Effectiveness of Single-dose Methotrexate in Management of Ectopic Pregnancy

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Background: *Nowadays, ectopic pregnancies can be diagnosed early, and medical treatment with methotrexate instead of surgery is being used more often than in the past. No study of the success rates and predictive factors of single-dose methotrexate in management of ectopic pregnancy have previously been performed in Rajavithi Hospital.*

Objective: *To determine the success rates and predictive factors of single-dose methotrexate in treatment of ectopic pregnancy.*

Material and Method: *A retrospective study was conducted of ectopic pregnant women treated with methotrexate at Rajavithi Hospital between 1st January 2011 and 31st May 2015. Successful treatment was defined as a decrease in serum beta-hCG levels to less than 5 mIU/ml with no need for further methotrexate or surgical treatment. Data collection and analysis of serum beta-hCG levels at pre-treatment (day 0) and post-treatment (days 4 and 7) were performed in all the subjects.*

Results: *In total, 106 ectopic pregnant women were initially treated with single-dose methotrexate, and seventy-two cases (67.9%) had successful outcomes. There was no association between patient characteristics or clinical presentations with success rates, with the exception of history of previous ectopic pregnancy (success group 4.2% vs. failure group 17.6%, p = 0.020). Median serum beta-hCG level at day 0 was significantly different between the success and failure groups (1,511 and 2,466 mIU/ml respectively, p = 0.040). A pre-treatment serum beta-hCG level of below 5,000 mIU/ml was the significant predictive factor for success based on multivariate logistic analysis (adjusted odds ratio 3.33; 95% CI, 1.18 to 9.40; p = 0.023).*

Conclusion: *Ectopic pregnant women with pre-treatment serum beta-hCG levels below 5,000 mIU/ml were the best candidates for methotrexate treatment.*

Keywords: *Beta-hCG, Ectopic pregnancy, Methotrexate, Success rate*

The incidence of ectopic pregnancy has increased significantly in the past decade, and this may be associated with more sensitive ultrasound technology resulting in earlier diagnosis; it may also be partially explained by a rise in sexually transmitted infections and assisted reproductive technologies[1]. Ectopic pregnancy can be effectively treated medically or surgically. Salpingectomy is a traditional technique for treatment; however, many new investigation modalities, such as serum quantitative beta-hCG levels and ultrasound, now allow early detection of this problem, and conservative treatment options are therefore available. Minimally-invasive surgical techniques and medical management with methotrexate are the most commonly used techniques in the armamentarium for ectopic pregnancies. Treatment approach depends on the clinical circumstances, the site of the ectopic pregnancy, and the available resources. Methotrexate is a folic acid analogue that inhibits dehydrofolate reductase and thereby prevents synthesis of DNA that affects growing cells, including trophoblastic tissues[2]. It is frequently used as a medical treatment for ectopic pregnancy because of its safety and efficacy[3].

Clair et al[4] initially used methotrexate for the treatment of gestational trophoblastic tissue left *in situ* after exploration for abdominal pregnancy. Single-dose regimen was designed to achieve simplification of methotrexate administration and to increase patient compliance. Earlier studies have indicated that approximately 90% of ectopic pregnancies were successfully treated with single-dose regimen while approximately 15% to 20% of those required a second dose due to persistent beta-hCG levels[5]. In addition, a meta-analysis showed that 14.5% of women required more than one dose of methotrexate[6]. The importance

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of suitable patient selection was emphasized because of many factors, including the presence of yolk sac on ultrasound, fetal cardiac activity, size of ectopic mass, and initial serum beta-hCG levels, which were correlated with successful outcomes[7-9].

Lipscomb et al[10] found that high levels of serum beta-hCG were the most important factor associated with failure of treatment using a single-dose methotrexate. In another study, Nguyen et al[11] reported that serum beta-hCG level changes between days 0 and 4 after methotrexate therapy were a predictor of success.

Ectopic pregnancies in Rajavithi Hospital have been dealt with by medical treatment for several years, but there has been no study of its success rates. This research aimed to determine the success rates and predictive factors of single-dose methotrexate in management of ectopic pregnancy.

Material and Method

This was a retrospective descriptive study approved by the Institute Research Board of Rajavithi Hospital (No. 112/2558). Medical records were reviewed of unruptured ectopic pregnant women who were treated with single-dose, intramuscular methotrexate 50 mg/m^2 in Rajavithi Hospital between January 1st 2011 and May 31st 2015. Data including sociodemographic characteristics, ectopic pregnancy-related characteristics, and serum beta-hCG levels on days 0, 4, and 7 after methotrexate treatment were collected.

The single-dose regimen[2] was detailed as follows: (1) methotrexate 50 mg/m^2 administered intramuscularly on day 0; (2) measurement of serum beta-hCG levels to be taken on days 4 and 7; (3) serial monitoring of serum beta-hCG levels to be performed weekly if the levels dropped by 15% or more until normalization (<5 mIU/ml); and (4) repetitive doses of methotrexate to be administered if serum beta-hCG levels did not drop by 15%. Successful treatment was defined as serum beta-hCG levels having decreased to below 5 mIU/ml, and neither further doses of methotrexate nor surgical treatment being required.

Sample size calculation with an added 20% was based on the formula for one sample proportion (n = Z$^2_{\alpha/2}$ x p x (1-p)/d^2) using 2-tail alpha equal 0.05 and with acceptable error at 0.06. The success rate after single-dose methotrexate treatment from the study of Nguyen et al of 0.91[11] was used for calculation; therefore, at least 106 participants were required.

Statistical analysis was performed using SPSS version 17.0 software. Categorical data were expressed as frequency and percentage, while continuous data were represented by mean, standard deviation, median and range. Comparisons between categorical data were calculated using Chi-square test or Fisher's exact test, as appropriate, while comparison between continuous data was calculated utilizing Student's t-test or Mann-Whitney U test. Significant risk factors associated with success of treatment were determined by logistic regression analysis, and a probability value of $p<0.05$ was considered statistically significant.

Results

A total of 106 patients with unruptured ectopic pregnancy who were being treated with single-dose methotrexate were recruited. Seventy-two patients (67.9%) had successful medical treatment by methotrexate without further doses or surgery. Among 34 ectopic pregnant women in whom single-dose methotrexate treatment failed, 18 (17.0%) received a second dose of methotrexate after day 8 due to rising beta-hCG levels; 4 (3.8%) were treated with more than two doses (all of these 4 ectopic pregnant women were treated with methotrexate three doses on day 0, 8 and 16); and 12 women (11.3%) required surgical treatment (salpingectomy before day 7) with 9 (8.5%) of those undergoing emergency operation due to ruptured ectopic pregnancies.

The demographic and clinical characteristics of patients are listed in Table 1. Nine women with history of previous ectopic pregnancy were significantly associated with failure of single-dose methotrexate treatment (success group history 4.2% vs. failure group history 17.6%, $p=0.020$). Two women in the success group had salpingectomy while another was treated with methotrexate; 2 of these had occurred on the same side, there were no data for the other. In the failure group, all 6 ectopic pregnancies occurred on the same side, (1 tubal abortion, 3 methotrexate treatment and 2 salpingectomies). However, there were no significant differences between the patients in the two groups in terms of mean age, body mass index, occupation, education, family income, history of previous pregnancy, gestational age, pregnancy forms, contraceptive methods, tobacco use, site of ectopic pregnancy, history of previous tubal surgery, history of sexually transmitted infections and clinical presentation of pain, vaginal bleeding, nausea/vomiting or presenting with adnexal mass.

Serum beta-hCG levels on days 0, 4 and 7 and number of days to resolution (serum beta-hCG <5 mIU/

Table 1. Comparison of characteristics between the success and failure groups after single dose methotrexate treatment

Characteristics	Total n = 106 (%)	Success n = 72 (%)	Failure n = 34 (%)	p-value
Age (years)	26.7+6.0	26.6+6.1	27.0+5.9	0.721^T
BMI	21.8+4.1	21.6+4.2	22.2+4.0	0.562^T
Occupation				0.278^F
Business	3 (2.8)	1 (1.4)	2 (5.9)	
Government	1 (0.9)	1 (1.4)	0 (0.0)	
Housework	17 (16.0)	9 (12.5)	8 (23.5)	
Employee	73 (68.9)	53 (73.6)	20 (58.8)	
Student	12 (11.3)	8 (11.1)	4 (11.8)	
Education				0.305^F
No education	5 (4.7)	5 (7.0)	0 (0.0)	
Primary/secondary school	65 (61.3)	42 (58.3)	23 (67.6)	
Graduate	36 (34.0)	25 (34.7)	11 (32.4)	
Family income (baht)				0.975
<10,000	33 (31.1)	22 (30.6)	11 (32.3)	
10,001 to 30,000	45 (42.5)	31(43.1)	14 (41.2)	
>30,000	12 (11.3)	8 (11.1)	4 (11.8)	
NA	16 (15.1)	11 (15.3)	5 (14.7)	
median (min-max)	15,000 (3,000 to 60,000)	15,000 (3,000 to 50,000)	15,000 (5,000 to 60,000)	
Parity				0.053
0	55 (51.9)	42 (58.3)	13 (38.2)	
≥1	51 (48.1)	30 (41.7)	21 (61.8)	
median (min-max)	0 (0 to 2)	0 (0 to 2)	1 (0 to 2)	
Abortion				0.831
0	71 (67.0)	49 (68.1)	22 (64.7)	
1	28 (26.4)	19 (26.4)	9 (26.5)	
≥2	7 (6.6)	4 (5.6)	3 (8.8)	
median (min-max)	0 (0-3)	0 (0-3)	0 (0-2)	
Gestational age (wk)	6.9+2.0	6.9+1.7	6.9+2.6	0.979^T
Pregnancy methods				1.000^F
Natural	105 (99.1)	71 (98.6)	34 (100.0)	
ART	1 (0.9)	1 (1.4)	0 (0.0)	
Contraception use	57 (53.8)	40 (55.6)	17 (50.0)	0.287
Method				0.601^F
Coitus interruptus	8 (14.0)	3 (7.5)	5 (29.4)	
Condom	7 (12.3)	6 (15.0)	1 (5.9)	
Emergency pills	8 (14.0)	6 (15.0)	2 (11.8)	
OCPs	7 (12.3)	5 (12.5)	2 (11.8)	
POPs	25 (43.9)	18 (45.0)	7 (41.2)	
TR	2 (3.5)	2 (5.0)	0 (0.0)	
Tobacco use	13 (12.3)	9 (12.5)	4 (11.8)	0.914
History of ectopic pregnancy	9 (8.5)	3 (4.2)	6 (17.6)	0.020*
History of tubal surgery	7 (6.6)	5 (6.9)	2 (5.9)	0.670^F
Type of surgery				0.619^F
TR	2 (28.6)	2 (40.0)	0 (0.0)	
Tubal reanastomosis	1 (14.3)	1 (20.0)	0 (0.0)	
Salpingos-/salpingectomy	4 (57.1)	2 (40.0)	2 (100.0)	

Values are presented as number (percent), mean ± SD, median (minimum to maximum).
* = Statistically significant at p-value <0.05; T = A p-value from independent t-test; F = A p-value from Fisher's exact test; BMI = body mass index; ART = assisted reproductive technology; OCPs = combined oral contraceptive pills; POPs = progestogen only pills; TR = tubal resection; STIs = sexual transmitted infections

Table 1. cont.

Characteristics	Total n = 106 (%)	Success n = 72 (%)	Failure n = 34 (%)	p-value
History of STIs	3 (2.8)	2 (2.8)	1 (2.9)	1.000F
Abdominopelvic pain	92 (86.8)	63 (87.5)	29 (85.3)	0.754
Vaginal bleeding	94 (88.7)	64 (88.9)	30 (88.2)	0.921
Nausea/vomiting	19 (17.9)	15 (20.8)	4 (11.8)	0.256
Presenting with adnexal mass	47 (44.3)	35 (48.6)	12 (35.3)	0.198
Size of adnexal mass (cm)				
>1.0 to 3.0	23 (52.3)	19 (59.4)	4 (33.3)	
>3.0 to 5.0	14 (31.8)	10 (31.3)	4 (33.3)	
>5.0	7 (15.9)	3 (9.4)	4 (33.3)	0.141

Values are presented as number (percent), mean $\pm$ SD, median (minimum to maximum).
* = Statistically significant at p-value <0.05; T = A p-value from independent t-test; F = A p-value from Fisher's exact test; BMI = body mass index; ART = assisted reproductive technology; OCPs = combined oral contraceptive pills; POPs = progestogen only pills; TR = tubal resection; STIs = sexual transmitted infections

Table 2. Serum beta-hCG levels in pre-post methotrexate treatment and number of days to resolution between success and failure groups

Beta-hCG(mIU/ml)	Success		Failure		p-value
	n	median (min-max)	n	median (min-max)	
Pre-treatment day 0	72	1,511.5 (135.0 to 34,253.8)	34	2,466.0 (272.1 to 12,141.0)	0.040*
Post-treatment day 4	54	1,122.5 (2.0 to 10,511.0)	27	2,570.0 (326 to 8,234.0)	0.005*
Post-treatment day 7	54	693.4 (2.2 to 6,000.0)	27	2,210.0 (47.6 to 10,230.0)	<0.001*
Number of days to resolution (days)	55	8.0 (4.0 to 45.0)	30	23.0 (4.0 to 42.0)	<0.001*

A p-value from Mann-Whitney U test, * = Statistical significant at p-value <0.05

ml) are presented in Table 2. Median pre-treatment (day 0) serum beta-hCG level was 1,511.5 mIU/ml for the successful cases and 2,466.0 mIU/ml for the unsuccessful ones (p = 0.040). Serum beta-hCG levels in pre-post methotrexate treatment and number of days to resolution in the success group were significantly different from those of the failure group. Serum beta-hCG levels of the success group declined from day 0 through day 7, whereas those of patients in the failure group remained fairly steady. Patients with declined serum beta-hCG levels by day 7 were monitored weekly until serum beta-hCG levels fell to below 5 mIU/ml. Median number of days to resolution in the success group was 8 compared with 23 in the failure group.

Serum beta-hCG levels were divided into four ranges (Table 3). Success rates decreased as serum beta-hCG levels on day 0 rose, especially at levels ≥5,000 mIU/ml, varying from 63.6 to 85.7% with lower levels to 47.6% with levels ≥5,000. The results in serum beta-

hCG levels on day 7 showed the same trend, with success rates dropping to 18.2% at levels ≥5,000 mIU/ml.

Odds ratios of success after single-dose methotrexate treatment were compared among various cut off points of pre-treatment serum beta-hCG levels, and the results are shown in Table 4. At a cutoff level of 5,000 mIU/ml, the odds ratio of 2.97 (95% CI, 1.11-7.91; p = 0.026) was higher than that of any other cut off point.

Results of multivariate analysis using logistic regression are displayed in Table 5. Potential predictive factors for success with p-value ≤0.2 are shown in the table. Serum beta-hCG levels on day 0 were the only significant predictive factor for success with adjusted odds ratio at 3.33 (95% CI, 1.18 to 9.40; p = 0.023).

Discussion

This study examined the success rate of

Table 3. Success rates at various serum beta-hCG levels at pre-treatment day 0 and post-treatment day 7

	Total n (%)	Success n (%)	Failure n (%)	Success Rate (%)	p-value
Pre-treatment Day 0		0.049*C			0.013*M
<1,000	31 (29.2)	23 (31.9)	8 (23.5)	74.2	
1,000 to 1,999	21 (19.8)	18 (25.0)	3 (8.8)	85.7	
2,000 to 4,999	33 (31.1)	21 (29.2)	12 (35.3)	63.6	
≥5,000	21 (19.8)	10 (13.9)	11 (32.4)	47.6	
median (min-max)	2,036.0 (135.0 to 34,253.8)	1,511.5 (135.0 to 34,253.8)	2,466.0 (272.1 to 12,141.0)		
Post-treatment Day 7		0.001*C			0.001*M
<1,000	37 (45.7)	33 (61.1)	4 (14.8)	89.1	
1,000 to 1,999	20 (24.7)	11 (20.4)	9 (33.3)	55.0	
2,000 to 4,999	13 (16.0)	8 (14.8)	5 (18.5)	61.5	
≥5,000	11 (13.6)	2 (3.7)	9 (33.3)	18.2	
median (min-max)	1,078 (2.2 to 10,230.0)	693.4 (2.2 to 6,000.0)	2,210.0(47.6 to 10,230.0)		

C = A p-value from Chi-Square test, M = A p-value from Mann-Whitney U test, *= Statistically significant at p-value < 0.05

single-dose methotrexate in management of ectopic pregnancy and predictive factors of successful treatment. The overall success rate was 67.9%, comparable with earlier studies in which the range of success rates varied between 61.8 and 96.7%[7,8,11,12]. Most demographic data were not different between the two groups such as age (26.6 vs. 27.0 years), BMI (21.6 vs. 22.2 kg/m²), occupation (mostly employees), education (primary/secondary school), family income (average 15,000 baht per month), no history of abortion, gestational age (6.9 weeks in both groups), natural pregnancy, history of contraceptive use and method (mostly progesterone-only pills in both groups), tobacco use, history of previous tubal surgery and sexual transmitted infections, clinical presentation of abdominopelvic pain (87.5% vs. 85.3%), vaginal bleeding (88.9% vs. 88.2%) and adnexal mass (48.6% vs. 35.3%). Although number of parity (0 vs. 1) ($p = 0.053$), types of tubal surgery (salpingectomy/ salpingostomy; 40% vs. 100%) ($p = 0.619$), nausea and vomiting (20.8% vs. 11.8%) ($p = 0.256$), and size of adnexal mass (>1.0 to 3.0 cm; 59.4% vs. 33.3%) ($p = 0.141$) showed dissimilar trends, they failed to achieve statistical significance due to the small number of patients. Only history of ectopic pregnancy was significantly lower in the success group. One possible explanation for the significantly higher failure rate in these patients could be that repeated pregnancy on the same side of prior ectopic pregnancy might result in relatively advanced and vigorous damage compared with the virgin Fallopian tube.

Both pre- and post-treatment serum beta-hCG levels, and their decline between pre- and post-treatment were the predictive factors for success rates of single-dose methotrexate treatment. Nguyen, et al[11] found a relationship between success rates and declining serum beta-hCG levels prior to, and day 4 after, methotrexate treatment (40% of cases (12/30)); all 12 cases with decreasing serum beta-hCG levels of from days 0 to 4 were successfully treated. This study demonstrated a similar trend: the success group had decreased serum beta-hCG levels from day 0 to day 4, while patients in the failure group showed the opposite trend. In addition, the serum beta-hCG levels of subjects in the success group had rapidly depleted on day 7, while there was no significant change in the failure group. Furthermore, the number of days to resolution in treatment outcomes in the success group was shorter than that of the failure group (8 vs. 23 days). Interestingly, days to resolution in both groups in the present study were fewer than found by Stovall et al (38.4 days in successful

Table 4. Odds ratio of success comparison in various cut off points of initial beta-hCG levels

Level of hCG (mlU/ml)	Odds ratio (95% CI)	*p*-value
<5,000 vs. ≥ 5,000	2.97 (1.11 to 7.91)	0.026*
<8,000 vs. ≥ 8,000	1.90 (0.54 to 6.71)	0.315
<10,000 vs. ≥ 10,000	0.69 (0.13 to 3.60)	0.656

A *p*-value from Chi-square test, * = Statistically significant at *p*-value <0.05

Table 5. Logistic regression analysis of prognostic factors for success rate

	Crude OR	Adjusted OR (95% CI)	*p*-value
Parity			
0	2.26	2.06 (0.83 to 5.15)	0.120
≥1	Ref	Ref	
History of ectopic pregnancy			
Yes	Ref	Ref	0.084
No	4.93	3.86 (0.83 to 17.18)	
Presenting with adnexal mass			
Yes	Ref	Ref	0.107
No	0.58	0.57 (0.23 to 1.38)	
Level of hCG (mIU/ml)			
<5,000	2.97	3.33 (1.18 to 9.40)	0.023*
>5,000	Ref	Ref	

* = Statistically significant at *p*-value <0.05

treatment)[8]. The reason for this may be that pre-treatment of serum beta-hCG levels both in the success and failure groups in this study were lower than in their study (median pre-treatment Day 0: success group = 1,511.5, failure group = 2,466.0 in our study, and mean beta-hCG level in Stovall et al = 4,558 mIU/ml).

The success rates according to four ranges of pre-treatment serum beta-hCG levels, <1,000; 1,000 to 1,999; 2,000 to 4,999; ≥5,000 mIU/ml, were 74.2, 85.7, 63.6 and 47.6%, respectively (*p* = 0.049). Post-treatment serum beta-hCG levels on day 7 showed a similar trend to those on day 0. These results indicated that initial beta-hCG levels below 5,000 mIU/ml were a good predictive factor for successful treatment, consistent with the study of Menon et al[7]. Likewise, Lipscomb et al[10] determined the cutoff value of the initial beta-hCG level below 10,000 mIU/ml as a predictor of successful treatment.

The odds ratio of success compared among various cutoff points of initial serum beta-hCG levels (<5,000 vs. ≥5,000; <8,000 vs. ≥8,000; and <10,000 vs. ≥10,000) were 2.97, 1.90 and 0.69 respectively. Thus, the cutoff level <5,000 mIU/ml was confirmed as a

significant predictive factor for successful treatment. The potential predictors for success in medical treatment from this study were number of parity, history of prior ectopic pregnancy, presentation of adnexal mass, and the initial serum beta-hCG levels; however, initial serum beta-hCG titer of 5,000 mIU/ml was the only significant predictive factor based on multivariate analysis (*p* = 0.023).

The present study had some limitations due to the nature of retrospective studies. Some sociodemographic and clinical data were missing; sample size was too small for analysis by logistic regression and reflected by its wide range of effect size. In order to supplement this research, a prospective study should be designed in the future that would investigate the variable factors predicting successful methotrexate therapy.

In summary, the effectiveness of single-dose methotrexate in management of unruptured ectopic pregnancy was 67.9%. The main predictive factor for success was pre-treatment serum beta-hCG levels at below 5,000 mIU/ml. These results can be clinically applied to counsel ectopic pregnant patients with regard

to their plan of treatment and surveillance.

What is already known on this topic?

Overall success rates of single-dose methotrexate in management of ectopic pregnancy were 61.8% to 96.7%.

What this study adds?

Pretreatment serum beta-hCG levels of <5,000 mIU/ml were a predictive factor for successful treatment of ectopic pregnant women with single-dose methotrexate. Using a cutoff point of this level was 2.97 times more successful than ≥5,000 mIU/ml.

Acknowledgements

Potential conflicts of interest

None.

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