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EFFICACY OF METHOTREXATE TO RESOLVE OR CLEAR THE UNRUPTURED TUBAL ECTOPIC PREGNANCY WITH HIGH CHORIONIC GONADOTROPINS- A RETROSPECTIVE STUDY

Dr Meghana D	Post Graduate MBBS MS Obstetrics And Gynecology Bangalore Medical college and Research Institute Krishna Rajendra Road, Kalasipalya Bangalore 560002
Dr Shilpa*	Post Graduate MBBS MS Obstetrics And Gynecology Bangalore Medical college and Research Institute Krishna Rajendra Road, Kalasipalya Bangalore 560002*Corresponding Author
Dr Jyothi NJ	Post Graduate MBBS MS Obstetrics And Gynecology Bangalore Medical college and Research Institute Krishna Rajendra Road, Kalasipalya Bangalore 560002
Dr Savitha C	Post Graduate MBBS MS Obstetrics And Gynecology Bangalore Medical college and Research Institute Krishna Rajendra Road, Kalasipalya Bangalore 560002

ABSTRACT **Background** Ectopic pregnancy, often located in the fallopian tube, poses significant risks to maternal health if untreated. Methotrexate, a folic acid antagonist, offers a non-surgical option to manage unruptured ectopic pregnancies by inhibiting trophoblastic cell growth. While generally effective, the success of methotrexate varies with initial β-human chorionic gonadotropin (β-hCG) levels, with higher levels often linked to lower treatment success. Limited research has explored methotrexate efficacy in cases with elevated β-hCG. **Objectives** This study aimed to evaluate the effectiveness of methotrexate as a first-line treatment for stable tubal ectopic pregnancies with high baseline β-hCG levels, examining the impact of single- and multi-dose protocols on treatment outcomes. **Methods** A retrospective observational study was conducted at Vanivilas Hospital, BMCRI, Bengaluru, over six months. A total of 59 pregnant women with unruptured tubal ectopic pregnancies and baseline β-hCG >3000 or gestational sac size >3.5 cm were included. Methotrexate was administered in single or multiple doses based on β-hCG reduction rates, with additional doses given if β-hCG did not decrease by 15% between days 4 and 7. Statistical analyses included chi-square tests and ANOVA to assess differences between groups. **Results** Patients receiving single-dose methotrexate exhibited higher success rates, with 96.2% achieving non-surgical resolution. Conversely, the three-dose group had a 53.8% success rate, with 38.5% requiring laparotomy. Beta HCG levels declined significantly across all groups, with single-dose treatment demonstrating the most pronounced reduction. Dose-dependent responses were observed, with higher doses associated with lower β-hCG reduction and increased need for surgical intervention. **Conclusion** Methotrexate is effective for managing unruptured tubal ectopic pregnancies, especially at lower doses in cases with manageable initial β-hCG levels. Tailoring methotrexate dosage based on initial β-hCG levels may optimize outcomes and minimize surgical intervention.

KEYWORDS : Ectopic pregnancy, Methotrexate, Beta HCG, Non-surgical management, Dose-response, Tubal ectopic pregnancy

INTRODUCTION:

Ectopic pregnancy, defined as the implantation of a fertilized egg outside the uterine cavity, most commonly occurs in the fallopian tube and poses significant risks to maternal health if not managed effectively. Among various therapeutic options, methotrexate, a folic acid antagonist, has gained widespread attention as a non-surgical intervention for unruptured ectopic pregnancies due to its effectiveness in inhibiting trophoblastic cell proliferation (1). Its use is particularly valuable in cases where preservation of tubal integrity and future fertility is a priority. Studies have documented that methotrexate therapy is generally effective and safe, especially when serum beta-human chorionic gonadotropin (β-hCG) levels are not excessively elevated (2,3). However, in cases with high initial β-hCG levels, the efficacy of methotrexate remains controversial due to a reported decrease in treatment success rates as β-hCG levels increase (4,5).

Despite the clinical significance of ectopic pregnancies with high β-hCG levels, limited research has focused on this specific population. Retrospective studies have shown varied success rates, suggesting that factors such as β-hCG levels, gestational age, and methotrexate dosing protocols might play a role in treatment outcomes (6,7). Furthermore, while single-dose methotrexate is commonly used, higher β-hCG levels often require a multidose protocol, raising concerns about the balance between efficacy and potential adverse effects (8). Hence, this study was conducted with the objective to evaluate the effectiveness of the first line medical management with methotrexate in the treatment of patients with stable tubal ectopic pregnancy and high Beta HCG levels.

MATERIAL AND METHODS:

A Retrospective observational study was done among pregnant women presenting with ectopic pregnancy at Vanivilas hospital, BMCRI, Bengaluru. Duration of the study was for 6 months between January 2024-june 2024. Informed consent was obtained from all the patients prior to inclusion and convenient method of sampling was used. Patient who were diagnosed as ectopic pregnancy and haemodynamically stable, with no evidence of tubal rupture, Beta hcg >3000 or G sac more than 3.5 cm were included in the study. Absolute contraindication for medical treatment such as active pulmonary disease, chronic liver disease, renal failure, immunodeficiency were excluded from the study. Sample size was calculated by using the formula n=Za2pq/d2. Where Za=standard table value for 95% confidence interval=1.96, P=proportion of participants who showed complete response to treatment p= 81.3%, q=1-p= 1-81.3%=18.7%. d= absolute precision=10, n=(1.96)2×81.3×18.7/102, n=58.

Data was collected using questionnaire. Patients fulfilling the inclusion criteria were subjected for detailed history, clinical examination and Laboratory investigations. Baseline investigation such as CBC,LFT, RFT, Beta HCG were done. Patient on single dose regimen, methotrexate 50mg/m2 on day 1 of treatment, Beta HCG reduction rate was evaluated between day 4 and day 7. If the Beta HCG levels reduce by 15% then it was measured weekly till it turns out to be negative. When the reduction was less than 15% between day 4 and day 7, additional methotrexate dose was administered.

Patients on multiple dose regimen, Inj Methotrexate given on day 1, day 3, day 5 and day 7 at a dose of 1mg/kg body weight with alternate folinic acid. Beta HCG repeated on alternative days, if there was reduction of Beta HCG, no additional dose of methotrexate was administered, follow up Beta HCG weekly was done till it becomes negative. Treatment failure was termed as need for laproscopic surgery after administrating the additional methotrexate dose.

Statistical analysis: Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software and Epi-info version 7.2.1 (CDC Atlanta) software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. ANOVA (Analysis of Variance) was the test of significance to identify the mean difference between more than

two groups for quantitative data. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

RESULTS:

Table 1:- Profile of subjects with ectopic pregnancy

		Frequency	Percent
Age	<20 yrs	6	10.2%
	21-30 yrs	44	74.6%
	>30 yrs	9	15.3%
Parity	Multigravida	29	49.2%
	Primigravida	30	50.8%
Site	Left	25	42.4%
	Right	34	57.6%
Methotrexate dose	1 dose	26	44.1%
	2 dose	20	33.9%
	3 dose	13	22.0%
Baseline HCG	3000-10000	55	93.2
	10001-20000	4	6.8
G-sac Size	<3.5cm	45	76.3
	>3.5cm	14	23.7

Majority 74.6% of the subjects were between 21-30yrs age group, 15.3% of Subjects were >30yrs and 10.2% of subjects were <20yrs. 49.2% of Subjects were multipara and 50.8% of subjects were primipara. 42.4% of Subjects had site on left and 57.6% of Subjects had site on right.

In our study 44.1% of Subjects had 1 dose of methotrexate, 33.9% of Subjects had 2 dose of methotrexate and 22% of Subjects had 3 dose of methotrexate. 44.1% of subjects received Single dose and 55.9% of subjects received multiple dose. Among subjects who received multiple dose 60.6% of them received 2dose and 39.4% of them received 3 dose. 93.2% of Subjects had Baseline HCG site between 3000-10000 and only 6.8% of Subjects had Baseline HCG site between 10001-20000. 76.3% of Subjects had G-sac Size <3.5cm and 23.7% of Subjects had Gsac Size >3.5cm [Table 1].

Table 2: Beta HCG levels at different periods of follow-up after methotrexate treatment

Beta HCG	Mean	SD	Median	P value
Baseline	5812.34	2256.10	5102	
DAY 1	5812.34	2256.10	5102	1.000
DAY 4	5581.90	2221.42	4692	<0.001*
DAY 7	4996.17	2331.52	4060	<0.001*
DAY 11	5527.16	2754.57	4947.5	<0.001*
DAY 14	5119.28	2705.56	4201.5	<0.001*

PAIRED T TEST

In the current study, Beta HCG levels were monitored at baseline and on Days 1, 4, 7, 11, and 14 following methotrexate treatment. The mean baseline Beta HCG level was 5812.34 ± 2256.10, with a median of 5102. By Day 4, there was a significant reduction in Beta HCG levels (mean: 5581.90 ± 2221.42, median: 4692, $p < 0.001$). The reduction continued over time, with levels further dropping to a mean of 4996.17 ± 2331.52 on Day 7 (median: 4060, $p < 0.001$), and by Day 14, the mean level was 5119.28 ± 2705.56 (median: 4201.5, $p < 0.001$). These findings indicate a statistically significant decline in Beta HCG levels after treatment, with a consistent downward trend over the follow-up period [Table 2].

Table 3: Comparison of Beta HCG levels with respect to Methotrexate doses at different periods of follow-up

	METHOTREXATE DOSES									P value
	1			2			3			
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	
Baseline	4205.96	629.93	4052	5840.90	1580.03	5606	8981.15	1830.73	8932	<0.001*
DAY 1	4205.96	629.93	4052	5840.90	1580.03	5606	8981.15	1830.73	8932	<0.001*
DAY 4	3979.88	571.51	3987	5666.70	1441.56	5509	8911.58	1750.73	8981	<0.001*
DAY 7	3167.20	491.79	3154	5068.65	1377.96	4884	8401.92	1669.53	8110	<0.001*
DAY 11	.	.	.	3868.41	942.32	3812.000	7696.30	2856.18	7890.000	<0.001*
DAY 14	.	.	.	3150.08	776.93	3045.0	7694.38	2051.35	7990.0	<0.001*

ANOVA TEST

When comparing Beta HCG levels among groups receiving different methotrexate doses, a significant difference was observed at all time points ($p < 0.001$). At baseline, the mean Beta HCG level was highest for those receiving three doses (8981.15 ± 1830.73) compared to one dose (4205.96 ± 629.93). By Day 7, the levels declined across all dose groups, with the three-dose group still showing the highest mean level of 8401.92 ± 1669.53 compared to the one-dose group at 3167.20 ± 491.79. These findings suggest a dose-dependent response, where Beta HCG levels reduced progressively with higher methotrexate doses[Table 3].

Table 4: Outcome among subjects with respect to Methotrexate doses

		Methotrexate Doses								P value
		1		2		3		Total		
		Count	%	Count	%	Count	%	Count	%	
% OF FALL IN BEATA HCG FROM DAY 4 AND 7	<15 %	2	7.7 %	19	95.0%	13	100.0%	34	57.6%	<0.001*
	>15 %	24	92.3 %	1	5.0 %	0	0.0 %	25	42.4%	
% OF FALL IN BEATA HCG FROM DAY 11 AND 14	<15 %	0	0.0 %	1	5.6 %	6	46.2%	7	19.4%	0.009*
	>15 %	5	100.0%	17	94.4%	7	53.8%	29	80.6%	

PEARSON CHI-SQUARE TESTS

The fall in Beta HCG levels between Days 4 and 7 showed that 92.3% of subjects in the one-dose group had a reduction of >15%, compared to only 5.0% in the two-dose group and none in the three-dose group ($p < 0.001$). Between Days 11 and 14, 80.6% of the total subjects had a reduction of >15%. The Chi-square test indicated significant differences in response rates between the dosing groups, highlighting that higher doses were associated with a slower reduction in Beta HCG levels [Table 4].

Table 5: Outcome among subjects with respect to Methotrexate doses

		Methotrexate Doses							
			1	2		3		Total	
		Count	%	Count	%	Count	%	Count	%
Outcome	Laparotomy (Failed Manage)	0	0.0 %	0	0.0 %	5	38.5 %	5	8.5%
	Laparotomy (Unstable)	1	3.8 %	3	15.0 %	1	7.7%	5	8.5%
	Successful	25	96.2 %	17	85.0 %	7	53.8 %	49	83.1%
	Total	26	100.0%	20	100.0%	13	100.0%	59	100.0 %

$\chi 2 = 21.24$, $df = 4$, $p < 0.001$* [Chi-square test]

Regarding treatment outcomes, 96.2% of the subjects in the one-dose group achieved a successful outcome without the need for laparotomy, compared to 85.0% in the two-dose group and 53.8% in the three-dose group ($\chi^2 = 21.24$, $df = 4$, $p < 0.001$). In the three-dose group, 38.5% of cases required laparotomy due to failed management. These results suggest that higher methotrexate doses are associated with a higher likelihood of requiring surgical intervention, while lower doses are more likely to result in a successful non-surgical outcome [Table 5].

DISCUSSION:

The current study provides a comprehensive analysis of ectopic pregnancy management using methotrexate, with a focus on dosage

effects and associated outcomes. The results indicate a dose-dependent relationship in Beta HCG reduction, where subjects receiving one dose of methotrexate had a more significant decline in Beta HCG levels by Days 4 and 7 compared to those receiving two or three doses. This aligns with previous studies such as Lipscomb et al., who observed that single-dose methotrexate was effective in lowering HCG levels significantly, particularly in cases where the initial HCG concentration was lower and the ectopic mass was smaller (10). In our study, the high success rate (96.2%) in the one-dose group also corroborates findings by Barnhart et al., who reported similar efficacy rates with lower methotrexate doses, emphasizing that careful patient selection could result in favorable outcomes without the need for surgical intervention (11). Conversely, our findings revealed that higher doses (three-dose regimens) were associated with slower HCG reduction and increased laparotomy rates, echoing research by Stovall et al., which highlighted that patients with higher initial HCG levels or larger ectopic masses might require more intensive intervention, yet this also increased the likelihood of non-responsiveness and surgical intervention due to either treatment failure or instability (12).

The dose-related variation in outcomes can be attributed to multiple factors. Higher methotrexate doses may reflect more severe cases or larger ectopic gestations, which are inherently less responsive to medical management alone. Furthermore, elevated initial HCG levels, as observed in the three-dose group in our study, have been documented as predictors of treatment failure with methotrexate alone, suggesting that these cases could benefit from closer monitoring or alternative strategies (13). Additionally, individual differences in methotrexate pharmacokinetics and tissue response may play a role in these variable outcomes, as suggested by Mavrelos et al., who reported that higher methotrexate doses were more likely to necessitate surgical intervention due to adverse tissue reactions and slower resolution of the ectopic mass (14).

The significant decline in HCG levels observed between Days 4 and 14 across all groups is consistent with the typical pharmacodynamics of methotrexate in ectopic pregnancy management. However, the lower efficacy in the three-dose group raises questions about optimal dosing thresholds and the potential benefits of combined or stepwise approaches to avoid escalation to surgery. Future studies with a larger sample size could provide further insights into personalized methotrexate dosing based on initial HCG levels and ectopic size.

CONCLUSION:

The retrospective study demonstrates that methotrexate is generally effective for managing unruptured tubal ectopic pregnancies, with varying success based on dosage and initial Beta HCG levels. The study findings indicate that a single-dose methotrexate regimen is associated with a higher likelihood of a successful outcome, with 96.2% of one-dose recipients avoiding surgical intervention. In contrast, three-dose recipients showed lower success rates, with 38.5% ultimately requiring laparotomy due to failed treatment. Beta HCG levels decreased significantly over the follow-up period across all dosage groups, though reductions were more pronounced with lower doses. The data reveal a dose-dependent response, as those with higher initial Beta HCG levels and larger gestational sacs required additional doses for efficacy, with reduced rates of Beta HCG decline over time. The study suggests that a higher methotrexate dose may be less efficient in achieving the desired non-surgical outcomes, emphasizing that single or two-dose regimens may be preferable in certain cases. These findings underline the importance of tailored methotrexate dosing based on initial Beta HCG levels to optimize patient outcomes in managing ectopic pregnancies.

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