Original Article

Success Rate of Single-Dose Regimen of Methotrexate Treatment in Ectopic Pregnancy at Ramathibodi Hospital: Twelve-Year Experience

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Objective: To evaluate the success rate of single-dose intramuscular methotrexate [MTX] regimen for the treatment of ectopic pregnancy at Ramathibodi Hospital and identify predictive factors of treatment success.

Materials and Methods: The present study was a retrospective observational study of 141 patients diagnosed as ectopic pregnancy and treated by single-dose MTX regimen at Ramathibodi Hospital between October 2005 and September 2017.

Results: Of the 141 patients included in the present study, the authors found 103 patients were successfully treated with single-dose MTX regimen (overall success rate 73.05%). The factors related to successful MTX treatment were pretreatment β-hCG level less than 3,000 mIU/ml (OR 3.07, 95% CI 1.20 to 7.84) and the decrease of β-hCG level on day 4 compared with day 0 (OR 7.45, 95% CI 2.84 to 19.58).

Conclusion: The single dose MTX regimen is a safe and effective treatment for ectopic pregnancy after a proper patient selection. The pretreatment β-hCG level and the change of β-hCG level between day 0 and day 4 are the important predictive factors that can predict the success of the treatment.

Keywords: Ectopic pregnancy, Methotrexate, Success rate

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Ectopic pregnancy means a blastocyst that is formed after fertilization and is implanted in a location other than the endometrium such as the fallopian tube, ovary, abdominal cavity, or cervix[1,2]. The Centers for Disease Control and Prevention [CDC] found that the incidence of ectopic pregnancy could be 1% to 2% of reported pregnancies and this condition has the maternal mortality rate of 4.9% in developed countries[3,4]. Nowadays, the improvements in diagnostic tools and treatments of ectopic pregnancy resulted in 57% reduction of death rate. However, ectopic pregnancy is still the primary cause of first-trimester maternal mortality[5]. The etiology of ectopic pregnancy is still unknown. However, there are several risk factors such as patients with history of previous ectopic pregnancy, pelvic infection, conceived with intrauterine device, infertility, and smoking[6].

Ectopic pregnancy can be treated medically or surgically depending on clinical circumstances, severity of pathology, location of ectopic pregnancy, and availability of resources. In the past, ectopic pregnancy was mainly treated surgically. With the advance of diagnostic technologies that allow earlier detection, more conservative treatment such as medical treatment is commonly used. The use of methotrexate [MTX] for the medical treatment of ectopic pregnancy was first described in 1982 by Tanaka et al[7]. They used 30 mg MTX on the first day and then 15 mg per day onward, where 12 doses were used, and this regimen could decrease serum beta human chorionic gonadotropin [β-hCG] from 64,000 IU/L to 40 IU/L without surgery. Since their introduction, medical treatment has gained popularity in treating ectopic pregnancy over the past 10 years.

There are several agents used for medical treatment such as MTX, potassium chloride, hyperosmolar glucose, prostaglandins, and RU-486. However, MTX is the most frequently used for medical treatment because of its efficacy, availability, and less side effects. MTX is a folic acid antagonist that inhibits dihydrofolate reductase [DHFR] preventing DNA

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and RNA synthesis[8]. Many studies have revealed that the effectiveness of MTX therapy ranges from 70% to 94%[9-13]. The factors that are related to outcome failure are high pretreatment β-hCG level, size of the gestational mass (greater than 4 cm), adnexal fetal cardiac activity, rapid rise in hCG concentration during MTX treatment, and presence of free peritoneal blood[14,15].

At Ramathibodi Hospital, the authors have been using a single dose of MTX regimen since 2005. The researchers were interested in collecting and reporting information about using MTX as a treatment option for ectopic pregnancy in Ramathibodi Hospital focusing on the success rate of the single-dose MTX regimen and factors affecting the success of medical treatment for ectopic pregnancy.

Materials and Methods

The present research was a retrospective observational study that reviewed medical records of patients diagnosed as ectopic pregnancy and treated in the Department of Obstetrics and Gynecology at Ramathibodi Hospital between October 2005 and September 2017. The present study was approved by the Research Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

The diagnosis of ectopic pregnancy was made in two ways. The first was visualization of gestational sac outside of the uterus by ultrasonography or absence of trophoblastic tissue by pathological report from uterine curettage. The other way of diagnosis was absence of an intrauterine pregnancy by ultrasonography when β-hCG level was above the discriminatory zone or abnormal rise/plateau of β-hCG level when β-hCG was below the discriminatory zone. The patients who were treated with a single-dose intramuscular MTX regimen and completed the β-hCG follow up protocol were included. The exclusion criteria were incomplete medical records and non-adherence to the protocol.

In Ramathibodi Hospital, ectopic pregnancy patients who do not have any contraindications of medical treatment are commonly treated with single-dose of MTX regimen. The contraindications to MTX treatments are hemodynamically unstable patient, ruptured ectopic pregnancy, inability to participate in follow-up sensitivity to MTX, moderate to severe anemia, leukopenia, or thrombocytopenia, active pulmonary or peptic ulcer disease, and clinically hepatic or renal dysfunction. Before MTX administration, the patient's serum β-hCG level, complete blood count, liver function test, coagulation, and chest X-ray were documented. The patients received 50 mg/m^2 of MTX intramuscular on day 0. Their serum β-hCG levels were monitored on day 4 and day 7. If the serum β-hCG level decreased at least 15% between the two measurements, serum β-hCG level would be monitored weekly until it reached non-pregnant level. However, if the serum β-hCG level decreased less than 15% and the patients did not have the contraindications, those patients would require repeated dose of MTX in the same dosing on day 7 and serum β-hCG level monitored on day 11 and 14. If serum β-hCG level between day 11 and 14 decreased more than 15%, serum β-hCG levels were monitored weekly until they reach non-pregnant level. If serum β-hCG level decreased less than 15%, this indicated treatment failure and these patients would require surgical treatment.

The treatment success was defined as serum β-hCG decreased to non-pregnant level without surgery. This included the patients who got single dose MTX and patients who needed repeated dose of MTX. The treatment failure was the patients who were primarily treated with single dose regimen of MTX and then required surgical treatment due to ruptured ectopic pregnancy or plateau β-hCG level.

According to the American Society of Reproductive Medicine [ASRM] and the American College of Obstetrics and Gynecology [ACOG], they suggest the predictive factors which are related to MTX treatment failure are high pretreatment hCG level, size of the gestational mass, adnexal fetal cardiac activity, rapid rise in hCG concentration during MTX treatment and presence of free peritoneal blood[14,15]. Therefore, this study selected these factors for multivariate analysis.

Statistical analysis was performed using Stata version 15.0 (StataCorp, College Station, Texas, USA). Quantitative data were described using the percentage, mean ± standard deviation, median (min, max), and compared using the Student t-test. Qualitative data were described by frequency and relative frequency and compared using the Chi-square test or the Fisher's exact test when frequency was less than five. A receiver operation characteristic [ROC] curve was plotted for the evaluation of the prognostic value of pretreatment serum β-hCG level and percentage change of serum β-hCG between day 0 and day 4. Statistical significance was set at *p*-value of less than 0.05.

Results

From retrospective review of medical records between 2005 and 2017, 689 patients were diagnosed as ectopic pregnancy at Ramathibodi Hospital. One

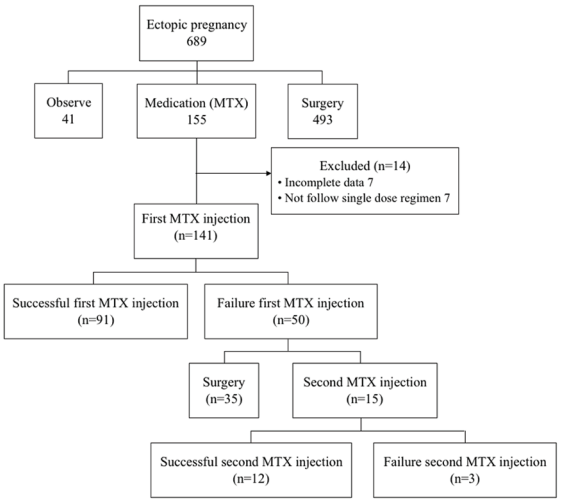

Figure 1. Treatment flowchart.

hundred fifty-five patients were treated with single-dose regimen of MTX, whereas 493 patients were initially treated surgically, and 41 patients were managed by observation. From 155 patients who were initially treated with single dose regimen of MTX included in the present study, 14 patients were excluded, among them seven that had incomplete medical record and seven that did not follow single dose regimen. Therefore, 141 patients were included in the present study as shown in Figure 1.

The mean age of patients was 30.76±5.06 years and the mean of gestational age was 52.86±12.65 days. Ninety-seven patients were primiparous (68.79%). Only 10 patients (7.09%) had history of ectopic pregnancy. The most common presenting symptoms were pelvic pain and vaginal bleeding (85 patients, 60.28%). The mean size of ectopic mass was 2.38±1.10 cm. Most ultrasonographic finding were complex mass that could not be clearly identify as gestational sac (84.40%). The most common location of ectopic pregnancy, as identified by ultrasonography, was at adnexa (119 patients, 84.40%). Twenty-two patients had unknown location (15.60%). The median pretreatment β-hCG was 2,031 mIU/ml. Ultrasonographic finding of pelvic free fluid was found in 72 patients (51.06%) and none had embryonic cardiac activity (Table 1).

From 141 patients included in the present study and treated with single dose regimen of MTX, 91 patients were successfully treated with first dose of MTX injection. This represented the success rate in first dose of 64.54%. Fifty patients' β-hCG failed to lower by more than 15% after first dose administration. Of these 50 patients, 35 patients were treated surgically because they were diagnosed ruptured ectopic pregnancy. The remaining 15 patients were treated with repeated dose of MTX and 12 patients were successfully treated. Therefore, the success rate of repeated dose of MTX was 80%. The overall success rate of single dose regimen of MTX (success rate of first dose and repeated dose) accounted for 73.05%. The mean time to resolution of serum β-hCG was 41.92±17.44 days (Figure 1).

Thirty-eight patients (26.95%) were treated surgically after MTX administration. The indications for surgery were suspected ruptured ectopic pregnancy (35 patients, 92.10%) and plateau β-hCG level (three patients, 7.89%). Surgical approaches were 30 cases of laparotomy (78.95%) and eight cases of laparoscopy (21.05%). Surgical procedures were 35 cases of salpingectomy (92.10%) and three cases of salpingostomy (7.89%).

In comparing the success and failure group of MTX treatment, there were no statistical differences in patient characteristics such as age, parity, body mass index [BMI], gestational age, clinical symptoms, history of previous ectopic pregnancy, location of ectopic mass, size of ectopic mass, embryonic cardiac activity, and free fluid. Only the pretreatment β-hCG level was significantly lowered in the success group (1,589 versus 3,505 mIU/ml, $p = 0.0004$). The percentage change of β-hCG level between days 0 and 4 decreased by 16.73% in the success group, but the level increased by 25.42% in the failure group, which were statistically significant ($p<0.001$) (Table 1).

Using multivariate analysis, the present study found that the factors related to successful MTX treatment were pretreatment β-hCG level and the change of β-hCG level between day 0 and day 4 as shown in Table 2. The patients who had pretreatment β-hCG level less than 3,000 mIU/ml had success rate three times greater than the group that had pretreatment β-hCG level more than 3,000 mIU/ml (OR 3.07, 95% CI 1.20 to 7.84). The group of patients who had β-hCG on day 4 lower than day 0 had success rate seven times greater than the group that had β-hCG on day 4 higher than day 0 (OR 7.45, 95% CI 2.84 to 19.58). Other factors such as size of ectopic mass, presence of gestational sac, and presence of free fluid in pelvic cavity had no statistically significant effect on success rate of treatment.

After we found the statistical relevance between pretreatment β-hCG level, the percentage change of serum β-hCG between day 0 and 4 and treatment

Table 1. Demographic data and clinical characteristics of subjects with methotrexate treatment

Characteristic	MTX treatment (n = 141)	Successful MTX treatment (n = 103)	Failure of MTX treatment (n = 38)	*p*-value
Age (years)	30.76±5.06	30.75±4.92	30.79±5.47	0.965
Parity				0.450
0	97 (68.79)	73 (70.87)	24 (63.16)	
1	32 (22.70)	20 (19.42)	12 (31.58)	
2	11 (7.80)	9 (8.74)	2 (5.26)	
3	1 (0.71)	1 (0.97)	0 (0.00)	
Previous ectopic pregnancy				0.062
No	131 (92.91)	93 (90.29)	38 (100)	
Yes	10 (7.09)	10 (9.71)	0 (0.00)	
BMI (kg/m2)	22.25±4.14	22.51±4.11	21.55±4.19	0.224
Gestational age (days)	52.86±12.65	53.50±12.76	51.11±12.33	0.319
Clinical symptoms				0.622
Vaginal bleeding	40 (28.37)	31 (30.10)	9 (23.68)	
Pelvic pain	13 (9.22)	8 (7.77)	5 (13.16)	
Vaginal bleeding and pelvic pain	85 (60.28)	62 (60.19)	23 (60.53)	
No symptom	3 (2.13)	2 (1.94)	1 (2.63)	
Size of ectopic mass (cms)	2.38±1.10	2.48±1.16	2.14±0.92	0.132
Gestational sac				0.114
Absent	119 (84.40)	90 (87.38)	29 (76.32)	
Present	22 (15.60)	13 (12.62)	9 (23.68)	
Location of ectopic mass				0.301
Adnexa	119 (84.40)	84 (81.55)	35 (92.11)	
Unknown location	22 (15.60)	19 (18.45)	3 (7.89)	
Embryonic cardiac activity				0.477
Absent	141 (100)	103 (100)	38 (100)	
Present	0 (0.00)	0 (0.00)	0 (0.00)	
Free fluid				0.324
Absent	69 (48.94)	53 (51.46)	16 (42.11)	
Present	72 (51.06)	50 (48.54)	22 (57.89)	
Serum β-hCG (mIU/ml)				
Day 0 (pretreatment)	2,031 (101, 22,693)	1,589 (101, 14,684)	3,505 (240, 22,693)	0.0004
Day 4	1,918 (37, 15,604)	938 (37, 15,604)	4,394 (173, 14,953)	<0.001
Day 7	960.5 (2, 13,027)	551 (2, 11,568)	4,080 (198, 13,027)	<0.001
Percentage change of serum β-hCG				
Day 0 to day 4	12.05 (-415.41, 96.57)	16.73 (-130.38, 96.57)	-25.42 (-415.41, 55.80)	<0.001
Day 4 to day 7	29.64 (-22.73, 94.59)	33.97 (-18.16, 94.59)	15.39 (-22.73, 55.53)	<0.001
Day 0 to day 7	40.49 (-325.22, 99.81)	48.85 (-156.20, 99.81)	-1.88 (-325.22, 54.38)	<0.001

MTX = methotrexate; BMI = body mass index; β-hCG = β-human chorionic gonadotropin

Day 0: day of the first methotrexate injection, Day 4: 4 days after methotrexate injection, and Day 7: 7 days after methotrexate injection

Data are presented as mean ± standard deviation, median (min, max), or n (%)

Table 2. Multivariate analysis comparing success and failure of methotrexate treatment

Characteristic	OR (95% CI)	*p*-value
Pretreatment β-hCG ≤3,000 mIU/ml	3.07 (1.20 to 7.84)	0.019
Serum β-hCG day 4 < day 0	7.45 (2.84 to 19.58)	<0.001
Size of ectopic mass ≤3.5 cm	0.36 (0.09 to 1.41)	0.143
Absent free fluid	2.33 (0.87 to 6.28)	0.094
Absent gestational sac	1.23 (0.41 to 3.70)	0.708

OR = odds ratio; CI = confidence interval; β-hCG = β-human chorionic gonadotropin

success of MTX treatment, we use the plotted ROC curve to identify the proper cut off β-hCG level. Figure 2 shows the plotted ROC curve and the area under the curve for evaluation of the prognostic value of pretreatment β-hCG level. The cut off value was 3,022 mIU/ml with sensitivity 70.87% and specificity 57.89%. The positive predictive value was 80.4% and negative predictive value was 40.8%. The success rate of single dose MTX regimen varied inversely with the level of pretreatment β-hCG. The present study also found that if pretreatment β-hCG level was greater than 3,000 mIU/ml, the success rate would decrease to 62.07%, whereas if pretreatment β-hCG level was lower than 3,000 mIU/ml, the success rate would increase to 80.74% (Figure 3).

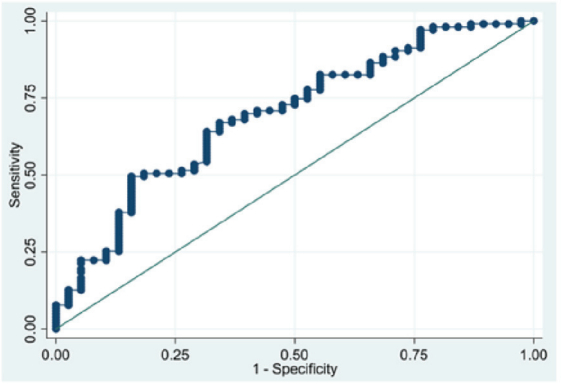

Figure 2. ROC Curve for the evaluation of the prognostic value of pretreatment serum β-hCG (mIU/ml), area under the curve: 69.58±5.03 (95% confidence interval 59.73 to 79.44).

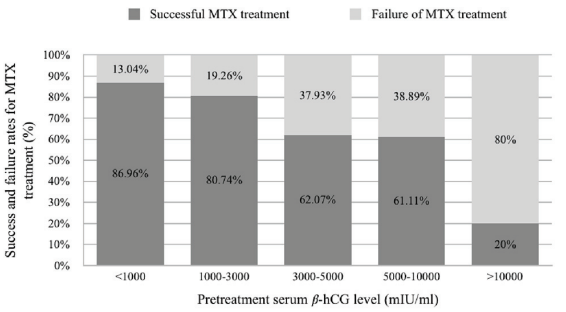

Figure 3. Success and failure rates for methotrexate treatment according to pretreatment serum β-hCG level.

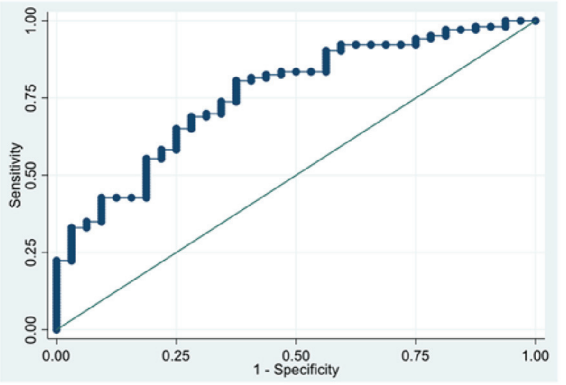

Figure 4. ROC Curve for the evaluation of the prognostic value of the percentage change of serum β-hCG day 0 and day 4, area under the curve: 76.12±4.71 (95% confidence interval 66.88 to 85.36).

Figure 4 shows the plotted ROC curve and area under the curve for evaluation of the prognostic value of the percentage change of serum β-hCG between day 0 and 4. The present study found the proper cutoff value of the percentage change of serum β-hCG on day 4 compared with day 0 should not increase more than 17% with sensitivity 80.6%, specificity 62.5%, positive predictive value 82%, and negative predictive value 48.8%.

In the present study, seven patients (4.96%) had adverse effect from MTX with five cases of nausea and vomiting (71%) and two cases of abnormal liver function test (29%).

Discussion

The present study reviewed the data of the ectopic pregnancy patients treated with single-dose MTX regimen at Ramathibodi hospital over the last 12 years. The results showed overall success rate at 73.05%, which is similar to other studies that had success rates ranging from 70% to 94%[9-13]. Srivichai et al[10] studied the efficacy of single-dose MTX regimen in Thai population and reported the success rate as high as 90.6%. This higher success rate might be due to different patients' characteristics, patients in their study had mean pretreatment β-hCG level at 873 mIU/ml (range 48 to 4,600 mIU/ml), which was lower than the present study that had median pretreatment β-hCG at 2,031 mIU/ml (range 101 to 22,693 mIU/ml).

According to ASRM and ACOG, suggest the predictive factors related to MTX treatment failure are high pretreatment hCG level (more than 5,000 mIU/ml), size of the gestational mass (greater than 4 cm), adnexal fetal cardiac activity, rapid rise in hCG concentration during MTX treatment and presence of free peritoneal blood[14,15]. The results of the present study are consistent with ASRM and ACOG. The pretreatment β-hCG level and the change of β-hCG level between day 0 and day 4 are related to success rate of single dose MTX treatment. However, the present study did not find statistical relevance between the success rate of MTX treatment and the size of ectopic mass, adnexal fetal cardiac activity, or free fluid. This might be the result of too small population for these characteristics. For example, the present study did not find any patient with adnexal fetal cardiac activity. The strict guideline of medical treatment for ectopic pregnancy at Ramathibodi Hospital does not allow the use of medical treatment in patients with adnexal fetal cardiac activity. Most of the ultrasonographic findings of ectopic mass was complex mass that had blood clot component in it, therefore, accurate gestational sac measurement was very difficult. Only 22 patients in the present study had measurable gestational sac (15.60%).

Pretreatment β-hCG level is the important predictive factor of successful MTX treatment. The proper cutoff β-hCG level varied between 1,000 and 5,000 mIU/ml[16-19]. Menon et al[17] carried out a systematic review that collected data from five studies with a population of 503. The failure rate of MTX treatment in the group that had pretreatment β-hCG level greater than 5,000 mIU/ml was five times higher than the group which had the pretreatment β-hCG level lower than 5,000 mIU/ml (OR 5.45, 95% CI 3.04 to 9.78). The ASRM committee opinion in 2013 suggested that primary MTX treatment should be withheld if the level of pretreatment β-hCG is greater than 5,000 mIU/ml[14]. In the present study, the proper cutoff level was 3,022 mIU/ml, which might result from different population characteristics. The present study was focused on Thai population, which is different from other studies that were conducted in European or American populations. Comparing to other studies that were conducted in Asian population, the cutoff values are similar[20,21]. Kim et al[20] conducted the study to investigate proper pretreatment serum β-hCG cutoff value for medical treatment success with single-dose regimen of MTX in ectopic pregnancy. They found the proper serum β-hCG cutoff value to predict the treatment success was 3,026 IU/L.

Another important predictive factor is the change of β-hCG level between day 0 and day 4. According to ASRM and ACOG recommendations, they suggest that the change of β-hCG level during MTX treatment is an effective predictor of success for MTX treatment[14,15]. Many studies found the reduction of β-hCG level on day 4 compared with day 0 can predict the success of MTX treatment[21-24]. Girija et al[21] found that a 10% decrease in β-hCG value between day 4 and day 0 was a predictor of successful MTX treatment with sensitivity of 77% and specificity of 81%. In the present study, the result aligned with those previous studies. The proper cutoff value of the percentage change of serum β-hCG level on day 4 compared with day 0 should not increase more than 17%.

The important advantage of the present study was the proper cutoff level in Thai population. Currently most of the recommendations are based on the studies in European and American populations which might not be suitable for Thai population. Therefore, this data can improve the efficacy of MTX treatment for ectopic pregnancy in our country. Moreover, the present study found that if the β-hCG level on day 4 compared with day 0 increased less than 17%, it could predict the success of single dose MTX treatment. This information can improve the efficacy of MTX treatment for ectopic pregnancy. Two dose MTX regimen was first introduced in 2007 by Barnhart et al[25]. This regimen requires MTX administrations on day 0 and 4 and then evaluate the treatment on day 7. This two-dose regimen was developed to improve the efficacy of single dose regimen, which had high failure rate, especially in patients who had high pretreatment β-hCG levels. Although the multiple dose regimen has high success rate, it also causes more side effects. A systematic review and meta-analysis performed by Yang et al[26] in 2017 found that overall success rate was the same among those three regimens, but multiple dose regimen has more side effects. The randomized controlled trial performed by Song et al[27] in 2016 reported no statistically significant difference of success rate between single and two dose regimens. However, that study showed higher success rate of patients treated with two-dose regimen in the group that had pretreatment β-hCG value greater than 5,000 mIU/ml. However, the two-dose regimen is not as well-known as the single dose regimen. Thus, if the information concerning the change of β-hCG value between day 0 and day 4 is used to evaluate the response and success rate of single dose regimen to switch to two-dose regimen in the patient whose β-hCG level between day 0 and day 4 increases more than 17% might improve the outcome of MTX treatment. However, further study is needed.

The strengths of the present study are that the study was conducted in a large group of Thai population, gathered information from medical records in the past 12 years, and the treatment data was homogenous due to clear treatment and follow up protocol. The limitations of the present study are that a retrospective study is known to have bias, and that the incomplete medical records were excluded from the analysis. Having all cases with complete records would be beneficial for this study. Moreover, some factors are too low in number to demonstrate statistically significant difference.

Conclusion

The single dose regimen of MTX treatment is a safe and effective treatment of ectopic pregnancy after a proper patient selection. The pretreatment β-hCG level less than 3,000 mIU/ml is the predictive factor for the success of treatment. The level of β-hCG between day 0 and day 4 increase less than 17% is the early predictive factor to evaluate the response and chance of success after treating by single-dose MTX regimen.

What is already known on this topic?

The single dose MTX regimen is a safe and effective treatment of ectopic pregnancy after a proper patient selection. According to the ASRM and the ACOG suggest the predictive factor that related to MTX treatment failure is high pretreatment hCG level (greater than 5,000 mIU/ml), size of the gestational mass (greater thaen 4 cm), adnexal fetal cardiac activity, rapid rise in hCG concentration during MTX treatment, and presence of free peritoneal blood. However, most of the recommendations are based on the studies in European and American population, which might not suitable for Thai population.

What this study adds?

This study reported the outcome of MTX treatment of ectopic pregnancy in Thai population. The authors found that success rate is comparable to other studies. Pretreatment β-hCG level is the most important predictive factor of successful MTX treatment. In this study, the proper cutoff pretreatment β-hCG level is set at 3,022 mIU/ml, which is lower than ACOG and ASRM had recommended. The change of β-hCG level between day 0 and day 4 that increase less than 17% is the early predictive factor of success after MTX treatment. Thus, if the change of β-hCG value between day 0 and day 4 is more than 17%, the treatment should switch to two-dose regimen, which might improve the outcome of MTX treatment. However, further study is needed.

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Potential conflict of interest

The authors declare no conflict of interest.

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