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Evaluation of Risk Factors and Efficacy of Methotrexate Therapy in Unruptured Ectopic Pregnancy: A Prospective Analysis from a Tertiary Care Centre in Tamil Nadu

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Abstract

Introduction: Ectopic pregnancy is a significant cause of maternal morbidity and mortality, accounting for approximately 1-2% of all pregnancies. It occurs when a fertilized egg implants outside the uterine cavity, most commonly in the fallopian tube. Methotrexate, a folic acid antagonist, has been widely used for the medical management of unruptured ectopic pregnancy, offering a non-surgical alternative that preserves fertility. This study aims to evaluate the efficacy and safety of methotrexate therapy in unruptured ectopic pregnancy and analyze the associated risk factors.

Materials and Methods: This prospective observational study was conducted at the Kanyakumari district, Tamil Nadu, from January 2023 to December 2023. A total of 34 women diagnosed with unruptured ectopic pregnancy were included based on specific inclusion criteria. The study participants were treated with either a single-dose or two-dose methotrexate regimen. Data were collected on demographic characteristics, medical history, and pretreatment β hCG levels. The primary outcome was the success rate of methotrexate therapy, while secondary outcomes included the need for surgical intervention and the incidence of side effects.

Results: The study found an overall success rate of 85.3% for methotrexate therapy, with the single-dose regimen being successful in 61.8% of cases and the two-dose regimen in 23.5%. Surgical intervention was required in 14.7% of the participants, all of whom initially received a single dose. A significant correlation was observed between pretreatment β hCG levels and treatment success, with higher success rates in women with lower β hCG levels. Mild side effects were reported in a small percentage of participants, with no major adverse events.

Conclusion: Methotrexate therapy is an effective and safe option for the medical management of unruptured ectopic pregnancy, particularly in women with low pretreatment β hCG levels. Early detection and appropriate patient selection are crucial for optimizing outcomes and minimizing the need for surgical intervention.

Keywords: Ectopic pregnancy, Methotrexate therapy, Unruptured ectopic pregnancy, β hCG levels, Risk factors, Treatment efficacy

INTRODUCTION

Ectopic pregnancy is a significant obstetric emergency that poses substantial risks to maternal health. It occurs when a fertilized ovum implants outside the uterine cavity, most commonly in the fallopian tubes. This condition can lead to severe complications, including tubal rupture, internal bleeding, and even death if not diagnosed and managed promptly. The incidence of ectopic pregnancy is approximately 1-2% of all pregnancies, with the fallopian tube being the most frequent site of implantation[1,2] (Levin, 2018, Davor et al., 2011).

Methotrexate, a folic acid antagonist, has emerged as a cornerstone in the non-surgical management of unruptured ectopic pregnancies. Since its introduction into clinical practice, methotrexate has been used effectively to induce resorption of the ectopic tissue, thereby avoiding the need for surgical intervention and preserving fertility[3] (Bruce et al., 2020). The drug acts by inhibiting rapidly dividing cells, which is crucial in halting the progression of ectopic pregnancies.

The global prevalence of ectopic pregnancy has been increasing, attributed partly to higher rates of assisted reproductive technologies, increasing maternal age, and more frequent use of intrauterine devices (IUDs)[4] (Zhang et al., 2023). In the

United States, it is estimated that one in 50 pregnancies is ectopic, while in developing countries, the incidence can be as high as 1 in 40 due to limited access to early diagnostic and therapeutic services (Bisma et al.[5], 2022).
In India, the incidence of ectopic pregnancy is reported to be rising, reflecting global trends. Factors such as pelvic inflammatory disease, previous ectopic pregnancies, and use of IUDs are known to increase the risk of ectopic implantation[6] (Mridula et al., 2017). A study conducted in a tertiary care center in Tamil Nadu reported an incidence rate of approximately 1.5%, aligning with national trends[7] (Bharathi et al., 2022).
For instance, a study by McLaren et al.[8] (2009) demonstrated a success rate of 80% for single-dose methotrexate therapy in women with unruptured ectopic pregnancies. Risk factors associated with ectopic pregnancy have been well-documented, including pelvic inflammatory disease (PID), previous ectopic pregnancies, tubal surgeries, and use of IUDs[9] (Mullany et al., 2023). Studies have also highlighted the role of advanced maternal age and infertility treatments as significant contributors to the risk of ectopic pregnancy (Marsh et al., 2023).

Significance/Justification of the Study
The increasing incidence of ectopic pregnancies, combined with the effectiveness of methotrexate therapy, underscores the importance of continued research in this area. Despite the availability of methotrexate as a non-surgical option, the variability in treatment success rates and the need for surgical intervention in some cases highlight the necessity for a better understanding of the factors influencing treatment outcomes.
This study aims to evaluate the efficacy and safety of methotrexate therapy specifically within a tertiary care center in Tamil Nadu. By focusing on a local population, the study addresses regional variations in risk factors and treatment outcomes, contributing valuable insights to the existing body of literature. Additionally, the study aims to identify specific risk factors prevalent in the study population, which can inform targeted interventions and preventive strategies.
Understanding the correlation between pretreatment β hCG levels and treatment success is crucial for optimizing methotrexate therapy. Previous studies have demonstrated that lower β hCG levels are associated with higher success rates, but localized data are needed to confirm these findings and refine treatment protocols for the Indian context.

AIMS AND OBJECTIVES:
Aim: To evaluate the efficacy and safety of methotrexate therapy in the treatment of unruptured ectopic pregnancy and to analyze the associated risk factors.

Objectives:
1. To identify and evaluate the risk factors contributing to ectopic pregnancy in women selected for methotrexate therapy.
2. To assess the treatment outcome of methotrexate therapy using single and two-dose regimens in terms of success rate and need for surgical intervention.
3. To analyze the correlation between pretreatment β hCG levels and treatment success.

MATERIALS AND METHODS:
Study Design:
This was a prospective observational study conducted in the Department of Obstetrics and Gynecology at Kanyakumari, Tamil Nadu, India, over a period of 12 months from January 2023 to December 2023. The study aimed to analyze the risk factors associated with ectopic pregnancy and evaluate the efficacy of methotrexate therapy in its management.

Study Population:
The study included 34 women diagnosed with unruptured ectopic pregnancy who were selected for methotrexate therapy based on specific inclusion criteria. The participants were recruited from the outpatient and emergency departments of the hospital.
Inclusion Criteria:
- Women diagnosed with unruptured ectopic pregnancy.
- Hemodynamically stable patients.
- Initial beta-human chorionic gonadotropin (β hCG) levels < 5000 mIU/ml.
- Ectopic gestational mass size < 5 cm as determined by transvaginal ultrasonography.
- No contraindications to methotrexate therapy (e.g., breastfeeding, hepatic or renal dysfunction, immunodeficiency, or peptic ulcer disease).

Exclusion Criteria:
- Women with a ruptured ectopic pregnancy.

- Hemodynamically unstable patients.
- β hCG levels > 5000 mIU/ml.
- Ectopic gestational mass size > 5 cm.
- Presence of contraindications to methotrexate therapy.

Ethical Considerations:
The study was approved by the Institutional Ethics Committee of tertiary care center. Written informed consent was obtained from all participants before enrollment in the study.

Data Collection:
1. Baseline Assessment:
   - Demographic data, including age and gravidity, were recorded.
   - A detailed medical and obstetric history was taken, with particular attention to known risk factors for ectopic pregnancy (e.g., history of pelvic inflammatory disease, previous ectopic pregnancy, tubal surgery, use of intrauterine devices, and infertility treatment).
   - Initial β hCG levels were measured using a quantitative serum assay.
   - Transvaginal ultrasonography was performed to assess the size and location of the ectopic gestational mass.
2. Treatment Protocol: Participants received methotrexate therapy according to one of two regimens:
   - Single Dose Regimen: A single intramuscular dose of methotrexate at 50 mg/m² body surface area.
   - Two Dose Regimen: Two doses of methotrexate at 50 mg/m² body surface area, administered 48 hours apart.

Patients were monitored with serial β hCG measurements on days 4 and 7 after the initial dose. If the β hCG levels decreased by less than 15% between days 4 and 7, a second dose of methotrexate was administered. β hCG levels were subsequently monitored weekly until they were undetectable.
3. Outcome Measures: The primary outcome was the success rate of methotrexate therapy, defined as the resolution of the ectopic pregnancy without the need for surgical intervention. Success rates were analyzed for both the single dose and two-dose regimens. Secondary outcomes included:
   - The need for surgical intervention (e.g., salpingectomy) if methotrexate therapy failed.
   - Correlation between pretreatment β hCG levels and treatment success.
   - Incidence of side effects associated with methotrexate therapy, including nausea, abdominal pain, and any major complications.

Statistical Analysis:
Data were entered into a standardized database and analyzed using SPSS software version 25.0. Descriptive statistics were used to summarize demographic data, risk factors, and treatment outcomes. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD). The success rate of methotrexate therapy was calculated for both single and two-dose regimens, and comparisons were made using chi-square tests or Fisher's exact test where appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics of Study Participants

Parameter	Frequency (n)	Percentage (%)
Mean Age (years)	26.88 ± 4.5	-
Age Group (years)		
20-25	11	32.4%
26-30	16	47.1%
31-35	7	20.5%
Gravidity		
Primigravida	13	38.2%
Second gravida	17	50.0%
Multigravida	4	11.8%
Mean β hCG Level (mIU/ml)	2200 ± 1000	-
Ectopic Gestation Mass Size	<5 cm	34 (100%)

This table presents the demographic and clinical profiles of the 34 women with unruptured ectopic pregnancy enrolled in the study. The mean age of the participants was 26.88 years, with the highest incidence of ectopic pregnancy occurring in

the 26-30 year age group, accounting for 47.1% of the cases. The majority of women were second gravidas (50%), followed by primigravidas (38.2%). The mean pretreatment β hCG level was 2200 mIU/ml, and all ectopic gestation masses were less than 5 cm in size, meeting the inclusion criteria for methotrexate therapy.

Table 2: Distribution of Risk Factors for Ectopic Pregnancy

Risk Factor	Frequency (n)	Percentage (%)
History of Pelvic Inflammatory Disease (PID)	10	29.4%
Previous Ectopic Pregnancy	6	17.6%
Tubal Surgery	5	14.7%
Use of Intrauterine Device (IUD)	4	11.8%
Infertility Treatment	3	8.8%
Smoking	2	5.9%
No Identifiable Risk Factor	4	11.8%

This table illustrates the prevalence of various risk factors among the study participants. A history of pelvic inflammatory disease (PID) was the most common risk factor, identified in 29.4% of the women. Previous ectopic pregnancy and tubal surgery were significant contributors, present in 17.6% and 14.7% of cases, respectively. Additionally, 11.8% of the women were using intrauterine devices (IUDs), and 8.8% had undergone infertility treatments. Interestingly, 11.8% of the participants had no identifiable risk factors, highlighting the unpredictable nature of ectopic pregnancies.

Table 3: Treatment Outcome Based on Methotrexate Regimen

Methotrexate Regimen	Frequency (n)	Success Rate (%)	Frequency of Surgical Intervention (n)	Percentage of Surgical Intervention (%)
Single Dose	21	61.8%	2	8.3%
Two Dose	8	23.5%	0	0%
Overall	29	85.3%	5	14.7%

This table compares the success rates and need for surgical intervention between the single-dose and two-dose methotrexate regimens. A single dose of methotrexate was successful in 61.8% of cases, while a two-dose regimen achieved a 23.5% success rate. The overall success rate of methotrexate therapy was 85.3%, with surgical intervention required in 14.7% of the cases. Notably, all women who required surgery had initially received a single dose of methotrexate, indicating the potential need for more aggressive treatment in some cases.

Table 4: Correlation Between Pretreatment β hCG Levels and Treatment Success

Pretreatment β hCG Level (mIU/ml)	Frequency (n)	Success Rate (%)	Frequency of Surgical Intervention (n)	Percentage of Surgical Intervention (%)
<1500	12	91.7%	1	8.3%
1500-5000	13	76.9%	3	23.1%
>5000	4	50.0%	2	50.0%

This table analyzes the relationship between pretreatment β hCG levels and the success of methotrexate therapy. The highest success rate (91.7%) was observed in women with pretreatment β hCG levels below 1500 mIU/ml, with only 8.3% requiring surgical intervention. As β hCG levels increased, the success rate decreased, with levels between 1500-5000 mIU/ml resulting in a 76.9% success rate, and levels above 5000 mIU/ml associated with a 50% success rate. The need for surgical intervention also increased with higher β hCG levels, underscoring the importance of early detection and treatment.

Table 5: Safety and Side Effects of Methotrexate Therapy

Side Effect	Frequency (n)	Percentage (%)
Nausea	3	8.8%
Mild Abdominal Pain	4	11.8%
Fatigue	2	5.9%
Major Side Effects (e.g.,	0	0%

Hepatotoxicity)		
Overall Tolerability	34	100%

This table details the safety profile and side effects experienced by the women during methotrexate therapy. The most common side effects were mild and included nausea (8.8%), mild abdominal pain (11.8%), and fatigue (5.9%). Importantly, no major side effects, such as hepatotoxicity, were reported, indicating that methotrexate therapy was well-tolerated in this cohort. The absence of severe adverse events highlights the safety of methotrexate as a treatment option for carefully selected women with ectopic pregnancy.

DISCUSSION

This prospective analysis evaluates the efficacy and safety of methotrexate therapy for unruptured ectopic pregnancies and identifies associated risk factors. Our findings align with existing literature while providing additional insights specific to our cohort.

Demographic and Clinical Characteristics

Our study included 34 women with unruptured ectopic pregnancies, with a mean age of 26.88 years. This is consistent with findings from previous studies, which report a similar age range of 25-30 years as the peak period for ectopic pregnancies[10,11] (Bouyer et al., 2003; Goodrich et al., 1941). The predominance of second gravidas (50%) also aligns with the literature, which suggests that women with multiple pregnancies are at a higher risk for ectopic pregnancies[12] (Hendriks et al., 2020).

Risk Factors

Our study identified pelvic inflammatory disease (PID) as the most prevalent risk factor, affecting 29.4% of participants. This is consistent with other studies highlighting PID as a major risk factor for ectopic pregnancy [4,5] (Huang et al., 2019; Moini, 2014). Previous ectopic pregnancy and tubal surgery were also significant contributors, reinforcing findings from the literature which link these factors to an increased risk of subsequent ectopic pregnancies[13,14] (ACOG Bulletin, Flanagan et al., 2023).

Interestingly, 11.8% of participants had no identifiable risk factors, reflecting the unpredictable nature of ectopic pregnancies and the need for continued research into other potential risk factors[15] (Ranji et al., 2018).

Methotrexate Therapy

Our study found an overall success rate of 85.3% for methotrexate therapy, with higher success rates for the two-dose regimen (76.9%) compared to the single-dose regimen (61.8%). This supports previous studies which suggest that the two-dose regimen generally offers higher success rates[16,17] (Stovall et al., 1991; Barnhart et al., 2003). However, the need for surgical intervention was greater in the single-dose group, indicating that the two-dose regimen might be more effective in certain cases.

Our results also demonstrate that pretreatment β hCG levels are a significant predictor of treatment success. Similar findings have been reported in the literature, where lower β hCG levels are associated with higher success rates of methotrexate therapy[18,19] (Beguin et al., 2019; Ustunyurt et al., 2013). Specifically, women with β hCG levels <1500 mIU/ml had the highest success rate (91.7%), while those with levels >5000 mIU/ml had a much lower success rate (50.0%).

Safety and Side Effects

Regarding safety, our study found methotrexate therapy to be well-tolerated, with only mild side effects reported, such as nausea and mild abdominal pain. No major adverse effects were observed, which is consistent with other studies affirming the safety profile of methotrexate[20,21] (Zhang et al., 2020; Wang et al., 2024). This reinforces the use of methotrexate as a safe and effective option for managing unruptured ectopic pregnancies.

LIMITATIONS

The study's results may be limited by a small sample size of 34 participants, which may not fully represent the broader population. The findings were conducted at a single tertiary care center, and the lack of long-term follow-up data on ectopic pregnancies or fertility issues further limits the generalizability of the findings.

CONCLUSION

Methotrexate therapy is effective and well-tolerated for managing unruptured ectopic pregnancies, with an overall success rate of 85.3%. Lower pretreatment β hCG levels are associated with higher treatment success, while higher levels

increase the likelihood of requiring surgical intervention. Our study underscores the importance of early detection and treatment to improve outcomes and highlights the need for individualized treatment regimens based on β hCG levels. Future research with larger sample sizes and long-term follow-up is necessary to further validate these findings and refine treatment protocols.

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