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ROLE OF FOLINIC ACID RESCUE AFTER METHOTREXATE IN ECTOPIC PREGNANCY

Dr. Amna Shahzadi

Post Graduate Resident (FCPS), Deptt. of Obstetrics & Gynaecology, Fatima Memorial Hospital, Lahore.

amnashahzadi62@gmail.com

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Corresponding Author: *
Dr. Amna Shahzadi

Abstract

Objective: *To determine the frequency of treatment success following the administration of folinic acid after methotrexate therapy in women with ectopic pregnancy.*

Methodology: *This descriptive study was conducted at the Department of Obstetrics & Gynecology, Fatima Memorial Hospital, Lahore, over a six-month period from July 2024 to December 2024. A total of 100 women aged 20–40 years diagnosed with ectopic pregnancy (confirmed on transvaginal ultrasound with β-hCG >1000 mIU/mL) were enrolled via non-probability consecutive sampling. All participants received intravenous methotrexate (100 mg/m² bolus followed by 200 mg/m² infusion over six hours) along with folinic acid rescue (15 mg orally for four doses). Treatment success was defined as a spontaneous β-hCG drop below 100 mIU/mL and sonographic evidence of conception material evacuation within 48–72 hours.*

Results*: Out of 100 participants, 92 (92%) achieved successful medical termination of ectopic pregnancy, while 8 (8%) required further management. No significant associations were found between treatment success and age (p = 0.392), BMI (p = 0.906), gestational age (p = 0.547), abortion history (p = 0.229), diabetes (p = 0.427), hypertension (p = 0.167), anemia (p = 0.119), previous ectopic pregnancy (p = 0.201), family history (p = 0.293), IVF status (p = 0.456), or socioeconomic status (p = 0.066).*

CONCLUSION*: Folinic acid administration following methotrexate therapy is associated with a high success rate for medical management of ectopic pregnancy and is effective across diverse patient profiles. These findings support incorporating folinic acid as routine adjunct therapy to improve outcomes and reduce the need for surgical intervention.*

INTRODUCTION

Affecting between 1–2% of pregnancies, ectopic pregnancy is the primary cause of maternal mortality in the first trimester and accounts for roughly 6% of all maternal deaths. Over 98% of these pregnancies occur in the Fallopian tubes, though they can also be found in other locations such as the ovary, uterine cornua or interstitium, and intra-abdominal sites.[1-3]

Methotrexate, introduced as a treatment in the late 1980s, has emerged as a viable, non-surgical, and effective option.[4] It functions as a folic acid antagonist, interfering with DNA synthesis and halting the growth of rapidly dividing cells like trophoblasts. This approach has helped reduce surgical need, providing a fertility-sparing treatment to

nearly 25% of women diagnosed with ectopic pregnancy.[5-6]

While methotrexate alone achieves a success rate of 55.9% to 69.75% in treating ectopic pregnancies,[7-9] this can be improved up to 93% with a second dose—though this may increase the risk of toxicity.[7] Given the patient's symptoms and fertility aspirations, a fertility-sparing combination therapy was chosen. This included a single oral dose of 600 mg mifepristone along with a multiple-dose regimen involving 1 mg/kg methotrexate and 0.1 mg/kg folinic acid, administered intramuscularly on alternate days for four doses. A β-hCG drop of over 15% from the previous reading marked therapeutic success.[10] Letrozole, which inhibits the aromatase enzyme and thus blocks estrogen synthesis, is widely used for estrogen-sensitive breast cancer in postmenopausal women and for ovulation induction in PCOS. Its effect on ectopic pregnancy, however, remains uncertain, given that progesterone plays a more central role than estrogen in early gestational maintenance.[11]

Laron and colleagues, in a 1995 study, demonstrated a 96% success rate for terminating ectopic pregnancies using folinic acid in combination with methotrexate.[12] Later, in 2015, Tanaka et al. conducted a clinical trial using a different protocol, which included a 100 mg methotrexate bolus followed by a 12-hour infusion of 200 mg methotrexate. This was followed by four oral doses of folinic acid (15 mg each). Among 33 patients with interstitial ectopic pregnancy, 31 (93.9%) were successfully treated—even those with β-hCG levels as high as 106,634 IU/L and fetal cardiac activity. Minor adverse effects occurred in only three cases.[13]

Rationale of this study is to determine the success of folinic acid following methotrexate in females with ectopic pregnancy. Literature showed adding folinic acid with methotrexate increase success of medical termination of ectopic pregnancy >90% and decrease the need for surgical evaluation in <10% cases. But in routine, it is not given with methotrexate. Therefore, we want to conduct this study to get evidence for local setting and in future, we can recommend the addition of folinic acid with methotrexate to increase chances of successful medical termination of ectopic pregnancy instead of planning invasive procedures. This will help us to improve our practice and knowledge and in future, we will implement findings of this study in local setting.

METHODOLOGY:

This descriptive study was conducted in the Department of Obstetrics & Gynecology at Fatima Memorial Hospital, Lahore, over a period of six months following approval of the research synopsis. A total of 100 patients were enrolled using non-probability consecutive sampling. The sample size was calculated using the WHO sample size calculator with a 95% confidence level, a 4% margin of error, and an expected treatment success rate of 96% for folinic acid following methotrexate in ectopic pregnancy.

Eligible participants were females aged 20 to 40 years with a parity of less than five, who were diagnosed with ectopic pregnancy confirmed through transvaginal ultrasound and a beta-HCG level exceeding 1000 mIU/mL. Patients were excluded if they had already received two doses of methotrexate, had known allergies or contraindications to the trial drugs, or suffered from liver toxicity (ALT and AST >40 IU), hepatitis, cirrhosis, or renal failure (serum creatinine >1.8 mg/dl).

After obtaining approval from the institutional ethical review board, all participants were recruited from the labor room and written informed consent was obtained. Demographic and clinical information, including age, BMI, gestational age, parity, history of abortions, diabetes (defined as BSR >200 mg/dl), hypertension (BP ≥140/90 mmHg), anemia (Hb <11 g/dl), history of ectopic pregnancy (personal or family), in-vitro fertilization, and socioeconomic status, was recorded on a predesigned proforma.

Each patient received methotrexate treatment (100 mg/m² intravenous bolus followed by a 200 mg/m² infusion over six hours) with folinic acid (leucovorin) rescue therapy. Participants were monitored for a minimum of 24 hours, during which blood samples were collected to assess beta-HCG levels. Treatment was considered successful if there was a spontaneous decline in beta-HCG to below 100 mIU/mL and sonographic evidence of conception material evacuation within 48 to 72 hours of methotrexate administration. If the treatment criteria were not met, a second dose of methotrexate was administered, and the patient was managed according to standard institutional protocol.

Data were entered and analyzed using SPSS version 25.0. Continuous variables such as age, BMI, gestational age, and beta-HCG levels were reported as mean ± standard deviation. Categorical variables including abortions, diabetes, hypertension, anemia, previous or family history of ectopic pregnancy, IVF status, socioeconomic class, and treatment success were presented as frequencies and percentages. Stratification was carried out for age, BMI, gestational age, parity, abortions, and other relevant clinical variables. Following stratification, the chi-square test was applied to compare treatment success rates among subgroups, and a p-value of ≤0.05 was considered statistically significant.

RESULTS:

Table 1 presents the demographic characteristics of the 100 female participants enrolled in the study. The majority of women were between 20 and 30 years of age, comprising 52% of the sample, while 48% were in the 31 to 40 age group. A similar distribution was observed for Body Mass Index (BMI), with 52% of participants falling within the 18–25 range and 48% having a BMI greater than 25. Regarding gestational age at the time of presentation, 40% of participants were between 5–6 weeks, and the remaining 60% were between 7–9 weeks. All participants (100%) were multigravida with parity between 0 and 2. Socioeconomic status varied, with 41% of women categorized as low-income, 47% as middle-income, and 12% as high-income.

Table 2 outlines the medical history of the study population. A history of previous abortions was noted in 57% of cases—43% had no prior abortions, 24% had experienced one, and 33% reported two abortions. Diabetes mellitus was present in 24% of women, while 76% had no history of diabetes. Hypertension was reported in 18% of the participants. Anemia was relatively common, affecting 37% of the cohort. Only 4% had a documented history of ectopic pregnancy, and 13% reported a family history of ectopic pregnancy. A small subset of participants (6%) had conceived through in vitro fertilization (IVF).

Table 3 summarizes the treatment outcome following administration of folinic acid after methotrexate therapy for ectopic pregnancy. The majority of participants (92%) achieved complete evacuation and clinical success. Only 8% did not respond successfully to the treatment, highlighting a high effectiveness rate of the regimen in this study population.

Table 4 details the frequency of treatment success according to various effect modifiers. Younger women (20–30 years) had a slightly higher success rate (53.3%) compared to older women (31–40 years, 46.7%), though this difference was not statistically significant (p = 0.392). Similar trends were observed for BMI groups, with no significant difference between women with BMI 18–25 and those with BMI >25 (p = 0.906). Gestational age also did not significantly influence treatment success (p = 0.547). All women had parity between 0–2, eliminating this as a differentiating factor.

Analysis by abortion history revealed that women with two previous abortions had a slightly higher proportion in the failure group, though the difference was statistically insignificant (p = 0.229). Diabetes, hypertension, and anemia were evaluated, with respective p-values of 0.427, 0.167, and 0.119, showing no significant impact on treatment outcome. While 12.5% of those with a previous ectopic pregnancy failed to respond to treatment, the difference compared to those without such history was not significant (p = 0.201). Likewise, family history of ectopic pregnancy (p = 0.293) and IVF conception (p = 0.456) did not significantly affect outcomes.

Interestingly, a trend toward statistical significance was noted in the comparison by socioeconomic status (p = 0.066), with higher failure rates observed among participants from high-income backgrounds (37.5%). Nonetheless, this difference did not reach the threshold for statistical significance. Overall, none of the assessed variables showed a statistically significant association with treatment success, affirming the general efficacy of the treatment across different subgroups.

Table 1: Demographics details of the participants(n=100)

Variable	Group	Count	Percent
Age	20-30	52	52.0%
	31-40	48	48.0%
BMI	18-25	52	52.0%
	>25	48	48.0%
Gestational Age (weeks)	5-6	40	40.0%
	7-9	60	60.0%
Parity	0-2	100	100.0%
Socioeconomic Status	Low	41	41.0%
	Middle	47	47.0%
	High	12	12.0%

Table 2: Medical History of the participants(n=100)

Variable	Group	Count	Percent
Abortions	0	43	43.0%
	1	24	24.0%
	2	33	33.0%
Diabetes	Yes	24	24.0%
	No	76	76.0%
Hypertension	Yes	18	18.0%
	No	82	82.0%
Anemia	Yes	37	37.0%
	No	63	63.0%
History of Ectopic Pregnancy	Yes	4	4.0%
	No	96	96.0%
Family History of Ectopic Pregnancy	Yes	13	13.0%
	No	87	87.0%
In vitro Fertilization	Yes	6	6.0%
	No	94	94.0%

Table 3: Frequency of success of folic acid following methotrexate in females with ectopic pregnancy

Variable	Outcome	Count	Percent
Complete Evacuation/Success	Yes	92	92.0%
Complete Evacuation	No	8	8.0%

Table 4: Frequency of success of folic acid following methotrexate in females with ectopic pregnancy according to various effect modifiers

Variable	Group	Group-A (Count & %)	Group-B (Count & %)	Total (Count & %)	Chi-Square p-value
Age	20-30	49 (53.3%)	3 (37.5%)	52 (52.0%)	0.392
	31-40	43 (46.7%)	5 (62.5%)	48 (48.0%)	
BMI	18-25	48 (52.2%)	4 (50.0%)	52 (52.0%)	0.906
	>25	44 (47.8%)	4 (50.0%)	48 (48.0%)	
Gestational Age	5-6	36 (39.1%)	4 (50.0%)	40 (40.0%)	0.547
	7-9	56 (60.9%)	4 (50.0%)	60 (60.0%)	
Parity	0-2	92 (100.0%)	8 (100.0%)	100 (100.0%)	N/A

Abortions	0	39 (42.4%)	4 (50.0%)	43 (43.0%)	0.229
	1	24 (26.1%)	0 (0.0%)	24 (24.0%)	
	2	29 (31.5%)	4 (50.0%)	33 (33.0%)	
Diabetes	Yes	23 (25.0%)	1 (12.5%)	24 (24.0%)	0.427
	No	69 (75.0%)	7 (87.5%)	76 (76.0%)	
Hypertension	Yes	18 (19.6%)	0 (0.0%)	18 (18.0%)	0.167
	No	74 (80.4%)	8 (100.0%)	82 (82.0%)	
Anemia	Yes	32 (34.8%)	5 (62.5%)	37 (37.0%)	0.119
	No	60 (65.2%)	3 (37.5%)	63 (63.0%)	
History of EP	Yes	3 (3.3%)	1 (12.5%)	4 (4.0%)	0.201
	No	89 (96.7%)	7 (87.5%)	96 (96.0%)	
Family History of EP	Yes	11 (12.0%)	2 (25.0%)	13 (13.0%)	0.293
	No	81 (88.0%)	6 (75.0%)	87 (87.0%)	
IVF	Yes	6 (6.5%)	0 (0.0%)	6 (6.0%)	0.456
	No	86 (93.5%)	8 (100.0%)	94 (94.0%)	
SES	Low	39 (42.4%)	2 (25.0%)	41 (41.0%)	0.066
	Middle	44 (47.8%)	3 (37.5%)	47 (47.0%)	
	High	9 (9.8%)	3 (37.5%)	12 (12.0%)	

DISCUSSION:

The present study investigated the efficacy of folinic acid rescue therapy following methotrexate administration in the medical management of ectopic pregnancy. Our findings demonstrate a high treatment success rate of 92%, with minimal adverse effects and no statistically significant association between success and demographic or clinical variables. These results contribute valuable evidence to the limited body of local literature and align closely with international studies endorsing the combined use of methotrexate and folinic acid.

Ectopic pregnancy remains a significant cause of first-trimester maternal morbidity and mortality, particularly in resource-limited settings where early detection and surgical expertise may be constrained. In this context, methotrexate, a folic acid antagonist, has gained widespread use due to its ability to inhibit DNA synthesis in rapidly dividing trophoblastic cells, allowing non-invasive termination of pregnancy while preserving fertility. However, the standard practice in many local facilities excludes the routine use of folinic acid as a rescue agent, despite growing global evidence supporting its benefit.

Our study's 92% success rate is consistent with that reported by Tanaka et al. (2015),[13] who treated 33 women with interstitial ectopic pregnancy using a combination of intravenous methotrexate (100 mg bolus + 200 mg infusion) followed by four oral doses of 15 mg folinic acid. They observed a 93.9% success rate, even among patients with β-hCG levels exceeding 100,000 IU/L and fetal cardiac activity—highlighting the regimen's effectiveness in high-risk cases.

Similarly, Larson et al. (1995)[12] reported a 96% success rate using an identical high-dose methotrexate infusion protocol with leucovorin (folinic acid) rescue in a cohort of 28 patients, with only one requiring a second dose and no serious toxicities recorded. These findings, along with ours, collectively validate the role of folinic acid in enhancing methotrexate's efficacy, particularly in cases that would otherwise be deemed candidates for surgical intervention.

A recent comparative review by Zahraa H. Barem (2025)[14] further strengthens the rationale for our protocol. The review emphasized the limitations of single-dose regimens, particularly the higher likelihood of treatment failure and delayed resolution. It concluded that the multidose methotrexate protocol, especially when combined with folinic acid rescue, offers superior outcomes in terms of efficacy and reduced toxicity. Our study protocol incorporated this evidence-based approach, likely contributing to the high success rate observed. However, it is critical to recognize potential modifying factors in methotrexate therapy. Takacs et al in 2004[15]

proposed that elevated baseline serum folic acid levels (>20.7 ng/mL) may paradoxically reduce the efficacy of methotrexate due to competitive inhibition, thereby increasing the risk of treatment failure. In their pilot study, failure occurred in 44% of women with high folic acid levels compared to none with lower levels ($p = 0.02$). Although we did not measure baseline folate levels in our cohort, this finding suggests an area for future research and potential refinement of treatment selection.

While folinic acid is primarily included in multidose protocols to mitigate toxicity, its use does not completely eliminate risk. Soysal et al[16] in 2016 presented a case of severe methotrexate toxicity in an otherwise healthy woman, involving hematological suppression, mucositis, and multi-organ symptoms that necessitated intensive care and plasmapheresis. Although rare, such cases highlight the importance of careful monitoring, especially in patients requiring more than one dose of methotrexate. Encouragingly, no severe toxicity was reported in our study population, and all patients were monitored post-treatment for potential complications.

Additionally, the stratified analysis of our data showed no statistically significant difference in treatment success across age groups, BMI, gestational age, history of abortion, diabetes, hypertension, anemia, previous ectopic pregnancy, or IVF status. This suggests that the methotrexate-folinic acid combination is broadly effective regardless of baseline patient characteristics. Interestingly, women from high-income socioeconomic groups exhibited a higher, though statistically insignificant, failure rate ($p = 0.066$). This observation warrants further investigation into potential psychosocial or biological differences affecting adherence or response to therapy.

From a clinical implementation perspective, the current standard of care in many local institutions involves methotrexate monotherapy without folinic acid, potentially due to lack of awareness or cost considerations. However, based on both our findings and corroborative international literature, the addition of folinic acid not only increases the likelihood of treatment success beyond 90% but also reduces the need for surgical intervention to <10%—a particularly important consideration in fertility preservation.

A major strength of our study is the application of a well-structured, evidence-based treatment protocol with systematic post-treatment follow-up. Additionally, the inclusion of a relatively diverse patient population enhances the generalizability of our findings within similar resource-limited settings.

However, several limitations must be acknowledged. First, this was a single-center, non-randomized study without a control group, limiting causal inference. Second, biochemical markers such as baseline folate levels were not assessed, which could influence methotrexate metabolism and outcomes. Third, long-term follow-up on reproductive outcomes post-treatment was not conducted. Despite these limitations, our study adds valuable local evidence supporting a combined medical therapy approach.

CONCLUSION

The addition of folinic acid to methotrexate therapy for ectopic pregnancy is associated with a high success rate (92%) and a low risk of adverse effects in our local patient population. Our findings are consistent with international studies and support the routine incorporation of folinic acid rescue into methotrexate protocols, particularly for patients seeking non-surgical, fertility-preserving treatment options. Future multi-center randomized controlled trials are warranted to confirm these findings and explore long-term reproductive outcomes.

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