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ORIGINAL ARTICLE

Clinical Outcome & Side Effect of Methotrexate in the Treatment of Unruptured Tubal Ectopic Pregnancy in a Tertiary Care Hospital

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ABSTRACT

Background: *Ectopic pregnancy is a major cause of maternal morbidity & mortality during early gestation. Methotrexate therapy offers a conservative, fertility-preserving alternative for unruptured tubal ectopic pregnancies; however, outcomes vary across populations.* ***Objectives:*** *This study aimed to evaluate the clinical outcomes and side effects of methotrexate in treating unruptured tubal ectopic pregnancy at a tertiary care hospital in Bangladesh.* ***Methods & Materials:*** *This prospective observational study was conducted at the Department of Obstetrics and Gynecology, Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh, from July 2024 to June 2025. A total of 100 hemodynamically stable women diagnosed with unruptured tubal ectopic pregnancy were treated with intramuscular methotrexate (50 mg/m^2). Serum β-hCG was monitored on days 4 and 7; success was defined as a ≥15% decline between these intervals and complete resolution without surgery. Data were analyzed using SPSS version 25.0.* ***Results:*** *The overall treatment success rate was 82%, with 72% of patients achieving resolution after a single dose and 10% requiring a second dose. Mean β-hCG resolution time was 31.6 ± 8.7 days. Significant predictors of success included baseline β-hCG levels <5000 mIU/mL (p = 0.02) and ectopic mass size <4.0 cm (p = 0.03). Adverse effects were mild, with abdominal pain (28%) and nausea/vomiting (22%) being the most common.* ***Conclusion:*** *Methotrexate is a highly effective, safe, and well-tolerated non-surgical option for appropriately selected patients with unruptured tubal ectopic pregnancy in tertiary care settings.*

Keywords: *Methotrexate, ectopic pregnancy, clinical outcomes, side effects, β-hCG, TVS*

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INTRODUCTION

Ectopic pregnancy remains one of the most significant causes of maternal morbidity and mortality in early gestation, accounting for approximately 1–2% of all pregnancies worldwide [1,2]. Among ectopic gestations, more than 95% occur within the fallopian tubes, often leading to life-threatening complications if undiagnosed or untreated [3]. The evolution of diagnostic tools such as transvaginal ultrasonography and serial serum β-hCG measurement has enabled earlier detection of unruptured cases, facilitating conservative management approaches [4,5].

Methotrexate, an antimetabolite and folic acid antagonist, has become the cornerstone of medical management for unruptured tubal ectopic pregnancies. Its mechanism involves inhibition of DNA synthesis in rapidly dividing trophoblastic cells, leading to resorption of ectopic tissue while preserving tubal integrity [6]. The success rate of single-dose methotrexate ranges between 80–95%, depending on initial β-hCG levels, ectopic mass size, and patient selection [7,8]. For patients with β-hCG values below 5000 mIU/mL, mass size less than 3.5–4 cm, absence of fetal heart beat and no pelvic collection, methotrexate offers a safe and effective alternative to surgery, minimizing the risk of future infertility [9,10].

While methotrexate therapy has shown remarkable success globally, variability in outcomes exists across populations due to genetic, environmental, and healthcare system differences [11]. Studies have demonstrated that elevated pretreatment β-hCG levels, presence of embryonic cardiac activity, and larger ectopic size are predictive of treatment failure [12,13]. Furthermore, side effects such as abdominal pain, stomatitis, and transient hepatic enzyme elevation, though generally mild, may influence patient compliance and safety monitoring requirements [14].

In low- and middle-income countries like Bangladesh, the adoption of medical therapy for ectopic pregnancy is increasing, yet limited local data exist on treatment outcomes and adverse profiles. Most available studies are either

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retrospective or conducted in limited-resource settings, lacking uniform protocols. Consequently, understanding real-world outcomes within tertiary care centers is essential to optimize patient selection criteria and refine follow-up protocols for methotrexate use.

This study was undertaken to evaluate the clinical outcomes and side effects of methotrexate in the management of unruptured tubal ectopic pregnancy at a tertiary care hospital in Bangladesh.

OBJECTIVES

General objective:

This study aimed to evaluate clinical outcomes and side effects of methotrexate in treating unruptured tubal ectopic pregnancy at a tertiary care hospital in Bangladesh.

Specific objectives:

1. Preserving fertility potential and supporting future reproductive capability.
2. Reducing the need for surgical intervention and its associated perioperative risks.
3. Minimizing patient complications during medical management compared to surgical management.

METHODS & MATERIALS

This prospective observational study was conducted in the Department of Obstetrics and Gynecology, Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh, over a one-year period from July 2024 to June 2025. A total of 100 women diagnosed with unruptured tubal ectopic pregnancy and fulfilling the inclusion criteria were enrolled consecutively after informed consent.

Selection Criteria

Inclusion Criteria:

- Hemodynamically stable women diagnosed with unruptured tubal ectopic pregnancy.
- Serum β-hCG level ≤5,000 mIU/mL.
- Ectopic mass size ≤4 cm on transvaginal ultrasound.
- Absence of fetal cardiac activity in the adnexal mass.
- Absence of pelvic collection.
- Patients who are agree to undergo follow-up until β-hCG normalization.

Exclusion Criteria:

- Hemodynamic instability or suspected tubal rupture.
- Contraindications to methotrexate (hepatic, renal, or hematologic disorders).
- Breastfeeding mothers.
- Patients who refuse to medical management.
- Known hypersensitivity to methotrexate.

Data Collection Procedure

Patients presenting with suspected ectopic pregnancy underwent a detailed clinical assessment, transvaginal sonography, and quantitative serum β-hCG measurement. Diagnosis of unruptured tubal ectopic pregnancy was confirmed based on sonographic evidence of an adnexal mass without intrauterine gestation and rising or plateaued β-hCG levels. Eligible participants received a single-dose intramuscular methotrexate regimen (50 mg/m^2). Serum β-hCG levels were monitored on days 4 and 7 post-injection to assess the percentage decline. A second dose was administered if the decrease in β-hCG between days 4 and 7 was <15%. Surgical management was indicated if β-hCG continued to rise, if the patient developed abdominal pain with signs of rupture, or if follow-up revealed treatment failure.

All clinical data, laboratory values, and ultrasonographic findings were recorded in a structured proforma. Follow-up continued until β-hCG returned to non-pregnant levels. Adverse effects such as abdominal discomfort, stomatitis, or hepatic enzyme elevation were documented and managed symptomatically. Informed consent was obtained from all patients, and confidentiality of patient data was strictly maintained.

Statistical Analysis

Data were analyzed using SPSS version 25.0. Descriptive statistics were expressed as mean ± standard deviation (SD) for continuous variables and frequency with percentage for categorical data. The Chi-square test and Fisher's exact test were used for categorical associations. A p-value <0.05 was considered statistically significant.

RESULTS

Table – I: Baseline Characteristics of Study Participants (*n* = 100)

Variable	Category	Frequency (n)	Percentage (%)
Age (years)	Mean± SD	29.4 ± 4.7	
Gravida	Primigravida	38	38.0
	Multigravida	62	62.0
Previous Ectopic Pregnancy	Yes	12	12.0
	No	88	88.0
Initial Serum β-hCG (mIU/mL)	<2000	45	36.0
	2000–5000	55	44.0
Ectopic Mass Size (cm)	<3.0	68	60.0
	3.0–4.0	32	28.0

Table I presents the demographic and clinical characteristics of 100 patients diagnosed with unruptured tubal ectopic pregnancy and managed with methotrexate. The majority of patients were aged between 26–30 years (34%), with a mean age of 29.4 ± 4.7 years. Most were multigravida (62%), and only 12% reported a previous ectopic pregnancy. Serum β-hCG levels were <2000 mIU/mL in 45% of participants and 2000-5000 in 55% patients. The ectopic mass size was <3.0 cm in 68% of cases and 3.0-4.0 in 32% cases.

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Table – II: Treatment Outcomes Following Methotrexate Therapy

Outcome Variable	Category	Frequency (n)	Percentage (%)
Mean Time to Resolution (days)		31.6 ± 8.7	
Mean β-hCG Decline (Day 4–7)	≥15%	86	86.0
	<15%	14	14.0
Side of Ectopic Mass	Right tube	58	58.0
	Left tube	42	42.0

Table II outlines the outcomes following methotrexate administration. The mean time to serum β-hCG resolution was 31.6 ± 8.7 days. A ≥15% β-hCG decline between days 4–7 was observed in 86% of cases, indicating an effective early response. The right fallopian tube was more commonly affected (58%) than the left (42%).

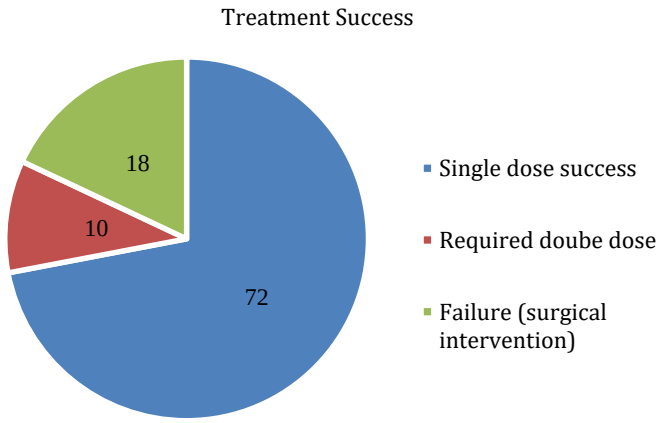

Figure – 1: Distribution of Treatment Outcomes Following Methotrexate Therapy

Treatment success was achieved in 82% of cases, of which 72% responded to a single-dose regimen, and 10% required a second dose. Eighteen patients (18%) failed medical therapy and underwent surgery.

Table – III: Correlation Between Pre-Treatment Factors and Treatment Success

Variable	Category	Treatment Success (%)	Treatment Failure (%)	p-value
Serum β-hCG (mIU/mL)	<2000	90.2	9.8	0.02
	2000-5000	60.0	40.0	
Ectopic Size (cm)	<3.0	88.0	12.0	0.03
	3.0-4.0	64.0	36.0	
Parity	Primigravida	81.6	18.4	0.47
	Multigravida	77.4	22.6	

Table III demonstrates the relationship between pre-treatment variables and treatment success. A significant association was found between lower initial β-hCG (<2000 mIU/mL) and higher treatment success (90.2%) compared with patients having β-hCG 2000-5000 mIU/mL (60.0%) (p = 0.02). Similarly, a smaller ectopic mass size (<3.0 cm) was associated with better outcomes (p = 0.03).

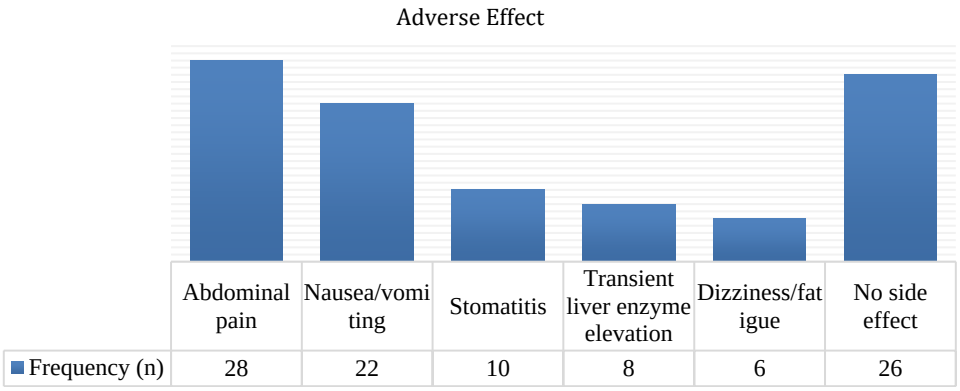

Figure – 2: Adverse Effects Observed After Methotrexate Administration

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Figure 2 illustrates the side effects experienced following methotrexate administration. The most common adverse effects were abdominal pain (28%) and nausea/vomiting (22%), followed by stomatitis (10%) and mild transient elevation of liver enzymes (8%). No patients experienced serious systemic toxicity, hepatic dysfunction requiring discontinuation, or hematologic suppression.

DISCUSSION

The present prospective observational study evaluated the clinical outcomes and side effects of methotrexate therapy in women with unruptured tubal ectopic pregnancy at a tertiary care center in Bangladesh. The overall treatment success rate of 82% is consistent with findings from several international studies that have reported success rates between 80% and 95% among appropriately selected patients [1,7]. This high efficacy emphasizes the importance of early diagnosis, proper patient selection, and adherence to standard treatment protocols in optimizing outcomes for medical management of ectopic pregnancy.

The mean time to resolution of β-hCG (31.6 ± 8.7 days) observed in this study corresponds closely with findings by Davenport et al., who reported a mean resolution period of 32.4 days in a large retrospective cohort [15]. A rapid β-hCG decline of ≥15% between days 4 and 7 post-treatment, seen in 86% of participants, was an early predictor of treatment success—consistent with Mackenzie et al., who established early β-hCG reduction as a strong prognostic marker [13]. The small subset of treatment failures (12%) primarily included patients with higher initial β-hCG levels (>5000 mIU/mL) and ectopic mass size <4.0 cm, reaffirming the predictive value of these factors, as reported by Abdelfattah-Arafa et al. and Tang et al. [11,12].

The correlation analysis in this study confirmed that both initial β-hCG levels and ectopic mass size significantly influenced treatment outcomes ($p < 0.05$). These findings corroborate prior evidence that lower β-hCG levels and smaller gestational mass sizes are favorable predictors for successful methotrexate therapy [6,8]. Several meta-analyses, including Solangon et al., have emphasized that women with β-hCG <5000 mIU/mL and mass size <3.5 cm are the best candidates for medical management [5]. This reinforces the clinical relevance of stringent selection criteria to prevent treatment failure and potential complications such as tubal rupture.

The absence of a statistically significant association between parity and treatment success in the present study aligns with findings from Scarpelli et al., who reported that parity does not independently influence methotrexate response once baseline β-hCG and mass size are accounted for [10].

Regarding adverse effects, methotrexate was generally well tolerated, with only mild side effects such as abdominal pain (28%) and nausea/vomiting (22%). These rates are comparable with the study by Lodha and Mali who documented similar minor gastrointestinal and mucosal toxicities [14]. The incidence of mild transient hepatic enzyme elevation (8%) in this cohort was within the expected range and self-limiting, as also described by Revzin et al. [4]. Importantly, no major hematologic or hepatic toxicity was observed, underscoring the safety of single-dose methotrexate in hemodynamically stable patients with careful monitoring.

The success rate of methotrexate therapy in the present study is comparable to studies from South and Southeast Asia, including Khakwani et al. in Pakistan (84% success) and Omar et al. in Malaysia (87% success) [9,16]. Regional consistency in outcomes may be attributed to similar demographic profiles, early presentation, and standardized management guidelines. However, studies involving higher baseline β-hCG populations, such as Keikha et al., have reported slightly lower success rates, supporting the need for individualized dosing strategies [7]. The observation that 10% of participants required a second dose before achieving success aligns with the double-dose success rates reported by Helvacıoğlu & Doğan and Pourali et al. [8,17].

Overall, the findings of this study strengthen the existing evidence that methotrexate is an effective and well-tolerated option for treating unruptured tubal ectopic pregnancies. By contributing local data from Bangladesh, this study addresses a critical knowledge gap in the regional literature, highlighting that standardized medical management protocols can achieve globally comparable outcomes, even within developing healthcare settings.

CONCLUSION

Methotrexate therapy for unruptured tubal ectopic pregnancy demonstrated a high success rate and minimal side effects in this study. Lower baseline β-hCG levels and smaller ectopic mass sizes were significant predictors of treatment success. These findings reinforce the role of MTX as a safe, effective, and fertility-preserving alternative to surgery when applied under strict selection and monitoring protocols in tertiary care centers.

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Conflicts of interest

There are no conflicts of interest.

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