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ORIGINAL ARTICLE

Predictors of single-dose methotrexate treatment success in ectopic pregnancies: A retrospective cohort study

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Abstract
Objective: The present study investigated the predictors of single-dose (50 mg/m^2) methotrexate (MTX) treatment success in ectopic pregnancies.
Method: A retrospective cohort study was conducted using information databases from a single academic tertiary care hospital among 396 participants referred for treatment of ectopic pregnancy (EP). Data were collected on age, history of EP, basal level of β-hCG, features of vaginal ultrasound (left or right), mass size, presence of hematoma around the mass and free pelvic fluid, and demand of subsequent doses of MTX or surgery. The patients were divided into success and failure groups based on whether they were treated with a single-dose of methotrexate (single dose MTX), or required subsequent doses of MTX or surgery.
Results: The success rate of single-dose MTX treatment was approximately 74%. The failure chance was significantly higher in right adnexal masses (OR: 3.45), history of EP (OR: 28.19), presence of hematoma on ultrasound (OR: 26.69), and serum β-hCG > 719 mIu/ml (OR: 5.19). A mass size > 19 mm was associated with a 79% increased chance of failure ($p = 0.10$). These variables accounted for approximately 45–66% of the failure variance for single-dose MTX treatment. Based on ROC curve analysis, initial β-hCG level of 719 mIu/ml was the best cutoff for patients with EP (with a sensitivity of 82% and specificity of 63%).

Introduction

Ectopic pregnancy (EP) refers to a growing blastocyst somewhere outside of the uterine endometrium [1]. The most common site (90-95%) for EP is the ampulla portion of the fallopian tube [2, 3]. The prevalence of EP varies in different populations and from 14 to 20

cases per 1000 pregnancies or about 0.5% to 2% of pregnancies in the general population [4-6], and 2-5% among individuals who have used assisted fertility methods [4, 7]. According to the World Health Organization, EP is one of the most common causes of maternal death in the first trimester of pregnancy and is responsible for approximately 5% of maternal deaths in developed countries [8]. In addition, tubal damage due to EP rupture reduces the chance of success in subsequent pregnancies [9].

EP is a potentially adverse outcome of pregnancy that requires prompt evaluation and treatment [10]. Diagnosis of EP in the case of clinical suspicion based on patient symptoms (delayed menstruation associated with vaginal bleeding or abdominal pain) and laboratory tests (serial measurement of β-hCG level and transvaginal ultrasound) [11, 12]. The management of EP includes three treatment options: (i) surgery (salpingectomy or salpingostomy), (ii) pharmacotherapy with methotrexate (MTX), or (iii) expectant therapy [11]. Nowadays, pharmacotherapy is comparable to surgical methods in terms of efficacy and consequences of subsequent pregnancies. Also, the application of pharmacotherapy in the management of EP has become very important due to lower tubal damages, lower costs, the higher chance of subsequent fertility, non-imposition of surgical complications, and anesthesia for the patient [13]. In the case of early diagnosis and confirmation of EP at the early stages with ultrasound, the use of pharmacotherapy has a success rate of approximately 90% [1].

The pharmacological treatment for tubal pregnancy is an intramuscular injection of MTX. This is a folic acid antagonist that can be used to eradicate trophoblastic tissue and induce the absorption of pregnancy products in EPs [1]. In case of stable hemodynamics of the patient, serum β-hCG < 5000 ml/ml, absence of fetal heart rate (FHR) in vaginal ultrasound, mass size < 4 cm, and patient access to the emergency room and the possibility of following β-hCG level, is the treatment of choice [1, 14]. MTX can be used as a single dose, double dose, or repeated dose. In most cases, a single dose is given to the patient [15].

Various factors have been reported in relation to the success rate regarding a single dose of MTX including lower serum level of β-hCG [16-21], absence of free fluid detection in abdominal ultrasound size, mother's younger age [20] and absence of fetal heart rate [21]. However, mixed findings have been reported regarding mass size [16, 17, 21], gestational age [17], yolk sac observation [17], and free fluid detection in abdominal ultrasound [16, 17]. Therefore, according to the mixed findings of previous studies, it seems that with the exception of serum level of β-hCG, there are no consistent results regarding the predictors of success of single-dose treatment. Therefore, the present study was designed to determine the predictors of success of single dose MTX treatment.

Methods

Study design

A retrospective observational study was carried out using hospital information databases. The studied population included all women with a diagnosis of EP that were treated with MTX and admitted to Kosar Hospital between 2013 and 2018. All hospitalized pregnant women with a diagnosis of unbroken tubular EP, stable hemodynamic status, a lack of fetal heart activity on ultrasound, and an initial novel single dose MTX (50 mg/m^2) were included in the present study. Patients were excluded if they had (i) unstable hemodynamic status, contraindications to MTX, surgery from the beginning of hospitalization, initiated multidose MTX treatment, received expectant therapy or abandoned their treatment.

Sampling procedure

All hospital information regarding EP-related admitted cases in Kosar Hospital of Qazvin from 2013 to 2018 were collected.

Measures

Data from the patients' records were collected from a single academic tertiary care hospital including age, history of EP, baseline β-hCG level with serum titration, vaginal ultrasound features including mass location (left or right), mass size, presence of hematoma around the mass, free pelvic fluid, and the demand of subsequent doses of MTX or surgery. Patients were required to receive subsequent doses of MTX or surgery (failure to respond to treatment or rupture of an EP) depending on whether they were treated with a single dose MTX (reduced serum β-hCG by more than 15% between days 4 to 7). Success and failure were divided into two groups and the association between variables including age, history of EP, mass location, mass size, presence of hematoma or free fluid on ultrasound, and serum β-hCG level with failure or success of treatment were examined. Therapeutic response to a single dose MTX was considered as success and the need for additional doses or surgery (laparoscopy or laparotomy) as failure.

Ethics

The present study was approved by the Ethics Committee in Biological Research of Qazvin University of Medical Sciences (code IR.QUMS.REC.1398.317). Because information was extracted from patients' files and no contact was made with patients, informed consent was not obtained. However, it should be noted that the informed consent of all patients at the time of admission is based on the possibility of using the data in the files.

Statistical analysis

Data were analyzed using SPSS 19 software. Descriptive results were calculated by reporting frequencies, means, and standard deviations based on the type of variable and were analyzed by statistical tests including independent *t*-tests (to investigate the association between quantitative ordinal variables) and chi-square tests (to examine the association between categorical variables). A multivariable (logistic regression) LR model was used to

more accurately identify the predictors of response to MTX treatment. The variables that were significant in the study of univariate association with *t*-tests and chi-square tests were entered into multivariable LR model using the ENTER method. To enter the LR model, serum level variables β-hCG based on serum level of 1000 mm/ml and mass size based on size 19 mm were converted into two groups. A significance level less than 0.05 was considered. A ROC (receiver operating characteristic) curve was used to evaluate the cut-off point of serum β-hCG level. The success of single dose MTX treatment was analyzed qualitatively. The β-hCG level was quantitatively analyzed using the ROC curve.

Results

Between 2013 and 2018, the number of hospitalized cases due to EPs was 600, of which 204 patients underwent direct surgery due to unstable hemodynamics or contraindications to MTX treatment, or had abandoned their treatment. Therefore, a total of 396 patients were included in the present study. The success rate of single does MTX was 71% (281 out of 396 patients). Among the 115 patients for who a single dose MTX treatment failed, 34 patients underwent laparoscopy, and 81 patients were administered a second or third dose of MTX.

Based on the ROC curve (Figure 1), an initial β-hCG < 719 mIU/ml was the best cutoff for patients with the sensitivity of 82% and specificity of 63%. Therefore, the initial β-hCG value has the necessary power to predict the success of MTX treatment with an AUC (area under the curve) of 0.82 (95% CI: 0.77; 0.87) and standard error of 0.03 and $p<0.001$.

Table 1 shows the distribution of variables (history of EP, presence of free fluid and hematoma in sonography and mass location in adnexa, age, mass size, and serum β-hCG) and their association with two outcomes of single dose MTX treatment success and the demand for surgical treatment (laparoscopy/laparotomy). The mass location, presence of free fluid, the hematoma on ultrasound, mass size, and serum β-hCG level were all significantly associated

with the need for surgery (p<0.001). There was a significant relationship between the history of EP, hematoma, adnexal mass location with response to treatment, mass size, and serum β-hCG level with successful response to MTX treatment (p<0.001).

The results of the multivariable LR model (Table 2) showed that the failure of single dose MTX was 3.45 times higher among patients with right adnexal masses, 28 times higher among patients with a history of EP, 27 times higher among patients with hematoma in ultrasound, and approximately five times higher among patients with serum β-hCG > 719 mIU/ml. A mass size > 19 mm was associated with a 79% increased chance of failure, but this finding was not significant. These variables accounted for approximately 45% to 66% of the failure.

Discussion

The aim of the present study was to determine the predictors of successful response to treatment with a single dose MTX. The results showed 71% success using a single dose of MTX. This finding was consistent with previous studies that reported a success rate of 70% to 90% [16-21].

According to the ROC curve analysis, patients with an initial β-hCG < 719 mIU/ml were successful cutoffs for treatment with MTX. In terms of serum level, there was no agreement between that in the present study and previous studies. The most successful response to treatment in Avcioglu et al.'s study of 91 patients was a serum β-hCG level of less than 1000 [22]. Beguin et al. studied 61 patients and reported a cut-off point of 2439 with 66% sensitivity and 93% specificity for treatment success [13]. Pulatoglu et al. reported a serum level of less than 1362 mIU/ml with a sensitivity of 71% and a specificity of 68% as the cut-off point for success in MTX treatment [16]. Differences between different studies may be due to differences in the study sample sizes. In addition, the results of multivariate LR model in the present study showed that the chance of failure of single-dose treatment among individuals

with serum β-hCG level higher than 719 mIU/ml was almost five times higher. The association of lower β-hCG levels with a positive response to medical treatment is consistent with all previous studies [13, 16-22].

In addition, the results of the multivariate LR model showed that the failure of single dose MTX was 3.45 times higher among patients with right adnexal masses, 28 times higher among patients with a history of EP, 27 times higher among patients with a hematoma on ultrasound. A mass size of more than 19mm was associated with a 79% increased chance of failure (although non-significant). These variables accounted for approximately 45% to 66% of the failure variance for single dose MTX treatment. In the present study, the history of EP was a significant predictor of failure of single dose MTX treatment. This finding is consistent with previous studies [1, 23-25]. Also, the presence of hematoma on ultrasound and a mass on the right adnexa were the other predictors of failure of single dose MTX treatment, but these variables have not not been evaluated in previous studies. The present study found no association between free fluid reporting on ultrasound and response to medical treatment. This finding was not consistent with studies by Pulatoglu et al. [16], Uğurlucan et al. [26], and Vaswani et al. [27], in which pelvic fluid was considered as an effective factor in the failure. However, Var et al. [17] reported no association between the free fluid in ultrasound and response to medical treatment. The number of participants in the present was higher than in the aforementioned studies.

The mean mass size was approximately 19mm in the group that responded to medical treatment and 25mm in the group that did not. This finding can be used by clinicians as a guide to predict the likelihood of success of MTX treatment. Moreover, the chance of failure among individuals with a mass size greater than 19mm in the multivariate LR model was not more than 79% significant. This finding is consistent with the studies by Vaswani et al. [27] and Avcioglu et al. [22] in terms of the effectiveness of mass size with response to treatment,

although the mean mass size for response to treatment in these studies was 30 mm [27], and 25 mm, respectively [22].

Limitations

Although the sample size in the present study was higher than many previous studies, the wide 95% OR confidence interval obtained in the results of multivariate model indicates that the sample size was not large enough to provide definitive results. Other limitations of the present study were the retrospective study design not having data on some variables (e.g., presence of fetal heart beat) and using the odds ratio index, which may be associated with a higher probability of index estimation. Due to the limitations of the present study, it is necessary to conduct studies with a prospective design, or meta-analysis studies to aggregate the results of existing studies and provide more conclusive evidence of factors affecting the prediction of response to single dose MTX treatment.

Conclusion

Based on the results of the present study, the predictors for success of a single dose MTX treatment are a history of EP, the presence of hematoma on ultrasound, the location of the mass, and the measurement of β-hCG levels before treatment. Therefore, with the appropriate selection of patients based on these variables, a single dose MTX appears more likely to be effective.

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Figure legend:

Figure 1- ROC curve analysis assessing the best cutoff for predicting the MTX success rate

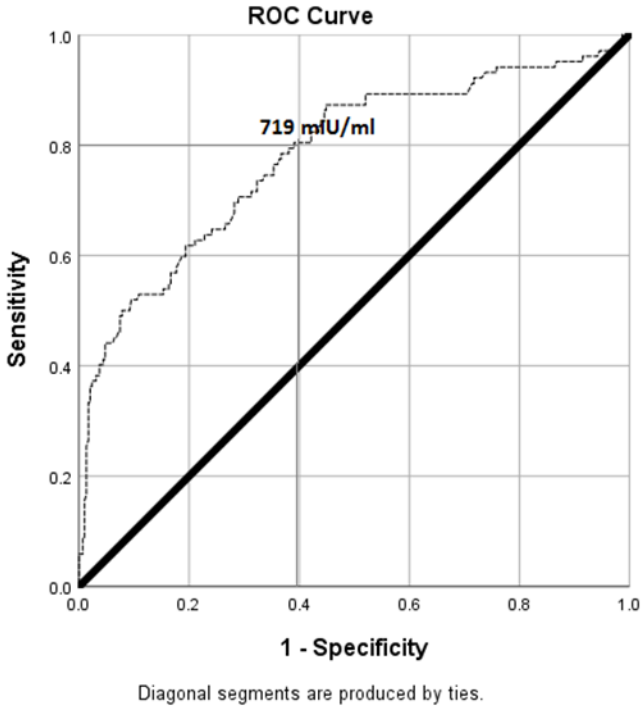

Figure 1- ROC curve analysis assessing the best cutoff for predicting the methotrexate success rate

Table 1. Distribution of descriptive characteristics of variables and their association with methotrexate (MTX) response success and need for laparoscopy/laparotomy via univariable analysis

		Total	MTX treatment success			Need for laparoscopy/laparotomy		
			Success	Failure	Significance (χ^2 test)	Yes	No	Significance (χ^2 test)
		No (%)	281 (71)	115 (29)		34 (8.6)	362 (91.4)	
Location of mass	Right	202 (51)	113 (55.9)	89 (44.1)	<0.001	25 (12.4)	177 (87.6)	0.006
	Left	194 (40)	168 (86.6)	26 (13.4)		9 (4.6)	185 (95.4)	
History of ectopic pregnancy	Yes	62 (15.7)	15 (24.2)	47 (75.8)	<0.001	4 (6/5)	58 (93/5)	0.51
	No	334 (84.3)	266 (79.6)	68 (20.4)		30 (9)	304 (91)	
Pelvic fluid in sonography	Yes	196 (49.5)	141 (71.9)	55 (28.1)	0.67	22 (11.2)	174 (88.8)	0.06
	No	200 (50.5)	140 (70)	60 (30)		12 (6)	188 (94)	
Presence of hematoma in sonography	Yes	99 (25)	28 (28.3)	71 (71.7)	<0.001	19 (19/2)	80 (80/8)	<0/001
	No	297 (25)	253 (85.2)	44 (14.8)		15 (5/1)	282 (94/9)	
Serum β-hCG	Below 719 mIU/ml	198 (50)	177 (89.4)	21 (10.6)	<0.001	1 (0.5)	197 (99.5)	<0/001
	Above 719 mIU/ml	198 (50)	104 (52.5)	94 (47.5)		33 (16.7)	165 (83.3)	
	Range	Mean (SD)			Significance (independent *t*-test)	Mean (SD)		Significance (independent *t*-test)
Age (years)	16-50	29.38 (5.96)	29.23 (6.01)	29.74 (5.84)	0.44	29.29 (5.43)	29.39 (6.01)	0.93
Mass size (millimeter)	5-169	20.38 (12.49)	18.78 (11.21)	24.32 (14.48)	<0/001	22.94 (8.21)	20.14 (12.80)	0.08

Table 2. Results of multivariable logistic regression analysis (via ENTER approach) assessing the predictors of methotrexate (MTX) failure response				
	B	S.E.	Sig.	OR (CI 95%)
MTX failure response				
Adnexa (right vs. left)	1.24	0.37	0.001	3.45 (1.67; 7.21)
Having positive history of ectopic pregnancy	3.34	0.47	<0.001	28.19 (11.26; 70.57)
Presence of hematoma in sonography	3.28	0.40	<0.001	26.69 (12.15; 58.60)
Serum β-hCG > 719 mu/ml	1.65	0.38	<0.001	5.19 (2.46; 10.95)
Mass size > 19 mm	0.58	0.36	0.10	1.79 (0.89; 3.59)
Model summary	-2 Log likelihood: 214.13 Cox & Snell R Square: 0.45 Nagelkerke R Square: 0.66 Hosmer and Lemeshow Test: Chi-square = 8.56; Sig:0.38			
B: unstandardized regression coefficient; SE: Standard Error; Sig: Significance level				