





The Use of Single Dose Methotrexate in the Management of Ectopic Pregnancy and Pregnancy of Unknown Location: 10 Years' Experience in a Tertiary Center

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Objective: To study factors associated with the success of single dose methotrexate (MTX) treatment in women with ectopic pregnancy.

Methods: This is a retrospective study of women (n=110) with ectopic pregnancy and treated with single dose of MTX. The clinical presentations, transvaginal sonography (TVS) findings, pretreatment beta-human chorionic gonadotropin (β -HCG), and progesterone values were compared between the treatment success (Group S) and treatment failure (Group F) groups.

Results: The overall success rate of treatment with single dose of MTX was 75.45%. The majority of patients in both groups presented with pain and bleeding (~55%), and bleeding only was the presenting symptom in about 20% of patients. Only 3 patients (3.61%) in Group S required a repeat dose of MTX. In contrast, 51.8% of the Group F patients required a repeat dose. The mean pretreatment β -HCG level was 2.3 times higher in Group F than in Group S (1734 \pm 1684 vs 4036 \pm 2940 IU/L). The data showed a β -HCG level of 3924 IU/L as a suitable cut-off value with 76.19% sensitivity and 62.5% specificity to predict MTX treatment success. History of ectopic pregnancy had no relation with success/treatment failure or a repeat dose. None of the TVS findings were related to the outcome of the treatment, whereas pretreatment HCG level was a significant predictor.

Conclusion: The single dose MTX treatment was successful in 75.45% (83/110) of cases, with 3.61% (3/83) requiring a repeat dose of the drug. Pretreatment β -HCG level is a significant predictor of the treatment outcome.

Keywords: ectopic pregnancy, methotrexate, pretreatment β HCG

Introduction

An ectopic pregnancy occurs when the blastocyst implants outside the endometrial cavity.¹ It is a complication of the first trimester of pregnancy, accounting for about 6% of pregnancy-associated mortalities.² Advancement in diagnostic and therapeutic modalities have drastically reduced maternal mortalities from extrauterine pregnancy worldwide.^{2,3} Yet ectopic pregnancy remains the leading cause of maternal mortality in the first trimester.⁴ Patients with an ectopic pregnancy may be treated either surgically or managed medically. Surgical approaches are the mainstay of the treatment; however, advances in early diagnosis have favored medical management, especially with the introduction of methotrexate (MTX) therapy.

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In the medical treatment of ectopic pregnancy, MTX has emerged as the single most commonly used drug as it is safe with virtually no adverse effects reported on reproductive outcome. There are three widely used protocols for treatment with MTX, which include single, double, and multiple-dose regimens.^{5,6} MTX therapy is, in general, effective with a good success rate, relatively less expensive, and notably avoids the inherent risks of anesthesia and surgery. However, a single dose regimen improves patient compliance and reduces the overall costs. All three regimes are effective and generally safe with studies involving treatment with MTX therapy have reported pregnancy rates of 79.6–100%.^{7–11}

The serum level of beta-human chorionic gonadotropin (β -HCG) plays an important role in conjunction with the findings of transvaginal ultrasonography (TVS) in the diagnostic evaluation of ectopic pregnancy and pregnancy of unknown location (PUL) which is defined as the situation when the pregnancy test is positive, but there are no signs of intrauterine pregnancy or an extrauterine pregnancy via TVS.¹² TVS may help in identifying ectopic pregnancy by observance of small masses (about 10 mm in diameters) in the adnexa and detailed evaluation of its character, the endometrial cavity contents as well as the presence of free peritoneal fluid. These above-mentioned multiple parameters also have very high sensitivity and specificity in the diagnosis.^{13,14}

Detection of ectopic pregnancy with 100% accuracy is aided by a β -HCG concentration of ≥ 1500 IU/L and an empty uterus on TVS. Therefore, β -HCG level combined with transvaginal ultrasonographic findings, have enabled the early diagnosis of ectopic pregnancy. Additionally, serum progesterone levels may be helpful for the evaluation of ectopic pregnancy.^{15,16}

Racial and ethnic disparities are observed in several maternal morbidities, including ectopic pregnancies. Black women are reported to be at higher risk than white women in the United States.^{17,18} Therefore, studies are required to understand different entities of ectopic pregnancy in geographically located different populations. Towards this end, this retrospective study investigates and shares the influence of pretreatment serum chorionic gonadotropin and progesterone levels in conjunction with findings of TVS as well as clinical presentations on the outcome of single dose of MTX administration in women with ectopic pregnancy from the middle-east.

Methodology

This study was approved by the Institutional Review Board of Jordan University of Science and Technology (JUST) (11/132/2020). Patient consent was waived as this retrospective study involves electronic medical records review and analysis was performed on de-identified data. Patient data privacy and confidentiality are maintained as this study was conducted in compliance with the ethical standards per the Helsinki declaration. The records of all patients admitted to King Abdullah University Hospital between 2010 and 2019 for the treatment of ectopic pregnancy and PUL were reviewed. Diagnosis of ectopic pregnancy and pregnancy of unknown location were made by history, clinical examination, ultrasound, abnormal serum β -HCG, and progesterone trends, and/or by the absence of products of conception after uterine evacuation.

During the period of study, a total of 372 patients were diagnosed with ectopic pregnancy and pregnancy of unknown location. Of these, 117 patients were treated medically, and 255 patients were treated surgically mainly by laparoscopic salpingectomy. Seven patients were excluded from the analysis due to missing data or loss of follow up. Therefore, data from 110 patients treated with MTX were available for final analysis.

Data collected from the medical records of the patients included demographic (age in years) and clinical variables (parity, gestational age, findings of TVS etc). TVS was performed using a 5MHz probe (Aloka SSD 900, 2000, or 4000, Keymed Ltd, South end, UK), which demonstrated endometrial thickness, pseudo sac presence, and free pelvic fluid. In addition, we collected data for serum levels of β -HCG and progesterone as measured by enzyme-linked immunosorbent assay (ELISA), number of doses of MTX administered, response to MTX treatment, need for surgical intervention, and weeks taken for β -HCG levels to reach normal post-treatment levels.

The hospital had followed a single dose MTX protocol for patients who were hemodynamically stable without severe or persistent abdominal pain, showed absence of cardiac activity in the ectopic, and with normal renal and liver parameters. All these patients fulfilling the above criteria had received a single IM injection of methotrexate 50 mg/m² given on day (0). Serum β -HCG levels were repeated on days 4, 7, and weekly thereafter. If β -HCG dropped by 15% on day 7 compared to day 0, the treatment was considered successful. However, a second dose was administered on day 7 if a 15% drop in β -HCG was not

observed and the patient remained an appropriate candidate for medical management. If there is no drop in β -HCG levels thereafter or patients displayed signs/symptoms of ruptured ectopic pregnancy at any time, the treatment was considered unsuccessful, and surgery was recommended.

The data was broadly divided into two groups based on treatment success (Group S, N= 83) and failure of the treatment (Group F, N= 27).

Statistical Analysis

All statistical analyses were carried out using GraphPad version 7. Non-parametric *t* test with Mann–Whitney test was used for comparing differences in age, pretreatment β -HCG, and progesterone levels between treatment success and treatment failure groups. Receiver operating characteristic (ROC) curve analysis was performed to derive a cut-off pretreatment

level of β -HCG to predict the MTX treatment success. The relationship between previous ectopic and (a) success or failure of treatment, or (b) repeat dose required was performed using the chi-square test (2X2 tabulation). Further, the association between the success and failure of treatment and ultrasonography findings was also studied using the chi-square test (2X2). Logistic regression analysis was carried out for variables to predict the outcome of treatment. P-value of <0.05 was considered significant for all the analyses.

Results

The mean age of patients was 30.74 \pm 5.244 years. Of the 110 patients, MTX treatment was successful in 83 (75.45%) and failed in 27 patients (24.55%), as shown in Table 1. No complications or side effects were observed among patients treated with single dose of MTX. The

Table 1 Characteristics of Patients Treated with Single-Dose Methotrexate, Overall, and According to Treatment Success

Characteristics		Total (N=110)	Treatment Successful	Treatment Failure	
			Group S N= 83	Group F N= 27	
Age in years (mean \pm SD)		30.74 \pm 5.24	30.59 \pm 5.43	31.18 \pm 4.71	
Patient history	Gravida: median (range)	3 (1–12)	3 (1–10)	3.5 (1–12)	
	Previous ectopic (%)	8 (07.27)	6 (7.23)	2 (7.41)	
	No previous ectopic (%)	102 (92.72)	77 (92.77)	25 (92.59)	
Clinical presentations: n (%)	Pain with bleeding	60 (54.5)	45 (54.21)	15 (55.55)	
	Pain only	17 (15.5)	13 (15.67)	4 (14.81)	
	Bleeding only	23 (20.9)	18 (21.68)	5 (18.51)	
	No complaint	10 (9.1)	7 (8.43)	3 (11.11)	
Ultrasound findings	Thick endometrium	77 (70.00)	58 (69.87)	19 (70.37)	
	Adnexal mass	29 (26.30)	19 (22.89)	10 (37.03)	
	Free fluid in POD	23 (20.90)	17 (20.48)	6 (22.22)	
	Empty uterus	39 (35.54)	30 (36.14)	9 (33.33)	
	Pseudo sac	4 (3.63)	3 (3.61)	1 (3.77)	
Type of Ectopic	Tubal	50 (45.45)	36 (43.37)	14 (51.85)	
	Pregnancy of unknown location	54 (49.09)	44 (53.01)	10 (37.03)	
	Other sites	Scar	2 (1.81)	1 (1.20)	1 (3.7)
		Cervical	3 (2.72)	1 (1.20)	2 (7.40)
Heterotopic-Tubal		1 (0.93)	1 (1.20)	0 (00.0)	
Follow up	Weeks till β HCG normalized: median (range)	4 (1–9)	4 (1–9)	4 (3–7)	
	Repeat dose				
	Not required n (%)	93 (85.32)	80 (96.39)	13 (48.2)	
	Required n (%)	17 (14.68)	3 (03.61)	14 (51.8)	
	Surgery				
Not required n (%)	83 (75.45)	83 (100)	00 (32)		
Required n (%)	27 (24.55)	00 (00)	27 (100)		

Abbreviation: POD, pouch of Douglas.

results showed that ectopic pregnancy was most common in gravida 3 (median value). The percentage of patients with past history of ectopic pregnancy was similar in both groups (Group S: 7.23% Group F: 7.41%). The majority of patients in both groups presented with pain and bleeding (~ 55%), and bleeding only was the presenting symptom in about 20% of patients. A thick endometrium on ultrasound was the most common feature in both groups. In Group F, 51.85% of patients had a tubal pregnancy, whereas 43.37% of Group S had a tubal pregnancy. In Group S, only 3 patients out of the 83 (3.61%) required a repeat dose of MTX. In contrast, 52% of Group F required a repeat dose.

Table 2 compares mean age, pretreatment levels β HCG and progesterone between Group S and Group F. The mean β -HCG levels were significantly higher ($P=0.03$) in patients with unsuccessful treatment (Group F: 4036 ± 2940 IU/L) compared to the group with successful treatment (Group S: 1734 ± 1684 IU/L).

Receiver operating characteristic (ROC) curve analysis revealed β -HCG cut-off value of 3924 IU/L with 76.19% sensitivity and 62.5% specificity to predict MTX treatment success (area under curve = 0.769, $P=0.005$; Figure 1).

The detailed analysis of patients with history of ectopic, treatment outcome and repeat dose of MTX administered is shown in Table 3. In treatment successful group, majority of patients ($N=75$, 90.36%) with no previous ectopic pregnancy needed no repeat dose of MTX. Further analysis of the results indicated that a history of previous ectopic

Table 2 Age, β HCG and Progesterone Levels According to the Outcome of MTX Treatment

	Total	MTX Treatment		P
		Successful	Failure	
	110	83 (75.45)	27 (24.55)	n (%)
Age (years)				
Mean \pm SD	30.74 \pm 5.24	30.59 \pm 5.43	31.18 \pm 4.71	0.4792
95% CI	29.75–31.73	29.40–31.78	29.35–33.01	
Pretreatment β-HCG (IU/L)				
Mean \pm SD	2016 \pm 2241	1734 \pm 1684	4036 \pm 2940	0.03
95% CI	1595–2438	1366–2101	1729–4859	
Progesterone (mg/dL)				
Mean \pm SD	6.533 \pm 5.21	6.102 \pm 4.66	6.95 \pm 4.63	0.31
95% CI	5.554–7.51	5.086–7.12	5.157–8.75	

Notes: Only mean β -HCG level appears to be significantly higher in the treatment failure group non-parametric t-test with Mann-Whitney test.

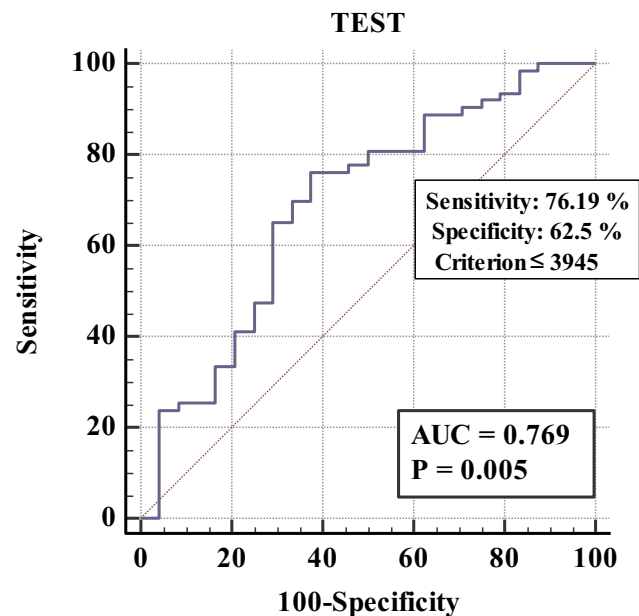


Figure 1 ROC curve for the ability of pretreatment HCG level (IU/L) to predict MTX treatment success.

pregnancy had no relation to success or failure treatment as well as requirement of an additional dose of MTX (Table 4).

We further studied the association between ultrasound findings and success or failure of treatment (Table 5). The

Table 3 Detail Analysis of Patients with History of Ectopic, Treatment Outcome and Repeat Dose of MTX Required

Treatment Outcome	Previous Ectopic (n=8)		No Previous Ectopic (n=102)	
	Repeat Dose		Repeat Dose	
	Required	Not Required	Required	Not Required
Successful (n=83)	1 (1.20%)	5 (6.02%)	2 (2.41%)	75 (90.36%)
Failure (n=27)	1 (3.70%)	1 (3.70%)	12 (44.44%)	13 (48.15%)

Table 4 Association Between the Previous Ectopic with Treatment Outcome and Requirement of Additional Dose of MTX

Previous Ectopic		No Previous Ectopic	Previous Ectopic	P
Treatment outcome	Success	77	6	0.630
	Failure	25	2	
Repeat MTX dose	Not required	88	6	0.302
	Required	13	2	

Note: Chi-square test.

Table 5 Relation Ultrasound Findings and Success of Treatment

Treatment Outcome	Thick Endometrium			Adnexal Mass			Empty Uterus			Free Fluid POD			Pseudo Sac		
	+	-	P	+	-	P	+	-	P	+	-	P	+	-	P
Success	58	25	1.00	20	63	0.22	17	66	1.00	30	53	1.00	3	80	1.00
Failure	19	8		10	17		6	21		9	18		1	26	

Notes: + Denotes presence and – denotes absence (Chi-square test).

Abbreviation: POD, pouch of Douglas.

presence of thick endometrium, adnexal mass, empty uterus, free fluid in the pouch of Douglas (POD), and the pseudo sac were not associated with success or failure of treatment.

Logistic regression analysis of variable predictors (Table 6) showed that only pretreatment β -HCG was a significant predictor of the outcome of treatment. The odds of treatment success decreased by 0.999 times, with a one-unit increase in pretreatment β -HCG level.

Discussion

This retrospective study investigated the influence of pretreatment serum β -HCG and progesterone levels in conjunction with findings of TVS on the outcome after intramuscular single dose MTX administration in patients. The data of 110 patients showed that treatment was successful in 83 (75.45%) patients. Several studies have reported that the success rate of the treatment of ectopic pregnancy medically ranges between 75% and 95%.^{19–21} A previous meta-analysis estimated the success rate of a single dose MTX regimen to be 88.1%.⁷ The high success rate has been attributed to the fact that only women with a good prognosis underwent treatment with a single dose. The success rate of this study is towards the lower end of the previous studies. We attribute this to the fact that the mean pretreatment β -HCG levels were relatively high, as evident from β -HCG levels in the failure group (4019 \pm 6362 IU/L). All patients of our study had opted for the single-dose protocol, perhaps because of convenience over efficacy as it requires fewer visits, fewer injections and less chances of side effects. In this

study, none of the patients reported any side-effects of MTX. In the treatment successful group, majority of patients (90.36%) with no previous ectopic pregnancy needed no repeat dose of MTX. However, the result indicated that a history of previous ectopic pregnancy had no relation to success or failure treatment as well as requirement of an additional dose of MTX. Using a multidose MTX regimen, Tug et al observed that BMI, MTX dose, number of MTX injections and the decrement of β -HCG levels highly predictive for the success of the treatment.²²

An elevated initial β -HCG level is considered as the most important factor associated with treatment failure. The mean pretreatment β -HCG level for all patients in this study was 2016 \pm 2241 IU/L, and the mean pretreatment level was 2.3 times higher in the failure group (4036 \pm 2940 vs 1734 \pm 1684 IU/L). In a study by Lipscomb et al, the mean β -HCG level of patients treated successfully was 4019 \pm 6362 IU/L, whereas it was 13,420 \pm 16,590 IU/L in patients whom treatment was unsuccessful.²³ A recent prospective study reported a high β -HCG level (3887 \pm 3300 IU/L) on the first day of MTX administration in patients in whom medical treatment failed and relatively low mean levels (2589 \pm 1784 IU/L) in the successfully treated group.²⁴ Studies in literature have reported high pretreatment β -HCG levels in the MTX treatment failure group.^{25,26}

We observed that the mean ages of patients in treatment success (30.59 \pm 5.430 years) and treatment failure groups (31.18 \pm 4.714 years) were similar. Previously, Mirbolouk et al also reported similar mean ages of the two groups.²⁵ Further, we failed to see a relationship

Table 6 Logistic Regression Analysis for Variables to Predict the Outcome of Treatment

Variables	Coefficient	SE	P	Chi Square	OR	95% CI
Age	-0.0214	0.0415	0.606	0.264	0.9789	0.9024–1.0618
Pretreatment β HCG	-0.0002	0.0001	0.023	6.549	0.9998	0.9996–0.9999
Progesterone	-0.0048	0.0140	0.733	0.110	0.9953	0.9684–1.0229

between MTX treatment success and maternal age. However, it is observed that increased maternal age reduces MTX treatment success.²⁷

Through the ROC curve analyses, we deduced a pretreatment β -HCG cut off value of 3924 IU/L with 76.19% sensitivity and 62.5% specificity with a treatment success rate of 75.45%. The success rate varies with initial levels of β -HCG. Lipscomb et al found a 94% success rate when the initial β -HCG level was less than 10,000 mIU/mL and a 75% success rate when the initial β HCG level was above 10,000 mIU/mL.²³ Similarly, Menon et al in a systematic review observed that failure rate was 3.77% in patients with initial β -HCG value in the 2000–4999-mIU/mL range, and it was 14.29% in patients with initial β -HCG value in the 5000- to 9999 mIU/mL range.²⁸

Wider variation is found in the literature, with β -HCG cutoff values ranging from 1500 mIU/mL to 9000 mIU/mL.^{29,30} Bachman and Barnhart in meta-analysis stated that cut-off values are only suggested value below which MTX therapy will be most likely to be successful, and clinician's interaction with the patient influences the decision about the medical or surgical management.¹⁹ Therefore, it is clear that success rates of treatment decrease with increasing β -HCG. Using logistic regression analysis, we report that the odds of treatment success decrease by 0.999 times with a one-unit increase in pretreatment β -HCG level.

The majority of patients with an ectopic pregnancy at the time of admission to the hospital usually have complained about pain and pain with bleeding.^{7,23,31} In the current study, as well, the majority of patients complained about pain and pain with bleeding, and about 9.1% of patients had no symptoms, as reported in other studies.^{32–34}

TVS has reformed the assessment of patients with early pregnancy problems as many diagnostic features can be easily visualized by TVS.³⁵ An ectopic pregnancy can be accompanied by a “pseudo sac”, a collection of fluid within the endometrial cavity that may be the result of a localized breakdown of the decidualized endometrium. Additionally, an ectopic pregnancy can be diagnosed by the presence of an adnexal mass and thick endometrium, etc. A large prospective study performed in 6621 patients reported that TVS could diagnose ectopic pregnancy with a sensitivity of 90.9% and specificity of 99.9%.³⁶

Conclusions

The study showed that single dose methotrexate treatment of ectopic pregnancy is a safe, convenient, and effective

option. The pretreatment β -HCG level was the only significant predictor of the outcome of the treatment.

Abbreviations

MTX, methotrexate; β -HCG, beta-human chorionic gonadotropin; TVS, transvaginal ultrasonography; ROC, receiver operating characteristic.

Data Sharing Statement

All the data and materials used in this paper will be available from the corresponding author upon reasonable request.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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