

## Evaluation of the Two-Dose Methotrexate for medical treatment of Ectopic Pregnancy: A Retrospective case series study.

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Cite this paper as: Batool A. Hashim Al Khalidi MD (2025) Evaluation of the Two-Dose Methotrexate for medical treatment of Ectopic Pregnancy: A Retrospective case series study.. *Frontiers in Health Informatics, Vol.14, No.2, 2474-2482*

### ABSTRACT

Background: Tubal ectopic pregnancy is a significant cause of maternal morbidity in first trimester of pregnancy, owing to wide resorting to ovulation induction and assisted reproduction it is said to be rising in incidence and with improved imaging modalities and their early accessibility early diagnosis of ectopic pregnancies dominates the current management practice and this makes methotrexate therapy offers a desired non-surgical treatment option. Variable methotrexate regimes has been tried to achieve medical cure of ectopic pregnancy, the two-dose methotrexate regimen is considered effective and well-tolerated for stable patients, and the current study is designed to test its effectiveness and find predictors of medical treatment success with two dose methotrexate regime.

Aim of the study: To demonstrate the medical treatment outcomes for tubal ectopic pregnancy at Al-Zahraa teaching hospital and to analyse the factors influencing treatment success, including patient demographics, clinical presentation, and initial  $\beta$ -hCG levels and to determine the rate of surgical intervention following medical treatment.

Patients and methods: Retrospective case series study included 25 patients with tubal ectopic pregnancy treated with a two-dose methotrexate protocol. Patient demographics, clinical characteristics, serum  $\beta$ -hCG levels, ectopic mass size, treatment outcomes, and complications were gathered and studied.

Results: Medical management was successful in 76% of cases. Patients with lower initial  $\beta$ -hCG levels (2,500–4,500 mIU/mL) and smaller ectopic masses (2–4 cm) had significantly higher success rates ( $p=0.021$  and  $p=0.037$ , respectively). Treatment failure occurred in 24% of patients who required surgical intervention, mainly due to persistent  $\beta$ -hCG or tubal rupture. Adverse events were minimal, reported in 8% of patients, and generally mild.

Conclusions: The two-dose methotrexate regimen is an effective and safe treatment for selected patients with tubal ectopic pregnancy. Initial  $\beta$ -hCG levels and ectopic mass size are significant predictors of treatment success. Careful monitoring and strict follow-up are essential to identify non-responders early.

### INTRODUCTION

Ectopic pregnancy (EP) is defined as the gestation that implants, develops, and draws its blood supply from the site of abnormal implantation. As it enlarges, it creates the potential for organ rupture, because only the uterine cavity is designed to expand and accommodate fetal development. EP can lead to massive hemorrhage, infertility, or death. (1) fallopian tubes accounts for a pproximately 97.7%) of all tubal pregnancies, the ampulla is the most common site of implantation (80%), followed by the isthmus (12%), fimbria (5%), cornua (2%), and interstitia (2-3%). (2) Non-tubal EPs are a rare occurrence, and these can abdominal, ovarian, cervical, in previous cesarean delivery scars or in a rudimentary uterine horn ectopic gestations. (3) The understanding and management of EP have evolved from being a near-certain fatality in the 19th century to a condition that can be managed effectively non surgically with minimal patients morbidities today. (4) Overall incidence of EP is 1-2% of all pregnancies, pelvic inflammatory diseases (PID), pelvic surgeries, endometriosis, infertility treatment and assisted reproductive techniques influencing its incidence. (5) there is a noted increase in developed countries, The prevalence is roughly 1 in 40 pregnancies or about 25 cases per 1000 pregnancies, as reported by the center of disease control (CDC) (6). Estimated incidence of EP in Iraq is 2.2 in 1000 of population at risk. The classic triad of pelvic pain, uterine bleeding and amenorrhoea is found in only 50% of all cases (7), the diagnosis is largely depends on high index of clinical suspicion, quantitative serum level of human chorionic gonadotrophin (HCG), supported by transvaginal sonography, as it is often non specific symptoms can mimic number of acute pelviabdominal pain conditions. (8) Early and accurate diagnosis is crucial to manage the condition effectively and prevent

complications, and probably minimizing future fertility compromise(9)by avoiding the surgical option for it is management by sacrificing a tube, allowing hemodynamically stable patients benefit the medical treatment option with methotrexate (MTX) when there is no embryonic cardiac activity with considerable chance of complete cure especially when serum HCG level is below predefined limits.(10) Methotrexate acts by inhibiting dihydrofolate reductase, crucial for DNA synthesis and cell multiplication, it has been long used for non malignant diseases like rheumatoid arthritis and psoriasis, valuable for cases to medically terminate pregnancy implanted in ectopic sites such as the cervix, ovary, or specific tubal sections, when surgical intervention risks severe complications like hemorrhage and potential loss of reproductive function.(11) Medical therapy for EP includes two main protocols: the multiple-dose regimen and the single-dose regimen, each tailored for different clinical scenarios.(12)MTX is the most common agent used for medical treatment with reported treatment success rate ranging between 60-95%, having BHCG and pretreatment EP mass size both as best predictors of treatment success(13), a necessary decline of at least 15% indicating a successful response when it is performed at day 4&7 after MTX dose, antiD immunoprophylaxis should be given for Rhesus negative patients.(14)

**Aim of the study** is to demonstrate the medical treatment outcomes for ectopic pregnancy at Al-Zahraa teaching hospital in Annajaf Alashraf province of Iraq choosing two dose methotrexate regime as standard patient care.

**Patient and method: Study Design and Setting;** Retrospective case series study. **Setting;** The study was conducted at the Department of Obstetrics and Gynecology, Al-Zahraa Maternity and Pediatric Teaching Hospital, Annajaf Alashraf, Iraq, affiliated to medical school of Kufa university. **Study population;** The study included 100 patients diagnosed with EP during one year period between 1st January 2024 till the end of December 2024 of them 25 patients were eligible for medical treatment, the remaining 75 patients were treated surgically, all women diagnosed with ectopic pregnancy who met the inclusion criteria eligible for medical management. Diagnosis was confirmed based on a combination of clinical findings, quantitative serum  $\beta$ -HCG testing and transvaginal sonography. Ultrasound criteria included the absence of intrauterine pregnancy and the presence of an adnexal mass suggestive of an ectopic gestation, serial  $\beta$ -hCG levels showing abnormal rise or plateauing also supported the diagnosis. **Inclusion Criteria;** Patients were included in the study if they fulfilled all of the following criteria: confirmed diagnosis of EP by transvaginal ultrasound and  $\beta$ -Hcg, hemodynamically stable at presentation, absence of fetal cardiac activity, no contraindications to methotrexate therapy, ability to comply with scheduled follow-up and treatment protocol. **Exclusion Criteria;** patients were excluded if they met any of the following: hemodynamic instability requiring immediate surgical intervention, presence of significant intra-abdominal bleeding or signs of rupture, contraindications to methotrexate, including abnormal renal or liver function tests (RFTs or LFTs), active systemic infection, blood dyscrasias, known hypersensitivity to methotrexate, significant comorbid conditions that could interfere with treatment, failure or inability to attend scheduled follow-up visits, indication for primary surgical management due to clinical or diagnostic findings. **Collection and Variables;** data were extracted from hospital records using a structured data sheet, and included: age of the patient, duration of marriage, history of infertility (tubal, ovulatory. ect), nature of conception (spontaneous or assisted), Gravidity, parity, and abortion history (G.P.A), number of methotrexate doses administered, initial and follow-up  $\beta$ -hCG levels, ectopic mass size at presentation, gestational age at diagnosis, requirement for surgical intervention, final outcome and side effects of methotrexate treatment. **Admission Protocol and Initial Assessment;** upon admission, patients underwent the following baseline investigations; Renal Function Tests (RFTs), Liver Function Tests (LFTs), Complete Blood Count (CBC) Baseline  $\beta$ -hCG level, Transvaginal pelvic ultrasound, patients were observed for vital sign stability and any signs of progression or complications. If eligible, they received the treatment protocol and discharged the next day with strict instructions for follow-up.

**Treatment Protocol;** all eligible patients received systemic intramuscular methotrexate at a dose of 100 mg/m<sup>2</sup> body surface area, calculated according to standard oncology dosing methods, unlike the single-dose approach used in some protocols, this study employed a two-dose regimen, in which methotrexate was administered on: Day 0 (initial dose), Day 4 (second dose), this modified protocol was chosen to improved efficacy and reduced risk of treatment failure and minimize the side effects of methotrexate to improve patients' tolerability and compliance.

**Follow-Up Schedule;** patients were closely monitored post-discharge through scheduled outpatient visits and phone calls. follow-up included: serum  $\beta$ -hCG monitoring on Days 0, 4, 7, 11, and 14, then weekly thereafter until resolution and additional transvaginal ultrasound scans were performed as clinically indicated. Follow-up duration ranged from two weeks to three months, depending on the time required for complete resolution of the adnexal mass. Patients were advised to avoid conception for at least three months after complete resolution to avoid the teratogenic effects of MTX, successful medical management was defined as a progressive decline in  $\beta$ -hCG levels over serial measurements (A decline of at least 15% in serum  $\beta$ -hCG levels between Day 4 and Day 7 is considered a positive response to treatment), a reduction in the size of the ectopic mass on ultrasound, less symptoms compared to initial presentation, no requirement for surgical intervention during the follow-up period. While failure of medical treatment was defined as plateauing or rising  $\beta$ -hCG levels after 2 weeks of treatment, progressive worsening of symptoms (e.g., pain, bleeding), detection of ruptured ectopic pregnancy or clinical

deterioration, requiring surgical management. Primary outcome measured; number of successful medical treatment of EP, Secondary outcomes measured; number of given doses of MTX , side effect, patients tolerability and complete resolution of adnexial mass and BHCG normalization.

### Ethical approval

The study protocol was approved by Kufa University/ Collage of medicine/ Ethical committee of obstetrics and Gynecology.

Patients' oral consents were obtained prior to participation in the study.

Data and information of the participants were kept confidential.

Administrative approvals were granted from Al-Zahraa Teaching Hospital.

**Statistical Analysis;** Data analysis was done using IBM® Statistical Package for Social Sciences (SPSS) version 27 for Microsoft® Windows 11, results were presented in simple measures of frequency, percentage, mean, range and standard deviation and illustrated as tablets and figures. An independent t test was used to evaluate the association between numerical variables. Chi square test was used to assess the association between categorical variables, while fisher exact test was used when the expected frequency was less than 5. A level of p- value less than 0.05 was considered statistically significant.

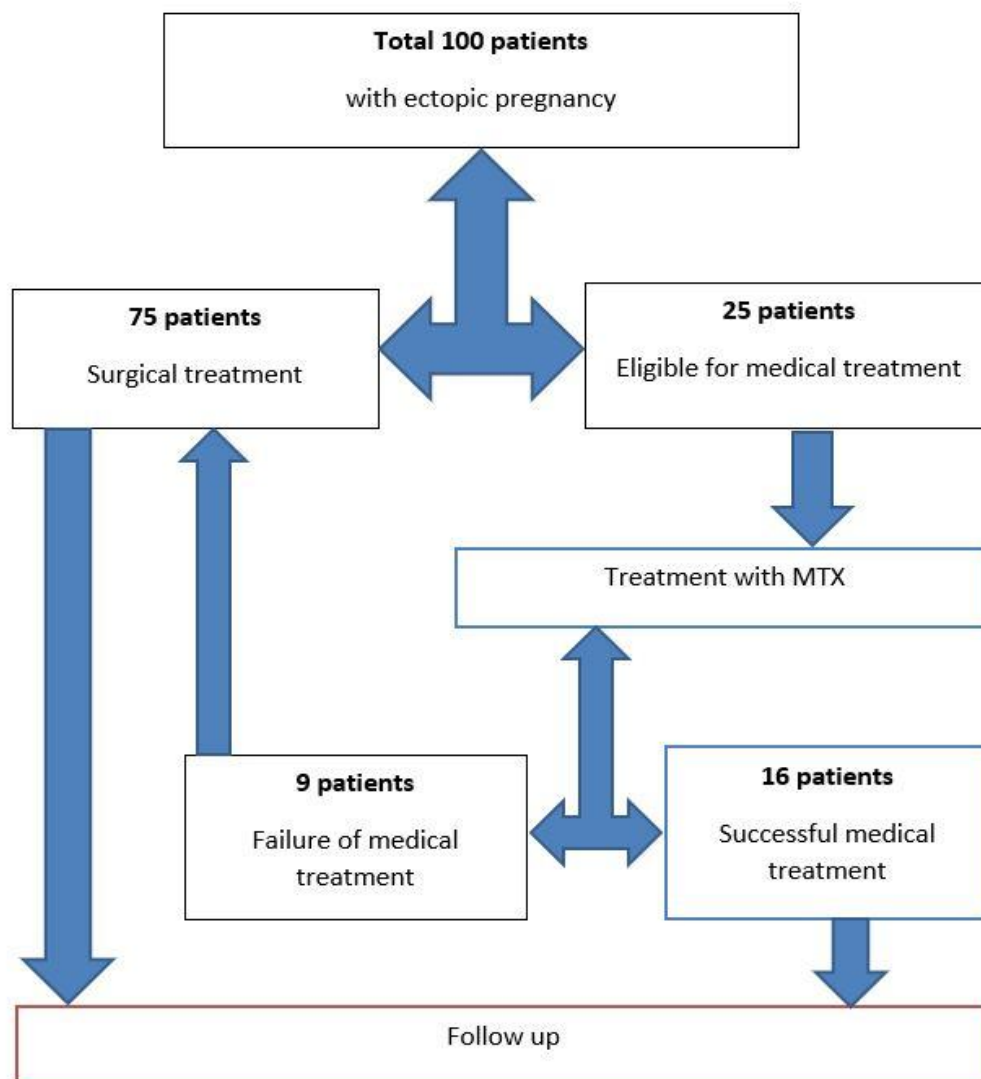


figure 1 patients-flow chart.

Results:

**Table 1: Demographic and clinical characteristics of the study sample (n = 25)**

Variable	Frequency	Percent
<b>Age (years)</b>		
<25	6	24
25-35	14	56
>35	5	20
Mean ± SD	28.9 ± 4.8	
Range	19-39	
<b>Body Mass Index (BMI)</b>		
<25 (Normal)	7	28
25–29.9 (Overweight)	10	40
≥30 (Obese)	8	32
<b>History of Infertility</b>		
Yes	8	32
No	17	68
<b>Type of Pregnancy</b>		
Spontaneous	22	88
Induced	3	12
<b>Previous Ectopic Pregnancy</b>		
Yes	1	4
No	24	96
<b>Previous Abortion</b>		
Yes	9	36
No	16	64
<b>Gravidity (mean ± SD)</b>	3.1 ± 1.5	
<b>Parity (mean ± SD)</b>	1.4 ± 1.1	

At presentation all the patients had abdominal ultrasound exam and β-hCG level measurements. The average gestational age was 6.3 ± 1.1 weeks. 14 patients (56%) presented between 5 and 6 weeks of gestation, while 11 (44%) presented at a gestational age of more than 6 weeks. Initial serum β-hCG levels mean was 2,750 ± 980 mIU/mL. 13 patients (52%) had β-hCG levels between 2,500 and 4,500 mIU/mL, while 12 (48%) had levels exceeding 4,500 mIU/mL. The size of the ectopic mass measured an average of 2.7±0.6 cm. 14 patients (60%) had a mass size between 2 and 4 cm, whereas 10 (40%) had a mass larger than 4 cm.

**Table 2 : Clinical and ultrasound characteristics**

Variable	Frequency	Percent
<b>Gestational Age at Presentation (weeks)</b>		
5-6 weeks	14	56
>6 weeks	11	48
Mean ± SD	6.3 ± 1.1	
<b>Initial BHCG level (mIU/mL)</b>		
2,500–4,500	13	52
>4,500	12	48
Mean ± SD	2,750 ± 980	
<b>Ectopic Mass Size (cm)</b>		

2-4 cm	15	60
>4 cm	10	40
Mean ± SD	2.7 ± 0.6	

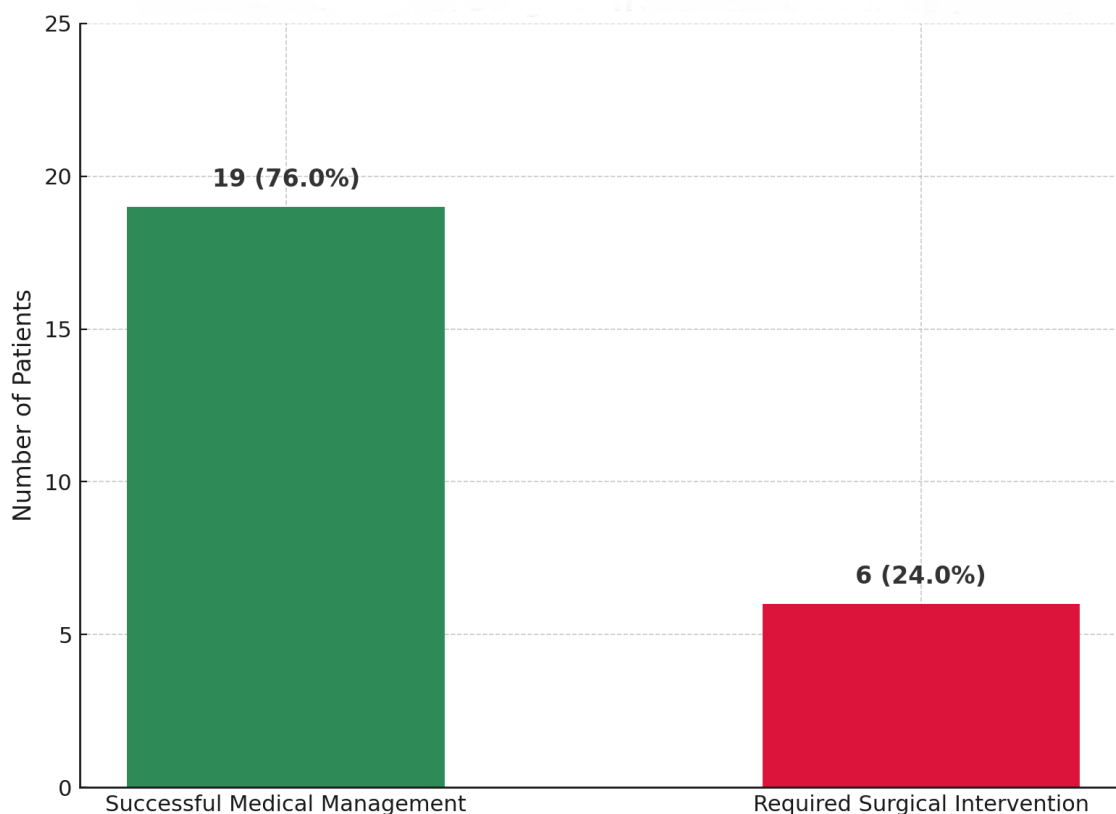
Medical management was successful in 19 (76%) of the patients, while 6 (24%) had treatment failure and surgical intervention was required. (Figure 3.1.)

Among those who underwent surgery, the primary indication was persistent  $\beta$ -hCG levels in 4 patients (66.7%), followed by rupture in 2 patients (33.3%).

Complications or adverse events occurred in 2 patients (8%) including nausea & vomiting in one patient and Allergic reaction with skin rash in another patient, while 23 (92%) experienced no such events. Hospital readmission was necessary for 8 (32%) patients, whereas 17 (68%) were not readmitted. As shown in table 3.2.

**Table 3: Treatment Outcomes and Complications.**

Outcome	Frequency	Percent
<b>Successful Medical Management</b>		
Yes	19	76
No	6	24
<b>Required Surgical Intervention</b>		
Yes	6	24
No	19	76
<b>Reason for Surgery</b>		
Rupture	2	33.3
Persistent BHCG	4	66.7
<b>Adverse Events / Complications</b>		
Yes	2	8
No	23	92
<b>Hospital Re-admission</b>		
Yes	8	32
No	17	68



**Figure 2.: outcomes of medical management with MTX.**

Among those who had successful medical treatment, 13 (68.4%) were under 30 years old, compared to 2 (33.3%) in the failure group. Although a higher proportion of younger patients succeeded, the difference in age was not statistically significant ( $p = 0.144$ ).

For gestational age, 6 (31.6%) of the successful cases presented at 5–6 weeks, compared to 1 (16.7%) among the failures, but the difference was also not significant ( $p = 0.329$ ).

Regarding BMI, 6 (31.6%) of those with BMI <25 achieved success, while only 1 (16.7%) in the failure group had a BMI <25. The distributions across other BMI categories showed no statistically significant differences with a  $p$  value of 0.147.

The initial  $\beta$ -hCG level was significantly associated with treatment outcome; among those with levels between 2,500–4,500 mIU/mL, 14 (73.7%) had successful MTX treatment versus only 1 (16.7%) failed, with a statistically significant  $p$  value of 0.021.

Mass size also showed a significant association, 15 patients (78.9%) of the successful group had a mass size between 2–4 cm compared to 2 (33.3%) in the failed group, with a  $p$  value of 0.037.

The type of pregnancy, whether spontaneous or induced, did not show a significant association with treatment outcome ( $p = 0.651$ ). As shown in table 3.4.

**Table 4: Factors associated with medical treatment outcome**

Factor	Successful n = 19 (%)	Cases	Failed n = 6 (%)	Cases	p-value
<b>Age (years)</b>					
<30	13 (68.4%)		2 (33.3%)		0.144
≥30	6 (31.6%)		4 (66.7%)		
<b>Gestational Age (weeks)</b>					

5-6	6 (31.6%)	1 (16.7%)	0.329
>6	13 (68.4%)	5 (83.3%)	
<b>BMI (kg/m<sup>2</sup>)</b>			
<25	6 (31.6%)	1 (16.7%)	0.147
25–29.9	8 (42.1%)	2 (33.3%)	
≥30	5 (26.3%)	3 (50.0%)	
<b>Initial BHCG (mIU/mL)</b>			
2500-4500	14 (73.7%)	1 (16.7%)	0.021 *
>4500	5 (26.3%)	5 (83.3%)	
<b>Mass Size (cm)</b>			
2-4 cm	15 (78.9%)	2 (33.3%)	0.037 *
>4 cm	4 (21.1%)	4 (66.7%)	
<b>Type of Pregnancy</b>			
Spontaneous	17 (89.5%)	5 (83.3%)	0.651
Induced	2 (10.5%)	1 (16.7%)	

**\* Statistically significant (p < 0.05)**

**Discussion:** This study evaluated the outcomes of methotrexate (MTX) treatment in 25 patients with tubal ectopic pregnancies. The mean age of patients was  $28.9 \pm 4.8$  years, with the majority (56%) between 25 and 35 years. This age distribution aligns with the peak reproductive years when ectopic pregnancies are most commonly diagnosed. Naje et al. study in Baghdad-Iraq reported that the incidence of ectopic pregnancy was 2.217 cases per 1,000 individuals at risk and that the majority of affected women were between 15 and 24 years of age.<sup>(15)</sup> 40% of patients were overweight and 32% were obese, this reflects the global trend of rising BMI and is consistent with the results from Hajenius et al. (2007),<sup>(16)</sup> who noted a high prevalence of elevated BMI in patients with ectopic pregnancy. Increased BMI is often associated with altered tubal function and hormonal imbalances, potentially contributing to the ectopic implantation.<sup>(17)</sup> The mean gestational age at presentation was  $6.3 \pm 1.1$  weeks, and over half (56%) presented between 5 and 6 weeks, this finding aligns with clinical expectations, as symptoms typically manifest around this period.<sup>(18)</sup> Initial serum BHCG levels averaged  $2,750 \pm 980$  mIU/mL. Approximately 52% of patients had levels between 2,500 and 4,500 mIU/mL, a range often associated with higher MTX success rates. This is supported by Zhang et al. study on 238 ectopic pregnancies treated with MTX, their study included 166 patients in the successful treatment group and 72 in the failed treatment group, yielding an overall methotrexate (MTX) therapy success rate of 69.75% for ectopic pregnancy. The mean baseline beta-human chorionic gonadotropin BHCG level was significantly lower in the successful group compared to the failed group (2538.08 IU/L vs. 3533.17 IU/L,  $P = 0.000$ ). Additionally, patients with an initial BHCG level below 4000 IU/L had a significantly higher treatment success rate than those with levels above 4000 IU/L.<sup>(19)</sup> The average ectopic mass size was  $2.7 \pm 0.6$  cm, with 60% measuring between 2 and 4 cm. These dimensions fall within the commonly accepted range for conservative management. Kimiaei et al. study on 185 patients also found that the size of the gestational sac and the baseline BHCG level were both significantly associated with an increased likelihood of methotrexate treatment failure in patients with ectopic pregnancy.<sup>(20)</sup> The overall success rate of medical management with MTX in our study was 76%, which is consistent with Beguin et al. study that reported a success rate of 80%, they also found that the success rate increased to 84% when patients with BHCG levels above 5,000 IU/L were excluded, suggesting that methotrexate should not be used in cases where BHCG levels exceed 5,000 IU/L.<sup>(21)</sup> Among the six patients who required surgical intervention, persistent BHCG levels were the leading indication (66.7%), followed by tubal rupture (33.3%). These findings are comparable to Dudley et al. who reported that EP rupture occurred in (15.1%) of their sample within 25 days following methotrexate treatment and was significantly associated with higher parity and more advanced gestational age. Rupture was also linked to significantly higher BHCG levels on days 0, 4, and 7 of treatment.<sup>(22)</sup> Adverse events were reported in 8% of cases, primarily mild and self-limiting. This corresponds with the findings of Alur-Gupta et al. who documented adverse effects in 5–10% of patients using two doses of MTX, mostly limited to gastrointestinal symptoms and minor allergic reactions. They also concluded that the two-dose methotrexate protocol shown superior effectiveness compared to the single-dose regimen in treating ectopic pregnancy, both in terms of overall treatment success and shorter time to resolution. Notably, this advantage remains significant even among patients considered less likely to respond to medical therapy, such as those with elevated BHCG levels or a large adnexal mass.<sup>(23)</sup> Bonin et al. study on 400 women that received methotrexate for ectopic pregnancy also found that Methotrexate treatment was effective in 314 patients, resulting in an overall success rate of 78.5%. A single dose was sufficient

in 63.5% of cases, while a second dose achieved success in 73.2% of those who required it. Treatment success declined with increasing initial BHCG levels. Key factors associated with methotrexate failure included BHCG levels on days 0, 4, and 7. Favorable early declines in BHCG levels were predictive of treatment success. Among women with day 0 BHCG levels below 1000 IU/L, the success rate reached 90%. Methotrexate was generally well tolerated, with only 9% of patients experiencing mild adverse effects. Following treatment, the post-therapy fertility rate, measured by successful delivery, was 80.7%.<sup>(24)</sup> The current study and all the above studies had agreed that BHCG level and ectopic pregnancy mass size are significantly associated with MTX medical treatment outcome while other factors like age of the patient, gestational age, BMI and type of pregnancy (spontaneous or induced) were not found to be significant. On the other hand, there are some studies like Abdelfattah-Arafa et al. have suggested that other factors were independently associated with successful methotrexate treatment for ectopic pregnancy. These included younger age, absence of pelvic pain, and absence of fetal cardiac activity and that the likelihood of treatment failure increased more than twofold with every 10-year increase in age, by 32% for every 1000 IU/L rise in initial BHCG level, and more than twofold in the presence of pelvic pain.<sup>(25)</sup>

**Conclusions and Recommendation:** Medical management of tubal ectopic pregnancy using a two-dose methotrexate regimen was successful in 76% of selected cases in the current study, demonstrating that non-surgical treatment is effective for hemodynamically stable patients who have lower initial BHCG levels and smaller ectopic mass size and that failure of medical management can still occur and these patients required surgical intervention. Medical treatment is usually well tolerated with complications and adverse events from methotrexate therapy were minimal thus, two-dose protocol appeared to balance efficacy with safety. Gynecologists should implement patient counselling that clearly explain treatment options, success rates, possible complications, and follow-up especially for the outpatient use of methotrexate therapy. A strict follow-up protocol is essential to monitor treatment progress, ensure early detection of non-responders, and prevent complications such as rupture or delayed intervention with preparations to surgical intervention in cases of BHCG persistence or clinical deterioration.

**Study limitations:** small sample size that may limit statistical power of the study, the current study had limited long-term follow-up that may be necessary to detect future fertility predict EP recurrence rate, the study did not include comparison with other established methotrexate regimens, such as the single-dose or multi-dose protocols, and finally limited assessment of patient-reported outcomes, such as pain levels, emotional impact, or treatment satisfaction, which are important considerations in evaluating overall treatment success and tolerability

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