Success Rates of Single-Dose versus Multiple-Dose Methotrexate Protocols in the Treatment of Unruptured Tubal Ectopic Pregnancy: A Hospital Based Comparative Study

Dr. Tanuja Mannepalli[1], Dr. K Geetha[2], Dr. Sreeja Shivaprakash[3], Dr. R Sindhuja[4*]

[1]*Post Graduate, Department of Obstetrics and Gynecology, Vinayaka Mission's Medical College and Hospital, Vinayaka Mission's Research Foundation (DU), Karaikal, Tamil Nadu, India. Email: mannepalli.tanuja@gmail.com*
[2]*Professor and Head, Department of Obstetrics and Gynecology, Vinayaka Mission's Medical College and Hospital, Vinayaka Mission's Research Foundation (DU), Karaikal, Tamil Nadu, India. Email: vemsrigeenan3@gmail.com*
[3]*Post Graduate, Department of Obstetrics and Gynecology, Vinayaka Mission's Medical College and Hospital, Vinayaka Mission's Research Foundation (DU), Karaikal, Tamil Nadu, India. Email: Drsreejaprakash@gmail.com*
[4]*Associate Professor, Department of Obstetrics and Gynecology, Vinayaka Mission's Medical College and Hospital, Vinayaka Mission's Research Foundation (DU), Karaikal, Tamil Nadu, India. Email: sindhujatmc@gmail.com*
**Corresponding Author: Dr. R Sindhuja*

KEYWORDS
Methotrexate, Ectopic pregnancy, Tubal pregnancy, India

ABSTRACT
Background: Methotrexate has become an established non-surgical treatment option for ectopic pregnancy, especially in cases where the pregnancy is unruptured and the patient is hemodynamically stable.
Objectives: To compare the success rates of single versus multiple dose methotrexate protocols for the treatment of unruptured tubal ectopic pregnancy.
Methods: This was a hospital based comparative study conducted in the Department of Obstetrics and Gynaecology, Vinayaka Missions Medical College & Hospital, Karaikal, Puducherry, India (tertiary care centre) between January and June 2024.
Results: In this study, 40 women with unruptured tubal ectopic pregnancy were divided into two groups: Group A received a single intramuscular dose of 50 mg/m² methotrexate, and Group B received multiple doses. Baseline characteristics such as age, gravida, parity, gestational age, hCG levels, and the size of the mass on sonograph were comparable between the two groups, with no statistically significant differences. Group A had an 80% success rate, while Group B had a 90% success rate. Analysis of potential confounding factors (sociodemographic, obstetric, laboratory, and sonographic variables) revealed no significant impact on the success rates between the two groups.
Conclusion: Both single and multiple doses of methotrexate were effective for treating unruptured tubal ectopic pregnancy, with no significant difference in outcomes or variables measured between the two groups.

1. Introduction

Ectopic pregnancy, a condition where the fertilized egg implants outside the uterine cavity, most commonly in the fallopian tube,(1) is a significant cause of morbidity and mortality in women of reproductive age.(2) It accounts for approximately 1-2% of all pregnancies and remains a major health concern due to its potential complications, including tubal rupture and severe internal bleeding.(3, 4) Early diagnosis and appropriate management are crucial to preserve the patient's fertility and prevent life-threatening complications.

Methotrexate, a folic acid antagonist, has become an established non-surgical treatment option for ectopic pregnancy,(5) especially in cases where the pregnancy is unruptured and the patient is hemodynamically stable. Methotrexate acts by inhibiting DNA synthesis and cell multiplication, effectively terminating the ectopic pregnancy.(6) Two main protocols for methotrexate administration have been widely studied: the single-dose and the multiple-dose regimens.(7) The single-dose protocol involves administering a single intramuscular injection of methotrexate at a dose of 50 mg/m², while the multiple-dose protocol involves administering multiple injections of methotrexate (on days 1, 3, 5, and 7) alternating with leucovorin, a folinic acid (on days 2, 4, 6, and 8).(8, 9)

Despite the widespread use of both protocols, there is ongoing debate regarding their comparative efficacy and safety. Some studies suggest that the multiple-dose protocol may have a higher success

rate, particularly in cases with higher initial hCG levels,(10) while others report no significant difference between the two regimens. The multiple-dose protocol, however, is associated with a higher incidence of side effects, including gastrointestinal disturbances and stomatitis, which can impact patient compliance and overall treatment experience.(11) Therefore, it is essential to evaluate the comparative success rates and side effect profiles of these two protocols to guide clinical decision-making and optimize patient outcomes.

The primary objective of the present study was to compare the success rates of single-dose versus multiple-dose methotrexate protocols in the treatment of unruptured tubal ectopic pregnancy. Success was defined as achieving a serum hCG level below 5 mU/mL without the need for surgical intervention. The secondary objectives included evaluating the side effect profiles of the two protocols and identifying any potential confounding factors that could affect treatment success, such as sociodemographic, obstetric, laboratory, and sonographic variables.

2. Materials and Methods

This was a hospital based comparative study conducted in the Department of Obstetrics and Gynaecology, Vinayaka Missions Medical College & Hospital, Karaikal, Puducherry, India (tertiary care centre) between January and June 2024. The study was approved by the Institute Human Ethics Committee (IHEC), Vinayaka Missions Medical College & Hospital. The Participant Information Sheet (PIS) was translated into the local language (Tamil) and given to the participants (and their attendants). The information was also verbally explained to them in their native language until they fully understood it. Participants were included in the study after they provided written informed consent. Initially, all women underwent transvaginal ultrasound evaluation and measurements of hCG levels. Those identified with ectopic pregnancy were then recruited for the study. The diagnosis of ectopic pregnancy was established based on the positive identification of an adnexal mass via transvaginal ultrasound. This diagnosis required the presence of one of two gray-scale findings: a heterogeneous mass or ‘blob sign’ adjacent to and moving independently of the ovary; or a mass with a hyperechoic ring surrounding the gestational sac (bagel sign). Additionally, the diagnosis was confirmed by an abnormal rise in serum hCG (<50% increase over two consecutive days) or plateau (<15% decline within three days). The definitive diagnosis of ectopic pregnancy combined the positive transvaginal ultrasound findings with an abnormal serum hCG trajectory (either a rise or plateau).(12-15) Eligibility criteria for methotrexate treatment included hemodynamic stability, serum hCG levels that either plateaued or increased by no more than 50% over a 48-hour period, the presence of an adnexal mass with a diameter of 3.5 cm or less, no history of previous tubal surgery, the patient's desire for future pregnancy, and their willingness to participate in the study. Patients were excluded if they were clinically unstable, had hepatic or renal diseases, or were unwilling to participate.

The enrolled women (n = 40) were grouped as, Group A (n = 20, receiving single intramuscular dose of 50mg/m2 methotrexate) and Group B (n = 20, receiving multiple doses of methotrexate). During the follow-up period, hCG levels were measured on days 0, 4, and 7 after administering methotrexate. Patients showing a 15% reduction in hCG levels between days 4 and 7 were deemed to have responded positively and continued weekly outpatient monitoring until hCG levels dropped below 5 mU/mL. If the 15% decrease did not occur between days 4 and 7, or during subsequent weekly checks, an additional methotrexate dose was administered. Group II received methotrexate at 1 mg/kg on days 1, 3, 5, and 7, along with leucovorin at 0.1 mg/kg on days 2, 4, 6, and 8. hCG levels were measured at the start (day 0) and on days 1, 3, 5, and 7 until a 15% decline from the previous measurement was achieved. A positive response was defined as a 15% reduction in hCG levels within 48 hours or after four methotrexate doses. All patients with a positive response were considered successfully treated and were monitored weekly until hCG levels were below 5 mU/mL. Success was defined as achieving hCG levels below 5 mU/mL, either after a single methotrexate injection in Group I or after completing four doses in Group II.

The collected data was manually entered into Microsoft Excel, where it was coded, recoded, and then analysed using SPSS version 23. Frequencies and percentages were used to summarize all categorical variables. Continuous variables were described using the mean (standard deviation) and/or median (interquartile range), depending on the results of data normality tests (Kolmogorov–Smirnov and Shapiro–Wilk tests). The Chi-square test or Fisher exact test was employed to determine statistical significance for categorical variables, while the independent t-test was used for continuous outcomes. A p-value of less than 0.05 was considered statistically significant.

3. Results

In the present study, a total of 52 women were assessed for eligibility – 40 women were enrolled – 20 in Group A receiving single intramuscular dose of 50mg/m2 methotrexate and 20 in Group B receiving multiple doses of methotrexate. The baseline characteristics of the present study showed that the mean (SD) age of women in Group A was 29.9 years (5.2) and that in Group B was 31.1 years (6.8) – the difference was not found to be statistically significant. The mean (SD) gravida and parity was found to be 2.3 (1.1) and 1.2 (1.1) in Group A respectively; and that in Group B was 2.4 (1.2) and 1.3 (1.1), respectively. However, the study groups did not vary significantly was gravida or parity ($p>0.05$). The mean (SD) gestational age among women in Group A was 53.5 days (12.5), and that among women in Group B was 54.2 days (13.1) – the difference was not found to be statistically significant ($p>0.05$). The mean (SD) hCG levels on admission in Group A was 2011.0 IU/L (2267.0); and that in Group B was 2314.2 IU/L (2634.6). The study groups did not vary significantly by hCG levels on admission ($p>0.05$). The mean (SD) size of mass on sonograph was 24.7 mm (9.9) in Group A and 24.2 mm (10.6) in Group B – the difference between the study groups was not statistically significant ($p>0.05$).

Of the 20 patients in Group A, 16 patients (80.0%) had successful outcomes; and of the 20 patients in Group B, 18 patients (90.0%) had successful outcomes. Additionally, we analysed for possible confounding factors affecting the success rate of single dose (Group A) and multiple dose (Group B) methotrexate therapy for unruptured tubal ectopic pregnancy. The results showed that none of the sociodemographic variables (including age (in years)), obstetric variables (including gravida, parity, gestational age), laboratory variables (including hCG (in IU/L)), sonographic variables (including size of mass on sonograph (in mm) varied significantly between the patients in Group A and Group B with successful outcomes ($p>0.05$).

4. Discussion

The aim of the present study was to compare the success rates of single versus multiple dose methotrexate protocols for the treatment of unruptured tubal ectopic pregnancy. The baseline characteristics of the participants, including age, gravida, parity, gestational age, and hCG were comparable between the two groups, ensuring that the differences in outcomes were not influenced by these variables. The similarity in baseline characteristics strengthens the validity of our comparison between the two methotrexate protocols. These findings are consistent with diagnostic criteria for ectopic pregnancy, and their similarity between groups further supports the comparability of the two cohorts.(16)

The present study compared the success rates of single-dose versus multiple-dose methotrexate protocols in treating unruptured tubal ectopic pregnancy. Our findings indicate that both protocols are highly effective, with successful outcomes in 80.0% of patients in the single-dose group (Group A) and 90.0% in the multiple-dose group (Group B). Although the success rate was slightly higher in Group B, the difference was not statistically significant. Importantly, no sociodemographic, obstetric, laboratory, or sonographic variables were identified as confounding factors affecting the success rates between the two groups.

Our findings are consistent with previous studies comparing methotrexate protocols for ectopic pregnancy. Sindiani et al. (2020) reported that the single-dose methotrexate protocol had a success rate

ranging from 65% to 95%,(17) while Pirog et al. (2024) noted that the multiple-dose protocol had a success rate ranging from 85% to 95%.(18) The success rates observed in our study fall within these ranges, confirming that both protocols are effective options for the medical management of ectopic pregnancy.

Alur-Gupta et al. (2019) conducted a meta-analysis comparing single-dose and multiple-dose methotrexate protocols, finding similar efficacy between the two treatments but noting a higher incidence of side effects in the multiple-dose group.(19) Our study also found a higher success rate for the multiple-dose protocol but observed more side effects in this group, reinforcing the need to consider side effects when choosing a treatment regimen.(20) Furthermore, our analysis showed that none of these variables significantly affected the success rates of the single-dose and multiple-dose methotrexate protocols. This indicates that the efficacy of methotrexate is robust across different patient demographics and clinical presentations, making it a versatile option for the treatment of ectopic pregnancy. Given the comparable success rates and the higher incidence of side effects in the multiple-dose group, clinicians should carefully consider patient-specific factors when selecting a treatment protocol.(21-23) The single-dose protocol may be preferred for patients who are less tolerant of side effects or who may have difficulty adhering to the multiple-dose regimen due to logistical challenges. Conversely, the multiple-dose protocol may be more suitable for patients with higher initial hCG levels or those who do not respond adequately to the single-dose protocol. This tailored approach can help optimize treatment outcomes while minimizing adverse effects, thereby enhancing patient satisfaction and compliance.

This study has several strengths, including its prospective design, rigorous follow-up, and comprehensive analysis of potential confounding factors. However, there are limitations to consider. The sample size was relatively small, which may limit the generalizability of the findings. Additionally, the study was conducted at a single tertiary care centre, and the results might not be applicable to other settings with different patient populations or resource availability. Future studies with larger, multi-centre cohorts are needed to confirm these findings and provide more robust evidence on the optimal methotrexate protocol for ectopic pregnancy.

5. Conclusion

The present study compared the efficacy of single-dose versus multiple-dose methotrexate protocols in the treatment of unruptured tubal ectopic pregnancy. Our findings demonstrate that both protocols are highly effective, with success rates of 80.0% for the single-dose group and 90.0% for the multiple-dose group, though the difference was not statistically significant. Importantly, no sociodemographic, obstetric, laboratory, or sonographic variables were found to significantly influence the success rates of either protocol. Both treatment regimens were generally well-tolerated, but the multiple-dose protocol was associated with a higher incidence of side effects. Given these findings, the choice between single-dose and multiple-dose methotrexate should be tailored to the individual patient's clinical condition, preferences, and ability to adhere to the treatment regimen. Clinicians should consider the higher side effect profile of the multiple-dose protocol and weigh this against its slightly higher success rate when making treatment decisions. Future research with larger, multi-centre cohorts is necessary to further validate these findings and refine treatment guidelines for the medical management of ectopic pregnancy.

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Tables and Figures:

Table 1: Baseline characteristics of the study groups

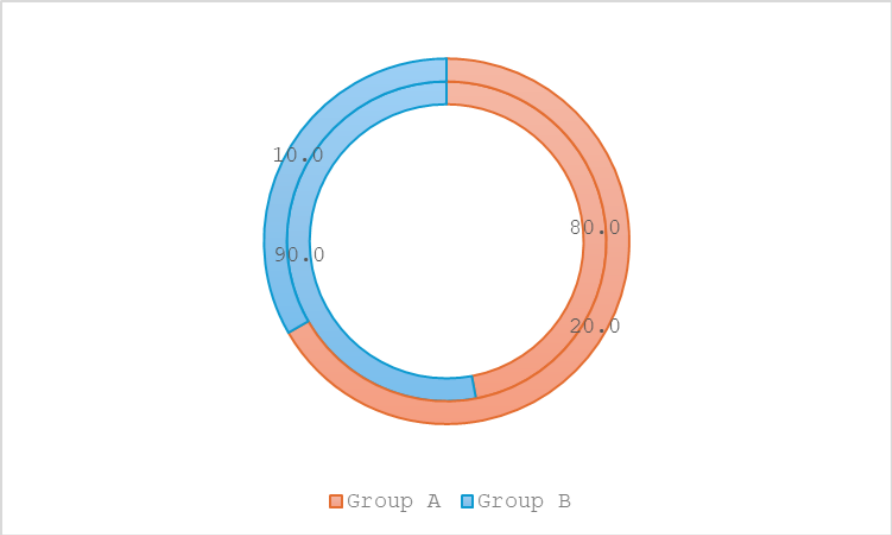
	Group A N = 20	**Group B N = 20**	**P value**
	Mean (SD)	**Mean (SD)**	
Age (in years)	29.9 (5.2)	31.1 (6.8)	0.535
Gravida	2.3 (1.1)	2.4 (1.2)	0.785
Parity	1.2 (1.1)	1.3 (1.1)	0.775
Gestational age (in days)	53.5 (12.5)	54.2 (13.1)	0.864
hCG on admission (in IU/L)	2011.0 (2267.0)	2314.2 (2634.6)	0.698
Size of mass on sonograph (in mm)	24.7 (9.9)	24.2 (10.6)	0.878
*Statistically significant at p<0.05 SD, Standard deviation; hCG, Human chorionic gonadotropin			

Table 2: Comparison of study groups, by outcome

		Group A N = 20	**Group B N = 20**	**P value**
		n (%)	**n (%)**	
Outcome	Successful	16 (80.0)	18 (90.0)	0.376
	Not successful	4 (20.0)	2 (10.0)	
*Statistically significant at p<0.05				

Table 3: Comparison of successful outcomes in Group A and Group B by patient characteristics (sociodemographic obstetric, laboratory, and sonographic)

		Group A N = 16	**Group B N = 18**	**P value**
		n (%)	**n (%)**	
Age (in years)	<30	6 (37.5)	6 (33.3)	0.799
	>30	10 (62.5)	12 (66.7)	
Gravida	<2	8 (50.0)	9 (50.0)	1.000
	>2	8 (50.0)	9 (50.0)	
Parity	<1	10 (62.5)	11 (61.1)	0.934
	>1	6 (37.5)	7 (38.9)	
Gestational age	<48	9 (56.3)	8 (44.4)	0.492
	>48	7 (43.7)	10 (55.6)	
hCG (in IU/L)	<800	7 (43.7)	10 (55.6)	0.492
	>800	9 (56.3)	8 (44.4)	
Size of mass on sonograph (in mm)	<20	5 (31.3)	10 (55.6)	0.154
	>20	11 (68.7)	8 (44.4)	
*Statistically significant at p<0.05				



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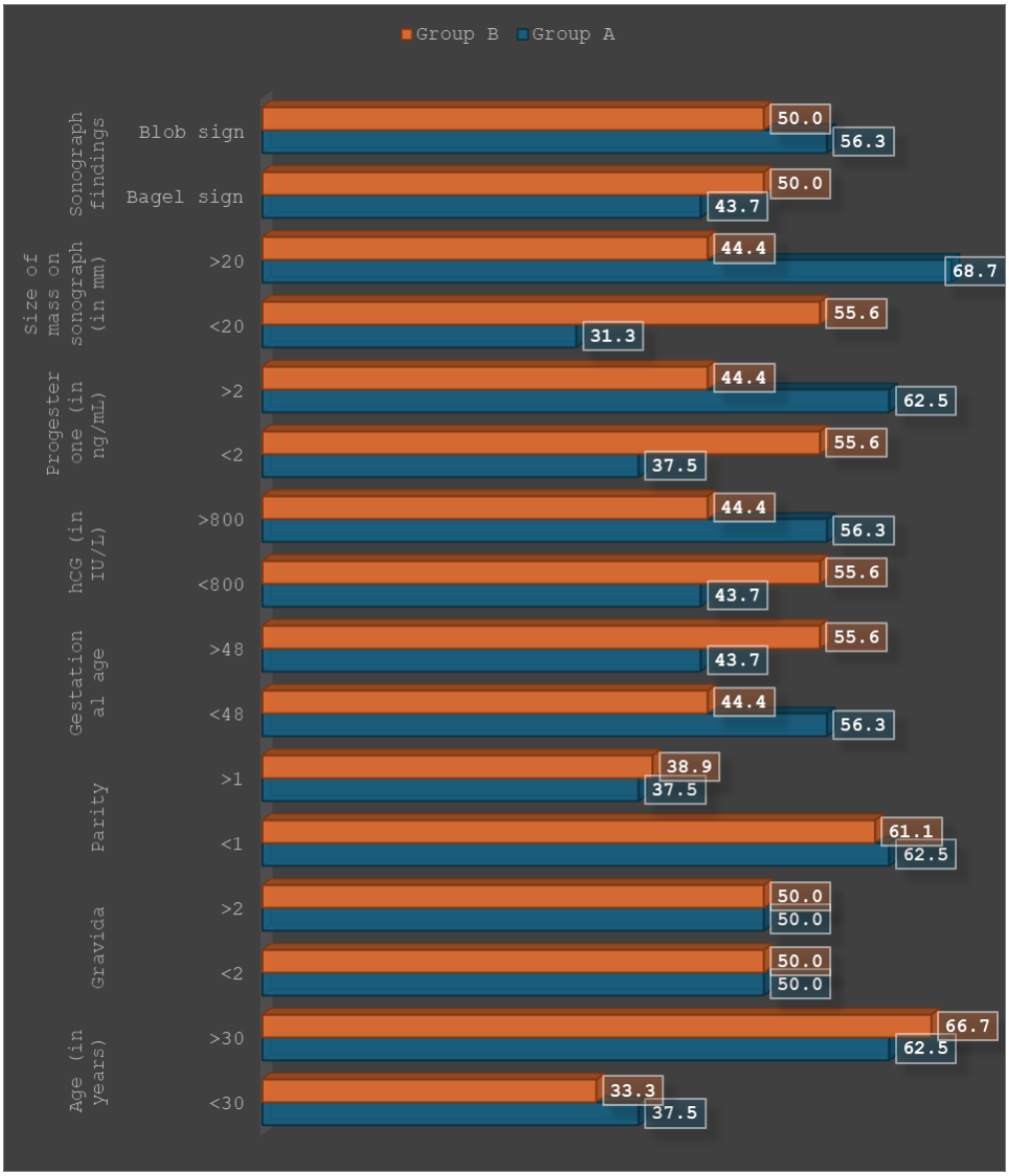

Figure 2: Comparison of successful outcomes in Group A and Group B by patient characteristics (sociodemographic obstetric, laboratory, and sonographic)