



EVALUATION OF EFFECTIVENESS AND SAFETY OF MEDICAL MANAGEMENT OF UNRUPTURED TUBAL ECTOPIC PREGNANCY WITH METHOTREXATE

Obstetrics & Gynaecology

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ABSTRACT

Background: Ectopic pregnancies occur in approximately 1.4% of all pregnancies and account for 15% of pregnancy-related deaths. Early detection of ectopic pregnancy and careful management are critical to prevent adverse clinical outcomes. Methotrexate (MTX) is widely accepted as first-line treatment of non-ruptured ectopic pregnancy. The present study was conducted to evaluate the safety and tolerability of Single dose method of MTX treatment in unruptured tubal ectopic pregnancy and to determine the decline of HCG levels 15% or more between day 4 and day 7 post second dose of MTX if needed. **Methodology:** Study was conducted on 30 patients diagnosed of an ectopic pregnancy with a serum β -hCG level of < 1500 IU/L. On Day 1 a single dose of intramuscular MTX, 50 mg/m² administered. For those who did not register a fall of 15% between day 4 and day 7, a second dose of MTX was administered and the same sequence was followed. Subsequent decline in beta HCG level to 5 ml U/ml with one or two doses were considered as successful treatment. Data was analyzed using SPSS V15.0 package and appropriate tests were applied. Results: The mean Age of mother in years was 22.3 $\pm$ 4.7. More than 2/3rd (70%) patients had gestational age < 8 weeks. 60% patients were multipara and 40% were primipara. Majority 80% had pelvic pain. One methotrexate injection was required in 80% and two injections were required in 20% cases. Beta hCG levels at baseline was 1447.4 $\pm$ 60.56 IU/mL which decreased on treatment to 785.6 $\pm$ 8.48 IU/mL on day 4 and 343.17 $\pm$ 50.01 IU/mL on day 7. Treatment outcome was very good. 83.33% had success rate only 16.67% failed. Association between number of injections required and treatment outcome was not statistically significant. **Conclusion:** Single dose methotrexate is sufficient to treat persistent trophoblastic tissue after salpingostomy and ectopic pregnancies associated with low initial β -hCG values. Systemic single dose methotrexate seems to offer the greatest benefits in terms of efficacy and tolerability. It has proved to be a good alternative to laparoscopy in selected cases.

KEYWORDS

Ectopic pregnancy, Methotrexate, β -hCG levels.

INTRODUCTION:

Ectopic pregnancies occur in approximately 1.4% of all pregnancies and account for 15% of pregnancy-related deaths. Considering the high degree of mortality, recognizing an ectopic pregnancy is important⁽¹⁾. Signs and symptoms of an ectopic pregnancy are nonspecific and include pain, vaginal bleeding, and an adnexal mass. Therefore, imaging can play a critical role in diagnosis. In the majority of patients, symptoms are usually nonspecific and similar to normal early intrauterine gestation or miscarriage, such as amenorrhea, adnexal tenderness, and cervical motion tenderness. The prevalence of ectopic pregnancies is variable and related to patient population and inherent risk factors⁽²⁾. There are different types of ectopic pregnancies, which are tubal, cornual, cesarean scar, cervical, heterotopic, abdominal, and ovarian. Initial imaging evaluation of pregnant patients with pelvic symptoms is by ultrasonography, transabdominal, transvaginal or both.

Early detection of ectopic pregnancy and careful management are critical to prevent adverse clinical outcomes, including fallopian tube rupture, decreased future fertility, and death. Methotrexate (MTX) is widely accepted as first-line treatment of non-ruptured ectopic pregnancy and may be considered for women with a confirmed ectopic pregnancy who are hemodynamically stable with an unruptured mass^(3,4).

Methotrexate is more effective when used to treat ectopic pregnancies with lower human chorionic gonadotropin (HCG) levels. However, there is no consensus on a threshold value that best predicts success or failure. Methotrexate can be used to treat ectopic pregnancies that occur in cornual, cervical, and caesarean scar locations, and it does not adversely affect ovarian reserve or subsequent fertility⁽⁵⁾. Women who strongly desired to retain their reproductive function could receive conservative medical treatment on the basis of informed consent regardless of the initial β -hCG level and the size of the adnexal mass⁽⁶⁾.

OBJECTIVES:

1. To evaluate the safety and tolerability of Single dose method of Methotrexate treatment in clinically stable women with unruptured tubal ectopic pregnancy and a serum β -hCG level of < 1500 IU/L. 2. To determine the decline of HCG levels 15% or more between day 4 and day 7 post second dose of Methotrexate in patients who did not register a fall of 15% between day 4 and day 7.

MATERIAL AND METHODS:

The present prospective observational study was conducted on 30 patients diagnosed an ectopic pregnancy, admitted in Inpatient department of Obstetrics & Gynaecology of tertiary care hospital between July 2020 to December 2021. At the time of registration, the baseline information was taken especially with respect to sociodemographic factors, clinical findings, and other investigations. The data thus collected was analyzed to study the effectiveness of Single dose method of Methotrexate treatment in clinically stable women with unruptured tubal ectopic pregnancy and a serum β -hCG level of < 1500 IU/L.

Women aged between 18 to 50 years diagnosed with an unruptured ectopic pregnancy with Serum β -hCG level of < 1500 IU/L, extraovarian adnexal mass less than 4.0 cm, absent embryonic heart beat and who were hemodynamically stable. Patients with intrauterine pregnancy, with immunodeficiency, moderate to severe anemia, leucopenia, Thrombocytopenia, sensitivity to Methotrexate, active pulmonary or peptic ulcer disease were excluded.

Methodology: After getting institutional ethical committee approval, study was started. It was carried out as per Ethical/ICMR guidelines. Informed consent was obtained prior to administering Methotrexate. Baseline investigation comprising of complete blood count, blood group and Rh factor, renal and liver function tests were done apart from HCG levels and transvaginal sonography. On Day 1 a single dose of intramuscular methotrexate, 50 mg/m² administered. On Days 4 and 7: β -hCG level are measured. The regimen is repeated if $< 15\%$ decrease in β -hCG level between days 4 and 7. After initial treatment response, β -hCG levels are measured weekly until it reaches nonpregnant level. The day of first dose of injection was considered as day 1 and the efficacy was then be observed. For those who did not register a fall of 15% between day 4 and day 7, a second dose of Methotrexate was administered and the same sequence was followed. Subsequent decline in beta HCG level to 5 ml U/ml with one or two doses were considered as successful treatment.

An inadequate fall in beta HCG after second dose or signs of tubal rupture, hemodynamic instability was considered as failure of medical management and surgical intervention were done. Surgery was also be considered for women who developed abdominal pain with evidence of hemoperitoneum on ultrasound. When β -hCG levels fell by $> 15\%$, weekly blood tests were arranged until it comes under nonpregnant

level . In women with static serum β -hCG (within $\pm 15\%$ of the previous reading), blood tests were carried out every 2 days to ensure that the levels were not increasing.

Statistical Analysis: Data was analyzed using SPSS V15.0 package (Statistical Package for Social Sciences, Version 15.0). Data was given as Mean $\pm$ SD and range for continuous normal data and median and range for non-normal data. Comparison was carried out by Student's unpaired t test for normal numerical data. Mann Whitney U test will be applied for non-normal data. Fisher Exact Probability test or Chi square tests was applied to compare percentages for categorical data between 2 groups. All statistical tests were two tailed. Alpha (α) Level of Significance was taken as $P \leq 0.05$.

RESULTS:

We included 30 diagnosed cases of ectopic pregnancy in our study. The mean Age of mother in years was 22.3 ± 4.7 , majority (50%) were in age group of 21 to 30 years. More than 2/3rd (70%) patients had gestational age <8 weeks. Mean gestational age was 7.5 ± 2.66 weeks. 60% patients were multipara and 40% were primipara. Majority 80% had pelvic pain. (Table 1)

Table 1: Patient characteristics:

Patient Characteristics	Frequency	Percentage
Age (Years)	18 to 20	12
	21 to 30	15
	>30	3
Gestational age	<8 weeks	21
	>8 weeks	9
Parity	Primi	12
	Multi	18
Pelvic pain	Yes	24
	No	6
Total	30	100%

Table 2: Interventions Required:

Patient Characteristics	Frequency	Percentage
Intra abdominal bleeding requiring blood transfusion	Yes	5
	No	25
Laparotomies performed	Yes	5
	No	25
Number of Methotrexate injections required	1	24
	2	6
Total	30	100%

Table 2 shows that in 16.67% cases with intra-abdominal bleeding, required blood transfusion and Laparotomies were performed in 16.67% patients. One methotrexate injection was required in 80% and two injections were required in 20% cases.

Beta hCG levels at baseline was 1447.4 ± 60.56 IU/mL which decreased on treatment to 785.6 ± 8.48 IU/mL on day 4 and 343.17 ± 50.01 IU/mL on day 7. P value $< 0.0001^*$, shows statistical significance. (Graph 1)

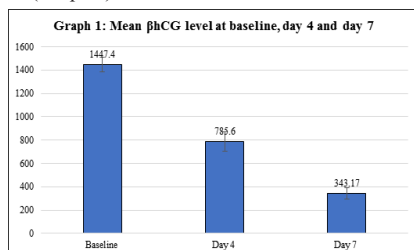


Table 3: Laboratory Investigations:

Parameter	Mean	SD
Hb (gm/dL)	11.1	0.65
TLC ($\times 100$)	84.79	14.31
Neutrophils (%)	57.8	19.0
Lymphocytes (%)	28.8	4.5
Platelets ($\times 109/L$)	159.7	20.6

Blood urea (mg/dL)	50.6	4.16
Blood creatinine (mg/dL)	1.42	0.64
BSL (mg/dL)	165.6	17.7
Na ⁺ (mEq/L)	125.5	25.3
K ⁺ (mEq/L)	3.3	1.31

Table 3 shows Laboratory investigation of the patients. Mean Hb count was 11.1 ± 0.65 gm/dL, mean TLC was 84.79 ± 14.31 etc. Mean Blood urea was 50.6 ± 4.16 mg/dL and mean Blood creatinine level was 1.42 ± 0.64 mg/dL.

Table 4: Number of injections required and treatment outcome:

Number of injections required	Treatment		Total	P value
	Success	Failure		
1	19 (79.6%)	5 (100%)	24 (80%)	0.553
2	6 (20.4%)	0 (0.0%)	6 (20%)	
Total	25 (100%)	5 (100%)	30 (100%)	

Treatment outcome was very good. 83.33% had success rate only 16.67% failed. Association between number of injections required and treatment outcome was not statistically significant. 24 cases needed 1 injection and among them 19 succeeded and among those requiring 2 doses all had good treatment outcome. (p value 0.553)

DISCUSSION:

An ectopic pregnancy is the development of the fertilized ovum outside of the uterine cavity. It can occur in a number of abnormal locations, each with different characteristic growth patterns and treatment options. In the present study we evaluated the safety and tolerability of single dose and second dose method of Methotrexate treatment in women with unruptured tubal ectopic pregnancy.

Present studies shows that the mean age of mother was 22.3 ± 4.7 years, majority 50% were in age group of 21 to 30 years. Study by Zhang, J et al⁽⁶⁾ showed that mean age was 29.05 ± 4.8 years. Study by Dhar et al⁽⁷⁾ showed that mean age was 30 years.

Majority 70% had gestational age <8 weeks. Study by Dhar et al⁽⁷⁾ showed that mean GA was 4.3 weeks. 71.4% were <4 weeks, 68.2% were 4 to 6 weeks. 60% were multipara and 40% were primipara. Study by Dhar et al⁽⁷⁾ showed that 60% were primipara. Majority of the patients had (80%) had pelvic pain. Study by Dhar et al⁽⁷⁾ showed that 80% had abdominal pain.

Beta hCG levels at baseline was 1447.4 ± 60.56 IU/mL which decreased on treatment to 785.6 ± 8.48 IU/mL on day 4 and 343.17 ± 50.01 IU/mL on day 7 (p value < 0.0001), shows statistical significance. Zhang, J et al⁽⁶⁾ showed that the mean initial beta-human chorionic gonadotropin (β -hCG) level was significantly lower in the successful treatment group than in the failed treatment group (2538.08 IU/L versus 3533.17 IU/L, $P = 0.000$). The treatment success rate of the group with an initial β -hCG concentration less than 4000 IU/L was significantly higher than that of the group with an initial β -hCG concentration greater than 4000 IU/L. However, the success rate of the group with an initial β -hCG concentration greater than 4000 IU/L was still relatively high (54.55%). Study by Dhar et al⁽⁷⁾ showed that the average value of β -hcg on day 1 in patients treated with single dose of MTX was 1234 (range 109-5269) and those treated with two doses or more was 1319.20 (range 865-6885). An increase in the day 4 value was observed in some cases, mainly due to the trophoblastic tissue breakdown releasing the hormone.

Number of methotrexate injection required were one in 80% and 2 in 20% cases. Study by Dhar et al⁽⁷⁾ showed that total number of women treated with single dose was 75% (n=45) and 25% (n=15) received two doses or more. Treatment outcome was very good. 83.33% had success rate only 16.67% failed. Hawrylyshyn, K et al⁽⁵⁾ showed that 30% failed only 70% had a good success rate. Study by Zhang, J et al⁽⁶⁾ showed that the overall success rate of MTX therapy for ectopic pregnancy was 69.75%.

Study by Dhar et al⁽⁷⁾ showed that overall success rate of treatment in our study was 65% (n=39). Surgical intervention was required for 35% (n=21) of patients with tubal rupture and abdominal pain. Thirty patients with small unruptured ectopic pregnancies achieved a success

rate of 86.7% with five women requiring a second dose and one woman was successfully treated with three doses⁽⁸⁾. Srivichai et al⁽⁹⁾ reported a success rate of 90.6% in 96 out of 106 patients were successfully treated with methotrexate though four required a second dose. Success reached 90% (n=10) in patients out of 11 with single dose treatment in Merisio's series⁽¹⁰⁾. Literature published so far shows a success rate ranging from 67% to 100% in single versus multidose treatment for ectopic pregnancies⁽¹¹⁾. Feras Sendy et al⁽¹²⁾ showed that 72% successful rate. Association between number of injections required and treatment outcome, no statistical significance was seen. 24 cases needed 1 injection and among them 19 succeeded and among those requiring 2 doses all had good treatment outcome.

CONCLUSION:

Both conservative surgery and medical therapy may be viewed as appropriate first-line therapies in many early unruptured ectopic pregnancies. Multiple-dose MTX treatment has a lower failure rate than single-dose MTX. Single dose methotrexate is sufficient to treat persistent trophoblastic tissue after salpingostomy and ectopic pregnancies associated with low initial β -hCG values. Systemic single dose methotrexate seems to offer the greatest benefits in terms of efficacy and tolerability. It has proved to be a good alternative to laparoscopy in selected cases.

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