and a brief or delayed menstrual cycle. An ectopic pregnancy may not even show any symptoms. Ectopic pregnancy may be diagnosed by transvaginal ultrasonography (Ultrasonographic features such as extrauterine gestational sac with empty endometrial cavity). Ectopic pregnancy is indicated by serum β-hCG readings that show no doubling, low decrease, or plateaued levels at 48 hours.[4]

In addition to keeping the fallopian tubes in place, medical management also reduces the chance of discomfort and the hefty expenses and complications that come with surgery. Since it has been shown effective, Methotrexate (MTX) is frequently used as a conservative treatment for ectopic pregnancy.[5]

For years, the first line of treatment for ectopic pregnancy has been Methotrexate (MTX) an antagonist of folinic acid. Based on clinical results and β-hCG values, systemic MTX (50 mg/m^2) can be administered in single-dose, two-dose, or fixed multiple-dose regimen protocols.[6] An intra-amniotic MTX may also be used in specific situations, such as interstitial, cervical, cesarean scar, and ovarian ectopic pregnancies.[7] When compared to surgical procedures, the success rate of MTX is around 90% in patients who are adequately selected, and it results in fewer problems, unfavorable treatment outcomes and

reduced economic costs.[8] The patient's S β-hCG level is tracked every week until it drops to less than 5 mIU/ml on days 4 and 7.[8]

The CMCH's 2020 statistics show that out of 3802 gynecological patients, 360 had an ectopic pregnancy. This is concerning. However, there are no statistics regarding this hospital's use of methotrexate in the medical therapy of ectopic pregnancy. So, the objective of this study is to evaluate the outcome of medical management of ectopic pregnancy by methotrexate.

Materials and methods

This cohort study was conducted in the Department of Obstetrics & Gynaecology of Chittagong Medical College Hospital, Chattogram during the period of July 2021 to June 2022. A total of 48 women with ectopic pregnancy were included in this study. Diagnosed unruptured ectopic pregnancy with haemodynamically stable without pelvic pain, unruptured ectopic mass, ectopic mass ≤ 4 cm, absent embryonic cardiac activity, no haemoperitonium and patients who having ß-hCG levels of ≤ 3000 mIU /ml were enrolled in the study. Breast feeding, Contraindications to MTX therapy- Moderate to severe anaemia, leukopenia or thrombocytopenin, the patient's incapacity to participate in follow-up, MTX sensitivity, active lung disease, active peptic ulcer disease, hepatic dysfunction, and renal insufficiency were excluded from the study. Data was gathered through standardized questionnaires and check lists with all the relevant factors, as well as interviews and physical examinations. The patient was given the ability to leave the study at any time after enrolling voluntarily and was encouraged to do so. A single dosage of 50 mg/m^2 of methotrexate was given intraperitoneally (I/M) on day 1 following written informed consent and baseline investigations included full blood count, ß-hCG, renal and liver functions tests, blood group, and Rh factor. Day 4 and Day 7 saw the repetition of serial ß-hCG. The patient was released and was to be monitored as an outpatient if the ß-hCG level on Day 7 was at least 15% lower than that on Day 4. A second dose of 50 mg/m^2 methotrexate was given to the patient if their ß-hCG level on Day 7 was the same or higher than it was on Day 4. Weekly serum ß-hCG follow-up was conducted until the result was negative, or less than 5 mIU/ml. When the serum ß-hCG level dropped without the need for surgery or additional MTX dose administration, the MTX treatment was deemed successful.Serum ß-hCG values falling or rising by less than 15% were considered cases with prolonged plateauing. When ß-hCG was either growing or plateauing, a second dosage of MTX was given. Surgical intervention was considered for patients exhibiting hemodynamic instability, symptoms of tubal rupture and decreasing hemoglobin level. By recording adverse events such mouth ulcers, sore throats, lower abdomen pain, irregular vaginal bleeding, gastrointestinal side effects, haematological malfunction or complaints of any rashes, the toxicity of methotrexate medication was assessed. Data was entered, cleaned and analyzed using Statistical Package for Social Sciences (SPSS -23) software. Proportions were compared using Chi-square test. Unpaired and paired 't'-test was used for continuous variables. Statistical significance was defined as $p < 0.05$.

Before commence this study necessary permission was taken from proper authority.

Results

In this study the mean age was 25.7±4.5 years. More than half (54.2%) were multigravida. H/O PID was 6(12.5%), H/O abortion/MR was 12(25.0%) (Table I). Majority 45(93.75%) patients received single dose of Methotrexate (MTX) and found 1 patient was failure treatment outcome due to she had rupture and need laparotomy. Three (6.25%) patients needed 2nd dose MTX and their ß-hCG level was decreased >15% without further surgery (Figure 1). Successful treatment outcome was found in 47(97.9%) and only 1(2.1%) patient was failure (Figure 2). Mean adnexal ectopic mass, duration of married and gravida were not statistically significant with treatment outcome. H/O PID was significantly higher in failed show than successful one (Table II). Mean ß-hCG levels in different follow up were significantly decrease in successful treatment group than failure group ($p<0.05$) (Table III). Only 1(2.1%) patient had lower abdominal pain.

Table I Distribution of the study patients by socio-demographic, obstetric history, gynecological history (n=48)

Socio-demographic characteristics	Number of patients	Percentage (%)
Age (Years)		
≤20	5	10.4
21-25	16	33.3
26-30	23	47.9
31-35	4	8.3
Mean±SD	25.7±4.5	
Educational status		
Primary	5	10.4
SSC	22	45.8
HSC	21	43.8
Occupational status		
Housewife	46	95.8
Employed	2	4.2
Residence		
Rural	29	60.4
Urban	19	39.6
Duration of married (Years)		
≤4	21	43.8
5-8	22	45.8
>8	5	10.4
Gravida		
Primi	22	45.8
Multi	26	54.2
Gynecological history		
H/O PID	6	12.5
H/O abortion/MR	12	25.0

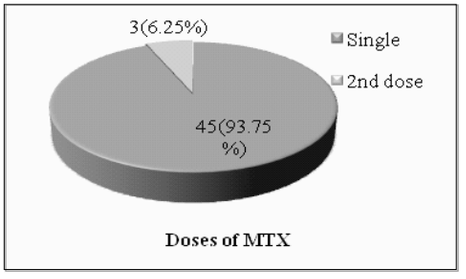

Figure 1 Distribution of the study patients according to doses of MTX (n=48)

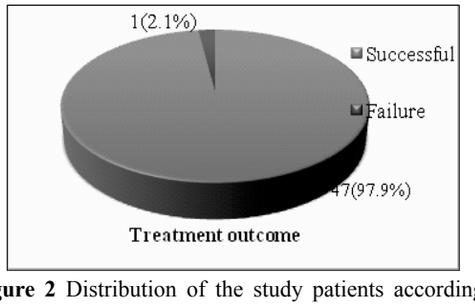

Figure 2 Distribution of the study patients according to treatment outcome (n=48)

Table II Association between TVS findings, obstetric history and gynecological history with treatment outcome (n=48)

Obstetric history	Outcome				p value
	Successful (n=47)		Failure (n=1)		
	n	%	n	%	
Adnexal ectopic mass	47	100.0	1	100.0	-
Size (cm)	2.8	±0.7	3.5	±0.0	0.300^{ns}
Duration of married (Years)					
	4	21	44.7	0	0.0
5-8	21	44.7	1	100.0	0.547^{ns}
>8	5	10.6	0	0.0	
Gravida					
Primi	22	46.8	0	0.0	0.542^{ns}
Multi	25	53.2	1	100.0	
Gynecological history					
H/O PID	5	10.6	1	100.0	0.008^{s}
H/O abortion/MR	11	23.4	1	100.0	0.080^{ns}

s=significant, ns= not significant
p value reached from unpaired and chi square test.

Table III Association between ß-hCG level in different follow up with treatment outcome (n=48)

ß-hCG level (mIU/ml)	Outcome		p value
	Successful (n=47)	Failure (n=1)	
	Mean±SD	Mean±SD	
On admission	1235.2±383.7	2500.0±0.0	0.002^{s}
Day 4	576.9±280.9	2200.0±0.0	0.001^{s}
Day 7	142.2±92.8	1050.0±0.0	0.001^{s}

s= significant, p value reached from unpaired 't'- test.

Discussion

Excellent outcomes have been achieved when methotrexate is used to treat ectopic pregnancy. Methotrexate was used in the early trials to treat ectopic pregnancy in a small group of stable patients. The use of methotrexate as an extremely safe and successful substitute for therapy in cases of ectopic pregnancy.[9]

Present study showed that on admission ß-hCG was 1261.5±411.2 mIU/ml, day 4 ß-hCG was 641.3±412.2 mIU/ml and day 7 ß-hCG was 244.9±426.7 mIU/ml. Mean ß-hCG was significantly decrease (p=0.001) when compared on admission with day 7. According to a study, ß-hCG levels were 2461±995.5 mIU/ml on day 0, 2241±877.4 mIU/ml on day 4 and 1654±870.4 mIU/ml on day 7.[10] According to a different study, the mean ß-hCG decreased significantly (p=0.001)

between the admission and day 7 values. BHCG was measured to be 2219 mIU/ml on day 1 and 1802 mIU/ml on day 7.[11]

In this study majority 45(93.75%) of patients received single dose of Methotrexate (MTX) and in 1 patient treatment was failure due to rupture and need laparotomy. Three (6.25%) patients needed 2nd dose MTX and their ß-hCG level was decreased during follow-up that was also successful treatment outcome. A study revealed that 30 (30.9%) instances received a double-dose of medication, whereas 67 (69.1%) cases received a single dose.[12] In cases of ectopic pregnancy, 61 patients (66.3%) received treatment with a single dosage of MTX, 21 patients (22.8%) required two doses and 10 patients (10.9%) required a multi-dose strategy.[13]

Regarding treatment outcome in this study it was observed that treatment outcome was successful in 47(97.9%) and in only 1(2.1%) patient was failed. The rough overall success percentage for 1327 women was reported to be 88.8% (1181 of 1327) in a review study published in 2003. The MTX therapy had an overall success rate of 69.75% (166/238), with 72 patients experiencing treatment failure (30.25%, 72/238).[1] 85% was the overall success rate.[9] Of the 67 patients, 47 (or 70.14%) responded well to a single dosage of MTX.[12] A single dose of methotrexate was effective in 162/225 individuals or 72% of the patients[11]. In a single dosage, the MTX success rate was 86.9%[13]. In the research, single-dose methotrexate therapy had a 65% success rate.[14] Similarly, it was reported that 96 out of 106 patients received methotrexate treatment satisfactorily, with a success rate of 90.6%, four of them needed a second dose.[15] In Merisio's series, 90% (n=10) of the patients who received a single dosage of therapy were successful.[16] According to published research, the success rate for treating ectopic pregnancies with single versus multidose treatments ranges from 67% to 100%.[17]

Regarding side effects, only 1(2.1%) patient had lower abdominal pain. 25% of women reportedly reported having lower abdominal pain.[14] The most common GI complications were nausea (5.1%) and vomiting (1.1%), along with stomach pain (6.8%).[18] Within two days of treatment, 40% (n=4) of patients in Thai's series experienced a remission of their pelvic pain without the need for surgery.[19]

Regarding TVS findings in this study observed that mean adnexal ectopic mass was higher in failure than successful treatment outcome (3.5±0.0 vs 2.8±0.7 cm) but not statistically significant between two groups. Reported that the success rate was lower (p=0.132) in patients with adnexal masses larger than 4 cm.[14]

In this study observed that mean ß-hCG levels on admission (1235.2±383.7 vs 2500.0±0.0), on day 4 (576.9±280.9 vs 2200.0±0.0) and on day 7 (142.2±92.8 vs 1050.0±0.0 mlU/ml) were significantly decrease in successful treatment group than failure group ($p<0.05$). Overall, 92.47% (135/146) of the patients whose ß-hCG levels dropped on the fourth day were included in the group receiving effective treatment.[1] Conversely, only 56.27% (31/67) of the patients in the group whose day-4 ß-hCG levels had increased responded well to MTX treatment (p value = 0.000). Low serum hCG levels were the study's predictors of Mtx success, as they were the cornerstone of a quick and early pregnancy diagnosis and a recognized biochemical marker for successful trophoblastic implantation.[12] A quick judgment may have led to a reported treatment failure based solely on a significant increase in ß-hCG levels from day 4 to day 7.[14] The previous studies feature was consistent with the current study.

Limitations

Because it was a single-center study with time constraints, our sample size was less. This study did not involve a big sample or a multicentered investigation. As a result, multicentered studies with high sample sizes may be conducted in the future.

Conclusion

For women with unruptured ectopic pregnancies who are hemodynamically stable, Methotrexate (MTX) medication is a safe and effective treatment option for ectopic pregnancy. One significant benefit of medicinal therapy is safety due to lack of surgical and anaesthetic complications and also reduce economic burden in terms of expense and hospital stay.

Recommendations

To assess the effectiveness of methotrexate-assisted medical therapy of ectopic pregnancy, multicentered trials are required. The days after the first methotrexate injection need to be spent closely monitoring the kinetics of hCG between D0 and D4 and between D0 and D7.

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Contribution of authors
RA-Conception, design, critical revision, acquisition of data, data analysis, manuscript writing & final approval.
RAJ-Design, critical revision & final approval.
KNB-Conception, critical revision & final approval.
ANU-Data analysis, critical revision & final approval.
SAC-Drafting, drafting, interpretation of data & final approval.
SB-Design, critical revision & final approval.

Disclosure
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References
1. Zhang Z, Zhang Y, Gan L, Liu X. and Du S. Predictors and clinical features of Methotrexate (MTX) therapy for ectopic pregnancy. BMC Pregnancy and Childbirth.2020; 20:654.

2. Helmy S, Koch M, Kölbl H, Grohmann-Izay B, Solomayer E, Bader Y. Correlation of the volume of ectopic pregnancy and MTX therapy outcome: a retrospective cohort study. Eur J ObstetGynecolReprod Biol. 2015; 184: 108–111.

3. Brady PC. New evidence to guide ectopic pregnancy diagnosis and management.ObstetGynecolSurv. 2017; 72(10):618–625.

4. Alkatout I, Honemeyer U, Strauss A. Clinical diagnosis and treatment of ectopic pregnancy. ObstetGynecolSurv. 2013; 68(08):571–581.

5. ACOG. Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin No. 191 summary: tubal ectopic pregnancy. Obstet Gynecol. 2018; 131(2): 409–411.

6. ACOG (American College of Obstetricians and Gynecologists). ACOG Practice Bulletin No. 94: Medical management of ectopic pregnancy. Obstet Gynecol. 2008; 111(06): 1479–1485.

7. Moon HS, Hyun JH, Kim KS, Kim HJ, Moon SE, Koo JS. Use of Tuohy needle for intraamniotic methotrexate injection through the cervical canal in a cervical pregnancy after failure of systemic methotrexate treatment. Am J ObstetGynecol, 2010; 202(05): e4–e6.

8. Bachman EA. and Barnhart K. Medical management of ectopic pregnancy: A comparison of regimens. ClinObstet Gynecol. 2012; 55(02): 440–447.

9. Forhad QE, Begum M, Alam IP, Alam MS. Safety and Efficacy of Methotrexate InUnruptured Ectopic Pregnancy. Bangladesh Journal of Obstetrics &Gynaecology. 2013;28(1):5-8.

10. Alawdi SH, Roumieh M, Alhalabi M. Management outcomes of ectopic pregnancy depending on different treatment modalities: A cohort study. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2021;10(3):843.

11. Sendy F, AlShehri E, AlAjmi A, Bamanie E, Appani S, Shams T. Failure rate of single dose methotrexate in managment of ectopic pregnancy. Obstetrics and Gynecology International. 2015;2015:1-5.

12. Avcio lu SN, Altinkaya SÖ, Küçük M, DemircanSezer S, Yüksel H. Predictors of success of different treatment modalities for management of ectopic pregnancy. Obstetrics and gynecology international. 2014;2014: 1-6.

13. Ozyuncu O, Tanacan A, Duru SA. andBeksac MS. Methotrexate Therapy for Ectopic Pregnancies: A Tertiary Center Experience. Rev Bras Ginecol Obstet. 2018; 40(11): 680-685.

14. Dhar H, Hamdi I, Rathi B. Methotrexate treatment of ectopic pregnancy: experience at Nizwa hospital with literature review. Oman Medical Journal. 2011;26(2):94.

15. Srivichai K, Uttavichai C, Tongsong T. Medical treatment of ectopic pregnancy: A ten-year review of 106 cases at MaharajNakorn Chiang Mai Hospital. J Med Assoc Thai. 2006;89(10):1567-1571.

16. Merisio C, Anfuso S, Berretta R, Gualdi M, Pultrone D. Single–dose methotrexate for Ectopic pregnancy treatment: Preliminary data Acta Bio Med. 2005; 76: 33-36.

17. Westaby DT, Wu O, Duncan WC, Critchley HO, Tong S, Horne AW. Has increased clinical experience with methotrexate reduced the direct costs of medical management of ectopic pregnancy compared to surgery?. BMC pregnancy and childbirth. 2012;12(1):1-6.

18. Mirbolouk F, Yousefnezhad A, Ghanbari A. Predicting factors of medical treatment success with single dose methotrexate in tubal ectopic pregnancy: A retrospective study. Iranian journal of reproductive medicine. 2015;13(6):351

19. Thia EW, Loi K, Wang JJ, Siow A. Methotrexate treatment for ectopic pregnancy at the KK Women's and Children's Hospital, Singapore. Singapore Med J. 2009; 50(11):1058-1061.