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Predictors of Success with Single-dose Methotrexate Regimen for the Treatment of Ectopic Pregnancy in Chonburi Hospital

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ABSTRACT

Objectives: To determine the factors that effect the success in management of tubal pregnancy with single–dose methotrexate regimen in Chonburi hospital.

Materials and Methods: Out-Patient Department (OPD) and In-Patient Department (IPD) charts of the patients who were diagnosed ectopic pregnancy and treated with methotrexate from January 2010 to December 2014 were reviewed from Chonburi hospital database. The successful treatment was defined in case of disease resolution without surgery.

Results: For all 70 patients were enrolled in this study. The overall success rate was 88.57% (62/70). The baseline characteristics of patients were not different between success and failure group and included age, BMI, parity gestational age, pretreatment serum β-hCG and average sized of adnexal mass. The absent fetal heart activity (OR 23.12, 95%CI 1.46-366.12, p=0.02) and size of adnexal mass less than 3.5 cms (OR 37.56, 95%CI 2.49-567.62, p=0.01) were independent predictors for successful treatment of ectopic pregnancy after analyzed with logistic regression model.

Conclusion: The independent predictors of success in treatment of tubal pregnancy with single dose methotrexate regimen were absence of fetal heart activity and adnexal mass less than 3.5 cms.

Keywords: ectopic pregnancy, methotrexate, success rate, predictor

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การศึกษาปัจจัยที่มีผลต่อความสำเร็จในการรักษาการตั้งครรภ์นอกมดลูกด้วยสูตรการให้ยาเมทโทรเทรกเสดแบบครั้งเดียวในโรงพยาบาลชลบุรี

ปาณิสรา นิยมแย้ม, พิมพิกา ตันสุภสวัสดิกุล

บทคัดย่อ

วัตถุประสงค์: *ศึกษาปัจจัยที่มีผลต่อความสำเร็จในการรักษาการตั้งครรภ์นอกมดลูกด้วยสูตรการให้ยาเมทโทรเทรกเสดแบบครั้งเดียวในโรงพยาบาลชลบุรี*

วัสดุและวิธีการ: *การศึกษาแบบย้อนหลังโดยรวบรวมข้อมูลจากเวชระเบียน ตั้งแต่มกราคม 2553 ถึงธันวาคม 2557 ในผู้ป่วยที่ได้รับการวินิจฉัยตั้งครรภ์นอกมดลูก และได้รับการรักษาด้วยยาเมทโทรเทรกเสด โดยพิจารณาความสำเร็จในการรักษา คือ เมื่อตรวจติดตามฮอร์โมนการตั้งครรภ์ผลเป็นปกติ โดยไม่ได้รับการผ่าตัด*

ผลการศึกษา: *ผู้ป่วยทั้งหมด 70 ราย ที่ได้รับการวินิจฉัยตั้งครรภ์นอกมดลูก และได้รับยาเมทโทรเทรกเสด พบว่าอัตราความสำเร็จทั้งหมด 88.57% จากการศึกษาพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในเรื่องข้อมูลพื้นฐาน ได้แก่ อายุ จำนวนครั้งของการตั้งครรภ์ อายุครรภ์ ปริมาณฮอร์โมนการตั้งครรภ์ก่อนการรักษา และขนาดของก้อนในอุ้งเชิงกราน และเมื่อวิเคราะห์ความสัมพันธ์แบบพหุตัวแปรพบว่า การไม่พบการเต้นของหัวใจทารก และขนาดของก้อนในอุ้งเชิงกราน <3.5 เซนติเมตร มีความสัมพันธ์ต่ออัตราความสำเร็จในการรักษาด้วยยาเมทโทรเทรกเสดอย่างมีนัยสำคัญทางสถิติ (ค่า OR:23.12, ค่า p = 0.02) และ (ค่า OR:37.56, ค่า p = 0.01) ตามลำดับ*

สรุป: *ปัจจัยที่มีผลต่อความสำเร็จในการรักษาผู้ป่วยตั้งครรภ์นอกมดลูกด้วยยาเมทโทรเทรกเสด คือ การไม่พบการเต้นของหัวใจทารก และขนาดของก้อนน้อยกว่า 3.5 เซนติเมตร*

Introduction

Ectopic pregnancy is an important cause of morbidity and mortality in pregnant women. The incidence of ectopic pregnancy is approximately 2% of all pregnancy[1-3]. The development of transvaginal ultrasonography and serum beta human chorionic gonadotropin (β-hCG) allow an early diagnosis of ectopic pregnancy which greatly decreases maternal morbidity and mortality and prevents emergency operation for rupture ectopic pregnancy[2,4]. The standard treatment of ectopic pregnancy is either surgery or medication with methotrexate depends on patient's condition[2,4].

Methotrexate is folate antagonist that inhibits DNA synthesis by inhibiting dihydrofolate reductase enzyme[5]. There was first report in 1982 that used methotrexate and leucovarin to treat ectopic pregnancy, called multiple dose regimen. The overall success rate of multiple dose regimen in the meta- analysis by Barnhart et al is 92.7%[5]. Single – dose methotrexate protocol was first used for ectopic pregnancy in 1991. This protocol used methotrexate 50 mg/m^2 and set the day giving medication as day 0. Then serum β-hCG was repeated on day 4 and day 7. They considered the success of treatment when serum β-hCG decreased from day 4 to day 7 by at least 15%. On the other hand, patients will be again given the 2nd dose of methotrexate if serum β-hCG reduced to less than 15% and the follow up serum β-hCG measurement would be performed in the same way as the first dose. If serum β-hCG decreased on the second dose, they also considered success treatment. In previous study, 96.7% of patients had been successfully treated with this protocol[5]. The advantage of single dose methotrexate is less side effect, less injection, and decrease time to stay in hospital comparing with multiple dose regimen[5].

The success rate of single-dose regimen for ectopic pregnancy in retrospective study by Megan B. Potter et al. is 85%[6]. The result of their study showed that patients in success group had less serum β-hCG than in the failure group. But the only significant factor for failure treatment was yolk sac presence in adnexal mass by transvaginal ultrasound.

Eskandar et al[7], retrospectively studied 70 patients diagnosed with ectopic pregnancy and receiving treatment with methotrexate and the success rate is 94.3% after a single dose. The significant factors for failure treatment are the size of gestational sac and the level of serum β-hCG before the treatment.

With evolving experience and high successful rate with medical treatment, the management with methotrexate is one of standard treatment and be chosen in selected case of ectopic pregnancy. We aimed to discover the factors that affected the success of treatment with single – dose methotrexate regimen for ectopic pregnancy in Chonburi hospital. In addition, we want to apply this information to set up guideline of treatment in the future.

Materials and Methods

This study was a retrospective study and approved by the Ethics Committee, Chonburi Hospital. Ectopic pregnancy was diagnosed by history taking, physical examination, serum β-hCG and transvaginal ultrasound in the first evaluation according to standard algorithm[3]. The methotrexate treatment was chosen in case of stable vital signs, unruptured ectopic pregnancy without spontaneous resolution and healthy patient without liver and/or kidney disease according to Chonburi clinical practice guideline (see in appendix). The outpatient and inpatient database were reviewed, incomplete database was excluded from the study.

The single dose methotrexate regimen was chosen in Chonburi Hospital because of lesser side effects when compare with multiple dose regimen. Methotrexate 50 mg/m^2 intramuscular was prescribed in selected case and counselled of abandon of folate supplement and alcohol intake. Then the serum β-hCG after injection 4 days (day 4) and after injection 7 days (day 7) were assessed and compared. If serum β-hCG on day 7 decline less than 15% from day 4, the second dose of methotrexate will be given and the follow up serum β-hCG measurement would be performed in the same way as the first dose. If serum

β-hCG decreased on the second dose, they were considered a success treatment. In the other way, if it declines 15% or more, the serum β-hCG will be assessed weekly until negative.

Sample size was estimated based on a previous study[6], which indicate that the success rate with methotrexate treatment is 85%. With a level of statistical significance of 0.05%, we obtained a sample size is 68 subjects.

This retrospective study collected data from January 1, 2010 to December 31, 2014. There were 623 ectopic pregnancies in Chonburi hospital. Five hundred and fifty three patients were excluded from the study due to 543 cases were diagnosed of ruptured ectopic pregnancy that need surgical treatment and 10 cases lost to follow up.

Seventy patients were enrolled in the study, the Out-Patient Department (OPD) and In-Patient Department (IPD) medical records were reviewed. The successful treatment was defined when serum β-hCG was normalized after treatment with methotrexate either single dose or 2nd dose without surgical intervention. The failure treatment was defined when the patient needs surgical treatment due to suspicious ruptured ectopic pregnancy. Time of resolution was defined as the duration after start methotrexate until normalized β-hCG (<5 mIU/ml).

Statistical analysis

Descriptive statistics [mean (SD) or median (range) and percentage] were used to express demographic, baseline, and measurement outcome data. Comparisons of quantitative data were analyzed by Student T-test or Mann Whitney U test if the data was nonparametric. The factors were compared between success and failure treatment by using logistic regression model. SPSS version 18.0 was used to analyze the data. A P level of < 0.05 was considered statistically significant.

Results

Seventy patients were enrolled in this study. The overall success rate was 88.57% (62/70). In the success group, there were 57 patients received single dose of methotrexate while 5 patients need second dose. The serum β-hCG was evaluated on day 4 and day 7 after administration of methotrexate and repeated serum β-hCG weekly until < 5 mIU/ml. The mean time of resolution in success group was 5.23 weeks.

There were 8 patients failed medical treatment and need surgical intervention, because they developed acute abdominal pain and unstable vital signs.

When stratified by pretreatment serum β-hCG, we found that the lower the serum β-hCG, the more success rate of the treatment. The success rates for serum β-hCG < 2,000 mIU/ml, 2,000-5,000 mIU/ml and > 5,000 mIU/ml were 100%, 97% and 77%, respectively. The average size of adnexal mass in overall cases were 3.12 cms. We found that the smaller size of adnexal mass, the more successful treatment. The success rate were 100%, 96% and 61% in case of adnexal mass < 1.5 cms, 1.5-3.5 cms and > 3.5 cms, respectively

The baseline characteristics of patients were shown in Table 1. There were no different between success and failure group included age, BMI, parity gestational age and pretreatment serum β-hCG.

The presence of free fluid in the success group was 35.5% and failure group was 25% (p 0.55). The presence of yolk sac in the success group was 12.9% and failure group was 37.5% (p 0.07). And these factors did not significantly different between success and failure group.

The presence of adnexal mass < 3.5 cms in the success group was 80.6% and failure group was 12.5% (p < 0.01) (OR 26.38, 95%CI 2.97-234.05). Serum β-hCG < 5,000 mIU/ml in the success group was 61.3% and failure group was 12.5% (p 0.01) (OR 11.08, 95%CI 1.28-95.78). Percentage of fetal heart activity absence in the success group was 95.2% and failure group was 50% (p<0.01) (OR 19.66, 95% 3.23-119.85). These three factors were significantly affected the success of treatment by single–dose methotrexate regimen.

From Table 2, we found that there were three factors affected the success of treatment included adnexal mass < 3.5 cms, absence of fetal heart activity and pre-treatment serum β-hCG level < 5,000 mIU/ml. Logistic regression analysis was employed to investigate

the independent predictors for successful treatment. The results was shown in Table 3. Serum β-hCG level < 5,000 mIU/ml and the presence of yolk sac had p-value 0.09 and 0.82, respectively. While adnexal mass < 3.5 cms and absence of fetal heart activity had p-value 0.01 and 0.02, respectively. Serum β-hCG level < 5,000 mIU/ml and presence of yolk sac were not statistical significant.

Table 1. The characteristics of patients between success and failure group.

Characteristics	Success group (n=62)	Failure group (n=8)	p value
Age (yr)	26.50 (21-32)	26.00 (20-33)	0.75
BMI (kg/m^2)	21.16 (18.95-23.33)	19.27 (18.79-21.89)	0.25
Parity	2 (1-3)	2 (1-3)	0.80
Gestational age (weeks)	7.45 (6.50-9.22)	7.15 (4.62-7.85)	0.11
Pretreatment β-hCG (mIU/ml)	3,934.00 (2,718.75-6,478.50)	8,216.50 (5,361.25-9,604.75)	0.12
Average size of adnexal mass (cms)	2.95 (2.27-3.40)	4.07 (3.65-4.20)	0.34

Analyzed by Mann Whitney U test

Table 2. The predictors of successful treatment for ectopic pregnancy who were treated with methotrexate.

Factors	Success group (n=62)	Failure group (n=8)	Odd ratio 95% CI	p value
Adnexal mass <3.5 cm	50 (80.60%)	1 (12.50%)	26.38 (2.97 - 234.05)	< 0.01
Pretreatment serum β-hCG <5,000 mIU/ml	38 (61.30%)	1 (12.50%)	11.08 (1.28 - 95.78)	0.01
Presence of yolk sac	8 (12.90%)	3 (37.50%)	0.24 (0.04 - 1.23)	0.07
Absence of fetal heart activity	59 (95.20%)	4 (50.00%)	19.66 (3.23 - 119.85)	< 0.01
Presence of free fluid	22 (35.50%)	2 (25.00%)	1.65 (0.30 - 8.87)	0.55

Table 3. Logistic regression analysisc.

Characteristics	Adjusted OR	95% CI	p value
Adnexal mass < 3.5 cm	37.56	2.49-567.62	0.01
Absence of fetal heart activity	23.12	1.46-366.12	0.02

Adjusted for serum β-hCG < 5,000 mIU/ml and presence of yolk sac

Discussion

Historically, the treatment of ectopic pregnancy was limited to surgery. With evolving experience with methotrexate, the treatment of selected ectopic pregnancy has been revolutionized. The current trends in the management of ectopic pregnancy in the United States from 2002 to 2007 showed that patient treated with medical treatment increase from 11.1% to 35.1%, whereas the surgical management decreased from 90% to 60%[8]. Because of the fertile preservation, hospitalization and noninvasiveness, the medical treatment was preferred to surgical management in well-selected patients.

At present, the early detection of unruptured

ectopic pregnancy by serial transvaginal ultrasonography and serial serum β-hCG allow the disease to be treated without surgery. We conducted this study to find out the predictors for successful treatment of unruptured ectopic pregnancy.

The overall success rate for treatment of tubal pregnancy by single-dose methotrexate regimen in this study was 88.57% that was similar to other studies which success rate about 85-94%[6-7, 9]. The seemingly high rate of success could potentially be explained by the selection bias of the enrolled patients. The patients in the study might not represent a true population of unruptured ectopic pregnancy because patients with relative contraindication such presence of fetal heart activity and/or size of adnexal mass larger than 3.5 cms were included only if they chose to be treated with medication after counselling.

Forty-four percentage of successful treatment with methotrexate was reported by de Waard et al[10]. The size of the ectopic mass at the time of diagnosis was significantly larger in the success group treated with methotrexate comparing with those required surgical intervention. It was possible that the size of that mass was not the actual size of ectopic mass but included the hematoma. So the measurement was not represented the active trophoblast that methotrexate will be acted on. The serum β-hCG levels were significantly higher in the failure group. The limitation of their study was the large amount of loss follow up patients (41%) that may effect the results.

Unlike previous studies, we used the average of all three dimensional diameters of the adnexal mass instead of a single measurement of the transverse diameter[11]. This approach is much more practical than traditional method and the average of three dimensional diameters would better represent the actual size of the adnexal mass than the traditional measurement of a single transverse diameter.

Our results showed that adnexal mass less than 3.5 cms, absence fetal heart activity and serum β-hCG less than 5,000 mIU/ml were the predictors of successful treatment with single dose methotrexate regimen similar to ACOG Practice Bulletin 2012[12]. However, when we employed the logistic regression analysis, we found that only adnexal mass < 3.5 cms and absence of fetal heart activity were the significant factors while β-hCG less than 5,000 mIU/ml was not the good predictor. Lipscomb et al[9], reported that 94% of 350 women whose initial serum β-hCG was less than 10,000 IU/ml had successful treatment with methotrexate. Therefore, an initial β-hCG level greater than 10,000 IU/ml was a factor for failure of a treatment. In addition, Yamashita et al[13], which studied 44 ectopic pregnancy patients. There were 14 patients who had initial serum β-hCG more than 5,000 mIU/ml and only one of them failed medical treatment (7.1%) while the failure treatment of serum β-hCG less than 5,000 mIU/ml was 16.6%. These results are still inconsistent. So, it is controversial to determine the suitable cut-off of serum β-hCG level to make the decision for methotrexate administration.

The important limitation of this study was the selection bias from retrospective study design. Prospective study should be conducted to confirm the results in future.

Conclusion

The independent predictors of success treatment of ectopic pregnancy with single dose methotrexate regimen were absence of fetal heart activity and adnexal mass less than 3.5 cms. These results can be used for counselling the patients who were diagnosed with ectopic pregnancy to provide them the non-surgical option. Also, this study shows that β-hCG less than 5,000 mIU/ml may not be a good predictor for successful candidates.

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Potential conflcts of interest

The authors declare no conflct of interest.

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