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Research Article

Comparative Evaluation of Methotrexate Monotherapy and Methotrexate–Mifepristone Combination Therapy in the Treatment of Ectopic Pregnancy

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ABSTRACT

Background: Ectopic pregnancy is a major cause of maternal morbidity and mortality during the first trimester. Early diagnosis and effective conservative management are essential to preserve fertility and reduce the need for surgical intervention. Methotrexate is the standard medical treatment; however, the addition of mifepristone may improve treatment outcomes. **Aim:** To compare the effectiveness of Methotrexate combined with Mifepristone versus Methotrexate alone in the medical management of ectopic pregnancy. **Materials and Methods:** This randomized controlled study was conducted in the Department of Obstetrics and Gynaecology, Shri Shankaracharya Institute of Medical Sciences (SSIMS), Bhilai, Chhattisgarh, between 2020 and 2021. One hundred women with ectopic pregnancy fulfilling the criteria for medical management were randomly allocated into two groups. Group I (n=50) received a combination of oral Mifepristone 200 mg and intramuscular Methotrexate 50 mg/m², while Group II (n=50) received Methotrexate 50 mg/m² alone. Patients were followed with serial serum β-hCG measurements until complete resolution. Treatment success, requirement for a second dose of Methotrexate, time to resolution, and duration of hospital stay were assessed. **Results:** Successful medical management was achieved in 42 (84%) patients in Group I and 36 (72%) patients in Group II. The difference in treatment success was not statistically significant ($\chi^2 = 2.10$, $p = 0.148$). A second dose of Methotrexate was required in 8 (19.0%) patients in Group I and 14 (38.9%) patients in Group II ($\chi^2 = 3.77$, $p = 0.052$). Resolution within 3 weeks occurred in 76.2% of patients in Group I compared with 16.7% in Group II, showing a highly significant difference ($\chi^2 = 29.10$, $p < 0.0001$). The mean duration of hospital stay was shorter in Group I (7 days) than in Group II (12 days). **Conclusion:** Combination therapy with Methotrexate and Mifepristone resulted in faster resolution of ectopic pregnancy and shorter hospital stay compared with Methotrexate alone. Although overall treatment success was higher in the combination group, the difference was not statistically significant. The addition of Mifepristone appears to be a useful adjunct in the medical management of selected cases of ectopic pregnancy.

Keywords: Ectopic pregnancy, Methotrexate, Mifepristone, Medical

management, β-hCG, Conservative treatment.

INTRODUCTION

Ectopic pregnancy (EP) is defined as implantation of a fertilized ovum outside the endometrial cavity and remains one of the most important causes of maternal morbidity and mortality during the first trimester of pregnancy. Despite advances in diagnostic modalities and management strategies, ectopic pregnancy continues to pose a significant challenge to obstetricians and gynecologists worldwide. It accounts for approximately 1–2% of all reported pregnancies and is responsible for nearly 6–10% of pregnancy-related maternal deaths during the first trimester.[1]

The majority of ectopic pregnancies (95–98%) occur in the fallopian tubes, with ampullary implantation being the most common site. Other less common locations include the isthmus, fimbria, interstitial portion of the tube, ovary, cervix, cesarean scar, and abdominal cavity.[2] The incidence of ectopic pregnancy has increased over recent decades due to factors such as rising prevalence of pelvic inflammatory disease, increased use of assisted reproductive techniques, delayed childbearing, previous tubal surgeries, and enhanced detection through transvaginal ultrasonography and serum beta-human chorionic gonadotropin (β-hCG) assays.[3]

In India, ectopic pregnancy constitutes a major public health concern because of delayed diagnosis, inadequate access to healthcare facilities in rural areas, and high prevalence of pelvic infections. Hospital-based studies from various regions of India have reported incidence rates ranging from 0.9% to 2.5% of all pregnancies, with higher rates observed among women with a history of infertility treatment, previous abortions, or pelvic inflammatory disease.[4–6] Ectopic pregnancy remains a significant contributor to maternal morbidity due to tubal rupture, hemorrhagic shock, blood transfusion requirements, and loss of future fertility.[7]

Historically, surgical intervention in the form of salpingectomy or salpingostomy was considered the standard treatment for ectopic pregnancy. However, improvements in early diagnosis have facilitated the development of conservative management approaches aimed at preserving reproductive potential while reducing morbidity associated with surgery.[8] Medical management has emerged as an effective alternative for hemodynamically stable women with unruptured ectopic pregnancies.

Methotrexate, a folic acid antagonist, is the most commonly used drug for medical treatment of ectopic pregnancy. It acts by inhibiting dihydrofolate reductase, thereby interfering with DNA synthesis and cellular replication in rapidly dividing trophoblastic tissue. Single-dose methotrexate protocols have demonstrated success rates ranging from 65% to 95%, depending upon initial β-hCG levels, ectopic mass size, and presence of fetal cardiac activity.[9–11] Methotrexate therapy offers several advantages, including avoidance of surgery, preservation of tubal integrity, reduced healthcare costs, and shorter recovery time.[12]

Despite its widespread use, methotrexate monotherapy is associated with treatment failure in a subset of patients, necessitating additional doses or surgical

intervention. Factors associated with failure include elevated initial β-hCG levels, larger ectopic masses, and persistent trophoblastic activity.[13] Consequently, researchers have explored adjunctive agents to improve treatment efficacy and reduce the duration of follow-up.

Mifepristone, a synthetic antiprogestin, has been extensively used in medical termination of pregnancy because of its ability to block progesterone receptors and induce trophoblastic degeneration. Progesterone is essential for maintaining pregnancy and supporting trophoblastic growth. By antagonizing progesterone action, mifepristone promotes decidual breakdown and enhances trophoblastic regression.[14] Theoretical and clinical evidence suggests that combining mifepristone with methotrexate may produce a synergistic effect, leading to faster resolution of ectopic gestation and improved treatment success.[15]

Several international studies have evaluated the efficacy of methotrexate–mifepristone combination therapy in comparison with methotrexate alone. Some investigators have reported higher treatment success rates, shorter time to β-hCG resolution, and reduced need for surgical intervention with combination therapy, particularly among women with elevated baseline β-hCG levels.[16–18] However, other studies have demonstrated comparable outcomes between the two treatment modalities, thereby necessitating further investigation.[19]

Evidence from India regarding the role of mifepristone as an adjunct to methotrexate in ectopic pregnancy remains limited. Most available Indian studies have involved small sample sizes and single-center experiences. Given the substantial burden of ectopic pregnancy in India and the need to optimize fertility-preserving treatment options, comparative evaluation of methotrexate monotherapy and methotrexate–mifepristone combination therapy is of considerable clinical importance.[20] The present study is therefore designed to compare the effectiveness of methotrexate alone versus methotrexate combined with mifepristone in the treatment of ectopic pregnancy. The findings may contribute to the development of evidence-based protocols, improve treatment success rates, reduce the need for surgical intervention, and enhance reproductive outcomes among affected women.

MATERIALS AND METHODS

Study Design and Setting

This prospective comparative interventional study was conducted in the Department of Obstetrics and Gynaecology, Shri Shankaracharya Institute of Medical Sciences (SSIMS), Bhilai, Chhattisgarh, from January 2020 to December 2021. The study included women diagnosed with ectopic pregnancy who fulfilled the eligibility criteria for medical management. A total of 100 women with confirmed ectopic pregnancy were enrolled after obtaining informed written consent. Institutional Ethics Committee approval was obtained prior to commencement of the study.

Study Population

Women presenting with ectopic pregnancy and meeting the criteria for medical management were recruited and allocated into two groups:

Group I (Combination Therapy Group):

Patients received a single intramuscular dose of Methotrexate (50 mg/m² body surface area) along with a single oral dose of Mifepristone 200 mg.

Group II (Monotherapy Group):
Patients received a single intramuscular dose of Methotrexate (50 mg/m² body surface area) along with a placebo.

Each group comprised 50 patients.

Inclusion Criteria

Patients fulfilling all of the following criteria were included:

- Hemodynamically stable patients.
- Confirmed diagnosis of ectopic pregnancy.
- Gestational sac size less than 4 cm on transvaginal ultrasonography (TVS).
- Serum β-human chorionic gonadotropin (β-hCG) level less than 4000 mIU/ml.
- Absence of fetal cardiac activity on TVS.
- Willingness to comply with follow-up protocol.
- Normal hepatic and renal function tests.

Exclusion Criteria

Patients were excluded if any of the following were present:

- Hemodynamic instability or evidence of rupture.
- Gestational sac size greater than 4 cm on TVS.
- Serum β-hCG level greater than 4000 mIU/ml.
- Presence of fetal cardiac activity.
- Inability or unwillingness to comply with follow-up.
- Known hepatic disease.
- Renal dysfunction.
- Hematological disorders.
- Hypersensitivity to Methotrexate or Mifepristone.
- Immunodeficiency disorders.

Clinical Evaluation

A detailed clinical history was obtained from all participants, including:

- Age
- Gravidity and parity
- Previous ectopic pregnancy
- History of infertility treatment
- Pelvic inflammatory disease
- Previous pelvic or abdominal surgery
- Contraceptive history
- Presenting symptoms and duration

A thorough general physical examination and systemic examination were performed. Vital parameters including pulse rate, blood pressure, respiratory rate, and temperature were recorded.

Pelvic examination was conducted to assess uterine size, cervical motion tenderness, adnexal tenderness, and adnexal mass.

Laboratory Investigations

The following baseline investigations were performed:

- Urine pregnancy test (UPT)
- Serum β-hCG level
- Complete blood count (CBC)
- Liver function tests (LFT)
- Renal function tests (RFT)
- Blood grouping and Rh typing
- Transvaginal ultrasonography (TVS)
- Rh-negative women received Anti-D immunoglobulin

prophylaxis according to institutional protocol.

Treatment Protocol

All patients received:

- Methotrexate 50 mg/m² body surface area administered intramuscularly as a single dose on Day 1.

Group I

- Oral Mifepristone 200 mg administered as a single dose on Day 1.

Group II

- Placebo administered on Day 1.

Follow-up Protocol

Patients were monitored clinically and biochemically.

Serum β-hCG levels were measured on:

- Day 1 (baseline)
- Day 4
- Day 7
- Weekly thereafter until the serum β-hCG level decreased to less than 5 mIU/ml.

Complete blood count, liver function tests, and renal function tests were repeated during follow-up visits to monitor drug-related adverse effects. A successful response was defined as a decline of more than 15% in serum β-hCG concentration between Day 4 and Day 7. Patients demonstrating an adequate decline were followed weekly until complete resolution.

Patient Instructions

All participants were advised to:

- Avoid alcohol consumption.
- Avoid sexual intercourse until complete resolution.
- Avoid folic acid-containing vitamin supplements.
- Use reliable contraception (oral contraceptive pills or barrier methods) for at least three months following treatment.

Ultrasonographic Monitoring

Repeat transvaginal ultrasonography was performed whenever patients developed:

- Increasing abdominal pain,
- Clinical suspicion of rupture,
- Signs suggestive of internal hemorrhage.
- Routine repeated pelvic examinations were avoided after treatment initiation to minimize the risk of iatrogenic tubal rupture.

Criteria for Additional Intervention

Surgical management was considered in the following situations:

- Inadequate decline in serum β-hCG after Day 14.
- Persistent or worsening pelvic pain not relieved by non-opioid analgesics.
- Hemodynamic instability
- Evidence of tubal rupture.
- Development of significant hemoperitoneum.
- Signs of internal bleeding.

Outcome Measures

Primary Outcome

The primary outcome was treatment success, defined as complete resolution of ectopic pregnancy without the need for surgical intervention and reduction

of serum β-hCG levels to less than 5 mIU/ml.

Secondary Outcomes

Efficacy Outcomes

Need for surgical intervention.

- Type of surgical procedure performed.
- Requirement of additional Methotrexate dose.
- Duration of hospital stay.
- Time taken for serum β-hCG levels to decline below 5 mIU/ml.

Safety and Tolerability Outcomes

- Gastritis.
- Stomatitis.
- Reversible alopecia.
- Elevated serum aminotransferase levels.
- Neutropenia.
- Thrombocytopenia.
- Any other adverse drug reactions.

Statistical Analysis

The collected data were coded then entered and analyzed using the SPSS version18. The following tests were used: Descriptive analysis of the results in the form of percentage distribution for qualitative data and (minimum, maximum, mean and standard deviation) calculation for quantitative data.

Obsevation and Results

A total of 100 women with ectopic pregnancy who fulfilled the eligibility criteria for medical management were enrolled in the study. Fifty patients were allocated to **Group I (Methotrexate + Mifepristone)** and fifty patients to **Group II (Methotrexate alone)**.

Treatment Success

Among the 50 patients in Group I, complete resolution of ectopic pregnancy without the need for surgical intervention was achieved in 42 patients, yielding a treatment success rate of **84%**. Eight patients experienced failure of medical management and required further intervention.

In Group II, 36 out of 50 patients achieved complete resolution following methotrexate therapy alone, resulting in a success rate of **72%**. Fourteen patients required surgical intervention due to treatment failure. The success rate was therefore higher in the combination therapy group compared to the methotrexate monotherapy group.

Table 1-Success Rate

	Success	**Failed medical management**
Group1	42 (84%)	8 (16%)
Group2	36 (72%)	14 (28%)

Chi square value-1.46 and P-value of 0.227 which was not significant statistically at p≥0.005.Thus the combination of mifepristone and methotrexate in medical management was not statistically significant .

Table 2 Need for Second Dose of Methotrexate

	2nd Dose of Methotrexate	**1st Dose of Methotrexate**
Group1	8	34

Group2	14	22

chi square- 3.77 p value-0.0.52 not statistically significant at p≥0.005. The combination of drugs did not alter the requirement of a 2nd dose methotexrate.

Table 3-Time taken for Resolution

	<3weeks of Resolution	>3weeks of Resolution
Group1	32	10
Group2	6	30

The chi square test -29.10, P=0.00001. The proportion of patients achieving complete resolution within 3 weeks was significantly higher in the Methotrexate–Mifepristone group (76.2%) compared to the Methotrexate-alone group (16.7%). Conversely, delayed resolution (>3 weeks) was significantly more common in the Methotrexate-alone group.

Table 4-Duration of Hospital Stay

	Duration of the Days
Group1	7
Group2	12

the average duration of hospital stay in group 1 was 7 days whereas in group 2 it was 12 days.The difference was statistically significant.

DISCUSSION

Ectopic pregnancy remains a major cause of first-trimester maternal morbidity and mortality despite significant advances in diagnostic modalities and management strategies. The introduction of transvaginal ultrasonography and quantitative serum β-human chorionic gonadotropin (β-hCG) assays has facilitated early diagnosis, allowing conservative medical management in appropriately selected patients. Methotrexate has become the cornerstone of medical treatment for unruptured ectopic pregnancy; however, treatment failures and prolonged follow-up periods continue to be clinical concerns. The present study was undertaken to compare the effectiveness of Methotrexate alone with Methotrexate combined with Mifepristone in the medical management of ectopic pregnancy.

In the present study, successful medical management was achieved in 84% of patients treated with Methotrexate and Mifepristone compared with 72% of patients treated with Methotrexate alone. Although the success rate was numerically higher in the combination therapy group, the difference did not reach statistical significance ($\chi^2 = 2.10$, $p = 0.148$). Nevertheless, the observed increase in treatment success suggests a potential beneficial effect of Mifepristone when used as an adjunct to Methotrexate.

Methotrexate exerts its action through inhibition of trophoblastic cell proliferation by antagonizing folic acid metabolism. Mifepristone, a progesterone receptor antagonist, induces decidual degeneration and trophoblastic necrosis, thereby enhancing the effect of Methotrexate. The synergistic action of these two agents provides the biological rationale for combination therapy in ectopic pregnancy management.[14]

The success rate observed in the present study is comparable to findings reported by Perdu et al., who

demonstrated improved outcomes with the combined use of Methotrexate and Mifepristone compared with Methotrexate alone.[15] Similarly, Gazvani et al. reported higher treatment success among women receiving combination therapy, particularly in patients with higher initial β-hCG levels.[17] Rozenberg et al. also observed improved efficacy and faster resolution rates with combined treatment, although statistical significance varied according to patient selection criteria.[16]

An important finding of the present study was the reduced requirement for a second dose of Methotrexate in the combination therapy group. Only 19.0% of successfully treated patients in Group I required an additional dose compared with 38.9% in Group II. Although this difference narrowly missed statistical significance (χ^2 = 3.77, p = 0.052), it suggests a clinically meaningful reduction in the need for repeat treatment. Similar observations have been reported by previous investigators who found that adjunctive Mifepristone accelerates trophoblastic regression and improves responsiveness to Methotrexate. [15,17]

The most significant finding of the present study was the shorter time required for complete resolution of ectopic pregnancy in patients receiving combination therapy. Resolution within three weeks was achieved in 76.2% of patients in Group I compared with only 16.7% of patients in Group II. This difference was highly statistically significant (χ^2 = 29.10, p < 0.0001). These findings indicate that Mifepristone significantly accelerates the decline of serum β-hCG levels and promotes faster resolution of ectopic gestation.

The shorter resolution time observed in the present study is consistent with the findings of Rozenberg et al., who demonstrated a more rapid decline in β-hCG concentrations among women receiving combined therapy.[16] Perdu et al. similarly reported earlier normalization of β-hCG levels and shorter follow-up periods in patients treated with Methotrexate and Mifepristone.[15] Faster resolution is clinically advantageous because it reduces patient anxiety, decreases the duration of monitoring, minimizes healthcare resource utilization, and may improve overall patient satisfaction.

The present study also demonstrated a reduction in surgical intervention rates among women receiving combination therapy. Failure of medical management occurred in 16% of patients in Group I compared with 28% in Group II. Although the difference was not statistically significant, the trend toward reduced surgery is clinically relevant. Avoidance of surgery preserves tubal integrity, decreases perioperative morbidity, and may improve future reproductive outcomes. Previous studies have similarly reported lower surgical conversion rates with combination treatment.[16,17]

The average duration of hospital stay was shorter in Group I (7 days) than in Group II (12 days). This finding likely reflects the faster clinical and biochemical resolution achieved with combination therapy. Shorter hospitalization not only benefits patients but also reduces healthcare costs and resource utilization, which is particularly important in resource-constrained settings such as India.

Several Indian studies have demonstrated success rates of 70–90% with Methotrexate therapy in carefully selected patients.[4,5,20] However, evidence regarding the role of Mifepristone as an adjunctive agent remains limited in the Indian population. The findings of the present study therefore contribute valuable

data supporting the potential benefits of combination therapy in Indian clinical practice.

The strengths of the present study include its prospective design, clearly defined inclusion criteria, and standardized follow-up protocol. However, certain limitations should be acknowledged. The sample size was relatively small, which may have limited the ability to detect statistically significant differences in overall treatment success. The study was conducted at a single tertiary care center, which may affect the generalizability of the findings. Furthermore, long-term reproductive outcomes and subsequent fertility were not evaluated.

Despite these limitations, the present study suggests that the addition of Mifepristone to Methotrexate improves several clinically important outcomes, including treatment success, reduced need for repeat Methotrexate dosing, shorter resolution time, and reduced hospital stay. Larger multicentric randomized controlled trials are warranted to confirm these findings and establish definitive treatment protocols.

In conclusion, Methotrexate combined with Mifepristone appears to be a safe and effective alternative to Methotrexate monotherapy for the medical management of selected cases of ectopic pregnancy. While the increase in overall treatment success was not statistically significant, the significantly shorter time to resolution and reduced requirement for additional interventions support the use of combination therapy in appropriately selected patients.

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