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ORIGINAL ARTICLE

ASSESSMENT OF METHOTREXATE'S EFFICACY IN THE TREATMENT OF UN-RUPTURED ECTOPIC PREGNANCY

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ABSTRACT

Background: Methotrexate has emerged as a promising alternative to surgical intervention for unruptured ectopic pregnancy. The aim of this study was to assess the effectiveness of methotrexate as a treatment option for unruptured ectopic pregnancy.

Materials & Methods: This descriptive study focused on women who were diagnosed with unruptured ectopic pregnancy and received methotrexate treatment at Lady Reading Hospital Peshawar between January 2021 and December 2022. Inclusion criteria were positive pregnancy test, abdominal pain, vaginal bleeding, stable hemodynamics, serum beta-human chorionic gonadotropin (BHCG) levels below 3000 IU/L, and transvaginal ultrasound (TVS) findings of an adnexal mass below 3cm without cardiac activity. Exclusion criteria were false pregnancy test results, BHCG levels exceeding 3000 IU/L, ruptured ectopic pregnancy, hemodynamic instability, shock, and sepsis. Data analysis was performed using SPSS v26.

Results: Total 63 patients were enrolled in this study, and overall success rate of methotrexate treatment for unruptured ectopic pregnancy was determined to be 88.88%. Also 77.77% of cases achieved complete recovery without any complications. Single-dose methotrexate was administered to 49 patients (77.77%), while 14 patients (22.22%) required multiple doses. Seven patients (11.11%) experienced tubal rupture, and an equal number of patients (11.11%) had tubal abortion. In terms of symptom resolution, 48% of patients experienced complete resolution within 14 days. Furthermore, 41% of patients reported symptom resolution within 7 days, with a smaller percentage of 11% achieving resolution within 4 days.

Conclusion: In this study the overall success rate was 88.88% and a majority of patients experiencing symptom resolution within 14 days. The study highlights the well-tolerated nature of methotrexate treatment, emphasizing its potential as a non-surgical alternative.

KEY WORDS: Methotrexate; Unruptured ectopic pregnancy; Safety; Efficacy; Success rate; Symptom resolution; Non-surgical treatment; Fertility preservation; Surgical risks.

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INTRODUCTION

Ectopic pregnancy is a significant global concern, contributing to maternal morbidity and mortality, accounting for approximately 10-15% of all maternal deaths.[1,2] The incidence of ectopic pregnancy has been on the rise, primarily attributed to factors like pelvic inflammatory disease, previous ectopic pregnancies, and assisted reproductive technologies. In Pakistan, reported incidence rates range from 1:112 to 1:1308, although the actual number of cases may be considerably higher due to under-diagnosis and inadequate statistical records.[3]

Advancements in scientific, laboratory, and imaging technologies have enabled early detection of ectopic pregnancy through techniques such as transvaginal ultrasonography (TVS) and serum beta-human chorionic gonadotropin (β-hCG) assays.[4] Traditional surgical intervention has been the standard treatment approach, aiming to remove the ectopic pregnancy while preserving the affected fallopian tube. However, medical management has emerged as a less invasive alternative specifically for unruptured ectopic pregnancies. Methotrexate (MTX) is a commonly employed medication for the medical management

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of unruptured ectopic pregnancy, boasting a success rate ranging from 75% to 95%. Its mechanism of action involves inhibiting cell division and growth, making it effective in targeting rapidly dividing cells like trophoblastic cells.[2,4]

Despite numerous studies investigating different regimens of methotrexate (MTX) for the treatment of unruptured ectopic pregnancy, a consensus on the optimal protocol has not been established. One meta-analysis, including 1327 women, found that the success rate of single-dose MTX was slightly lower than that of the multi-dose regimen, but there was no significant difference between the two approaches (88% vs. 93%).[5] The National Institute for Health and Care Excellence (NICE) recommends MTX as the first-line treatment for women with unruptured ectopic pregnancy who meet specific criteria, such as having a mass smaller than 35 mm with no visible heartbeat, serum β-hCG levels below 1500 IU/L, no confirmed intrauterine pregnancy on ultrasound, and absence of significant pain. These women should also be able to return for follow-up.[6] Furthermore, studies have shown that MTX does not negatively impact ovarian reserve or subsequent fertility.[2,7,8]

The aim of this study was to evaluate the efficacy of methotrexate for the medical management of unruptured ectopic pregnancy in our setting. This single-center experience may provide valuable information on the optimal dosing and administration regimen of methotrexate, as well as its safety profile and impact on subsequent fertility. The findings of this study will help guide clinicians in their decision-making regarding the use of methotrexate for the treatment of unruptured ectopic pregnancy, ultimately leading to better outcomes for patients.

MATERIALS AND METHODS

This descriptive study focused on women diagnosed with unruptured ectopic pregnancy who underwent methotrexate treatment at Lady Reading Hospital Peshawar between January 2021 and December 2022. The study received approval from the institutional review board. Inclusion criteria consisted of a positive pregnancy test, abdominal pain, vaginal bleeding, stable hemodynamics, serum beta-human chorionic gonadotropin (BHCG) levels below 3000 IU/L, and transvaginal ultrasound (TVS) findings of an adnexal mass below 3cm without cardiac activity. Exclusion criteria encompassed false pregnancy test results, BHCG levels exceeding 3000 IU/L, ruptured ectopic pregnancy, hemodynamic instability, shock, and sepsis. A total of 63 patients were included during the study period.

A pre-designed questionnaire was developed to note patient demographics, medical history, laboratory findings, treatment regimen, and clinical outcomes. Follow-up includes monitoring beta hCG levels on days 4, 7, and 14. When levels drop below 5 mIU/mL, it indicates the resolution of ectopic pregnancy. The success rate of methotrexate was defined by a greater than 15% decrease in beta hCG levels on days 4 and 7 after the initiation of methotrexate treatment. Adverse events such as bleeding, and allergic reactions were documented and analyzed.

The data analysis was performed using the SPSS Statistics for Windows version 26.0 (SPSS Inc., Chicago, Ill., USA). Frequencies and percentages were used to represent categorical and demographic variables, while means and SDs were used to represent continuous variables.

RESULTS

This study included a total of 63 patients, with the majority (32 or 50.79%) falling within the age group of 25-29 years. This was followed by 16 patients (25.39%) in the age group of 30-35 years. The highest number of patients were classified as Gravida 2 with 21 (33.33%) patients, followed by Gravida 3 with 19 patients (30.15%). Out of the participants in this study, only 15 patients (28.8%) had a history of previous ectopic pregnancies, while 9 patients (14.28%) had undergone tubal surgeries. A comprehensive overview of the patients' demographic data can be found in Table 1.

Table 1: demographic characteristics of the participants (n=63)

Variables	Frequency	Percentages
Age group		
<25	11	17.46
25-29	32	50.79
30-35	16	25.39
>35	4	6.34
Gravida		
1	13	20.63
2	21	33.33
3	19	30.15
4	7	11.11
>5	3	4.76
Previous ectopic pregnancy		
Yes	15	28.80
No	48	76.19
Tubal surgery		
Yes	9	14.28
No	54	85.71

The study demonstrated an overall success rate of 88.88%. Complete and uneventful recovery was achieved in 77.77% of the cases. Among the treatment modalities used, single-dose methotrexate was administered to 49 patients (77.77%), while 14 patients (22.22%) required multiple doses. Tubal rupture was observed in 7 patients (11.11%), and tubal abortion occurred in 7 patients (11.11%). Detailed information regarding these outcomes can be found in Table 2. No major adverse events such as severe bleeding, infection, or allergic reactions were observed during the treatment course. The treatment with methotrexate was generally well-tolerated, with minimal side effects reported.

Table 2: Outcomes of treatment (n=63)

Events	n(%)
Complete and Uneventful Recovery	49(77.77)
Tubal Rupture	7(11.11)
Tubal Abortion	7(11.11)
Single Dose Methotrexate	49(77.77)
Multidose (2 Doses)	14(22.22)
Complication of Drug	Nil
Overall, Success Rate	56 (88.88)

In the majority of patients 30(48%), the symptoms resolved within 14 days. Furthermore, 26(41%) of patients experienced symptom resolution within 7 days, while only 7(11%) of patients reported symptom resolution within 4 days. For a graphical representation of these findings, please refer to Figure 1.

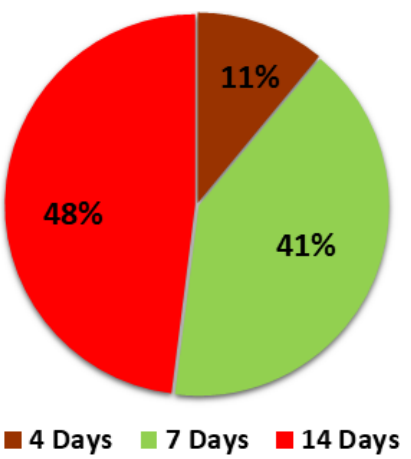

Figure 1: Time taken for resolution of symptoms

DISCUSSION

Ectopic pregnancy affects approximately 1% of pregnant women and poses significant risks to women's health and fertility. Timely diagnosis is crucial, and transvaginal ultrasound and serum human chorionic gonadotropin measurement are essential tools for detecting ectopic pregnancy before the patient's condition worsens.[9] The approach to managing ectopic pregnancy has evolved from emergency life-saving interventions to more conservative treatment options, with the objectives of reducing mortality and morbidity, preserving fertility, and minimizing costs. While various treatment modalities are available, laparoscopic surgery remains the primary method for treating the majority of women with tubal pregnancy.[10,11]

From the late 1980s onwards, systemic Methotrexate has been utilized as an effective treatment for ectopic pregnancy. The initial investigations focused on the use of Methotrexate and Leucoverin to treat stable patients with unruptured ectopic pregnancy. Throughout the treatment process, patients received thorough monitoring, including regular assessments of complete blood count, liver and renal function, as well as measurements of β-hCG levels.[12-14]

The findings of this study provide evidence supporting the utilization of methotrexate as a secure and remarkably efficient alternative for treating ectopic pregnancies. The study demonstrates a success rate of 88.88% for this treatment approach. According to Srivichai et al.[15], 96 out of 106 patients (90.6%) were effectively treated with methotrexate, with only four individuals requiring a second dose. In Merisio's series, a success rate of 90% (10 out of 11 patients) was achieved with single-dose treatment.[16] Existing literature on the subject reveals success rates ranging from 67% to 100% for both single and multidose treatments in cases of ectopic pregnancies.[5,17,18]

In our study it was evident that after the first dose of MTX, the success rate was 77.77%, however 22.22% needed second dose. Similarly, a previous study reported a success rate of 65% with a single dose of MTX.[17,19,20] Therefore, based on the results, it can be concluded that patients who received a second dose of methotrexate exhibited better outcomes compared to those who received only one dose. This highlights the importance of appropriate follow-up and personalized evaluation to assess the necessity of a second dose in individual cases.

The findings of this study contribute valuable evidence regarding the notable success rates of methotrexate (MTX) in the medical management of ectopic pregnancies. However, it should be noted that subsequent infertility remains a significant complication associated with both the condition itself and its treatment using MTX. It is important to acknowledge the limitations of this study, such as the small sample size, which is influenced by the relatively low incidence of ectopic pregnancy. To improve the outcomes and enhance the research,

conducting multi-center studies with larger sample sizes would be beneficial.

CONCLUSION

In conclusion, this descriptive study provides evidence supporting the efficacy of methotrexate in the management of unruptured ectopic pregnancy. With an overall success rate of 88.88% and a significant proportion of patients achieving complete and uneventful recovery, methotrexate emerges as a promising non-surgical treatment option. The majority of patients experienced symptom resolution within 14 days, further highlighting the effectiveness of this approach. The study demonstrates that methotrexate treatment is well-tolerated, with minimal adverse events and no major complications observed. Large-scale studies should be conducted to explore long-term outcomes, assess the impact on future fertility, and refine the selection criteria for patient eligibility.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	SS, SAS
Acquisition, Analysis or Interpretation of Data:	SS, SAS
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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.