Middle East Fertility Society Journal Vol. 12, No. 1, 2007

Single dose methotrexate for treatment of ectopic pregnancy: risk factors for treatment failure

Mamdoh Eskandar, F.R.C.S.C.

Department of Obstetrics and Gynecology and Reproductive Medicine, King Khalid University, College of Medicine, Abha, Saudi Arabia

ABSTRACT

Objective: To identify risk factors for single dose methotrexate (MTX) failure among patients treated for ectopic pregnancies.

Design: Retrospective cohort.

Materials and methods: Seventy women diagnosed with an ectopic gestation treated with MTX. After a single dose, 66 (94.3%) patients experienced ectopic resolution, three (4.3%) patients needed a second dose of MTX, and one (1.4%) patient had a subsequent tubal rupture.

Main outcome measure(s): Predictive variables for failure of single dose MTX, including human chorionic gonadotropin (hCG) value, fetal sac size, patient age, parity and history of previous miscarriages.

Result(s): Ectopic pregnancies that failed to resolve following a single dose MTX were associated with increased maternal age, history of spontaneous abortions, larger sac sizes (>3.4 cm), and higher β-HCG levels (>2000 mIU/mL). Multiple regression analysis demonstrated that the size of the embryonic sac was the most important variable in failures of single dose methotrexate treatment.

Conclusion: Size of gestational sac and the pre-treatment level of HCG should be considered as independent risk factors for treatment failure of single dose methotrexate treatment.

Key words: Ectopic pregnancy, methotrexate, human chorionic gonadotropin, embryonic sac size, tubal rupture.

In modern obstetrics, ectopic pregnancy (EP) still remains one of the leading causes of maternal morbidity and mortality. The increased availability of transvaginal ultrasound and β-human chorionic gonadotropin (β-hCG) determination has increased the likelihood of an early detection and intervention prior to tubal disturbance. Outpatient management of unruptured ectopic pregnancy and single dose methotrexate (MTX) treatment were first described by Stovall et al. (1) and have now become a major alternative to laparoscopic surgical intervention in non-disturbed tubal ectopic pregnancies (2).

Correspondence: Dr. Mamdoh A. Eskandar FRCSC, Associate Professor, Consultant Obstetrics and Gynecology, Department of Obstetrics and Gynecology and Reproductive Medicine, King Khalid University, College of Medicine, Abha, Saudi Arabia, PO Box 641, Tel.: +996 7 2284635, Fax: +996 7 2257201, E-mail: maeskandar@kku.edu.sa

Previous studies have shown MTX to be comparable to laparoscopic salpingostomy in terms of both primary efficacy, as well as long-term measures of tubal patency and fertility (3, 4). However, among women who received medical management, the risk of requiring a second dosage of MTX, surgical intervention or possible tubal rupture needs further investigation (5).

The risk of tubal rupture with MTX ranges from 7% to 14% (6 - 13), and previous efforts to predict its occurrence have been only moderately successful (14 - 16). This is mainly confounded by the subjective pain in patients who may either be resolving or rupturing. Since many patients without rupture experience pain, it is difficult to distinguish patients who have resolution pain from those who are rupturing. Fear of rupture continues to persuade clinicians to operate on unruptured ectopic pregnancies

Table 1. Patient demographics, ectopic sac size and ß- HCG concentrations.

	Successful treatment	Failed treatment	Significance
Demographics			
No.	66	4	
Age	28.82 ± 6.16	35.25 ± 5.74	P = 0.0458
Parity	2.89 ± 1.94	4.25 ± 2.63	P = 0.1867
SA	0.70 ± 1.20	2.00 ± 1.41	P = 0.0406
sac size cm	2.52 ± 0.80	3.75 ± 0.29	P = 0.0035
βhCG prior to treatment	1491.79 ± 1094.69	2701.50 ± 1417.28	P = 0.0381
βhCG after treatment			
1st Week	845.71 ± 724.46	2789.00 ± 1691.44	P = 0.0134
2nd Week	417.91 ± 394.23	1493.33 ± 869.55	P = 0.0263
3rd Week	149.21 ± 144.64	450.00 ± 245.96	P = 0.001
4th Week	0.00 ± 0.00	0.00 ± 0.00	NA

that would otherwise resolve with medical management.

We investigated the risk factors of failure of single dose MTX in a large cohort of women with diagnosed ectopic pregnancies and receiving MTX treatment. This group was divided and compared according to the success of single-MTX treatment. The study objective was to determine whether unique attributes of the patient demographics, obstetric history or ectopic diagnosis could be used to guide preemptive need for a second dose of MTX.

MATERIALS AND METHODS

The present study included seventy patients that were diagnosed as nonruptured tubal pregnancies (TP) and received at least one dose of methotrexate for medical management. Women were eligible for entry into the trial if they had a serum β-hCG concentration below 5000 mIU/mL, minimal hemoperitoneum on transvaginal ultrasound.

Women irrespective of desire for future fertility were eligible for entry into the study. Exclusion criteria were: unstable vital signs, generalized peritonism on abdominal palpation, a falling serum ß-hCG concentration, diagnostic uncertainty requiring laparoscopy, an ultrasonically diagnosed interstitial, cervical, ovarian or heterotopic pregnancy, contraindications to methotrexate (i.e. leukopaenia, thrombocytopaenia, or elevated serum liver enzymes or creatinine); and contraindications to laparoscopy (i.e. documented severe pelvic adhesions, large fibroid uterus, or ovarian hyperstimulation syndrome). All Women gave written informed consent.

Women received a single intramuscular dose of 50 mg per m2 of body surface area. Women were reviewed clinically on day 4 and again on day 7 and a serum β-hCG, and full blood count were measured. Thereafter, women were seen weekly for a follow up and measurement of serum β-hCG. Patients who exhibited tubal rupture, or received a second dose of MTX were considered to be single-dose MTX failures.

In all cases, transvaginal ultrasonography (2101 Falcon, β -K medical, Japan) was performed using a 6.5 MHz vaginal probe. Serum β-hCG was measured using monoclonal assay (VIDAS® HCG) utilizing the ELFA technique (enzyme liked fluorescent assay), and follow up was done weekly. The intra-assay and inter-assay variation was < 5% and all results were expressed in mIU/mL according to the WHO Third International Standard 75/537.

The patient demographics (e.g. age, parity, and history of spontaneous abortions), the current EP sac size, pre-treatment ß-HCG, and post-treatment sequential ß-HCG follow-up patterns were compared between the success group and the failure group.

Statistical analysis was performed using the Student t-test, ROC analysis, multiple regression and tests for diagnostic accuracy (e.g. sensitivity, specificity, positive predictive value, negative

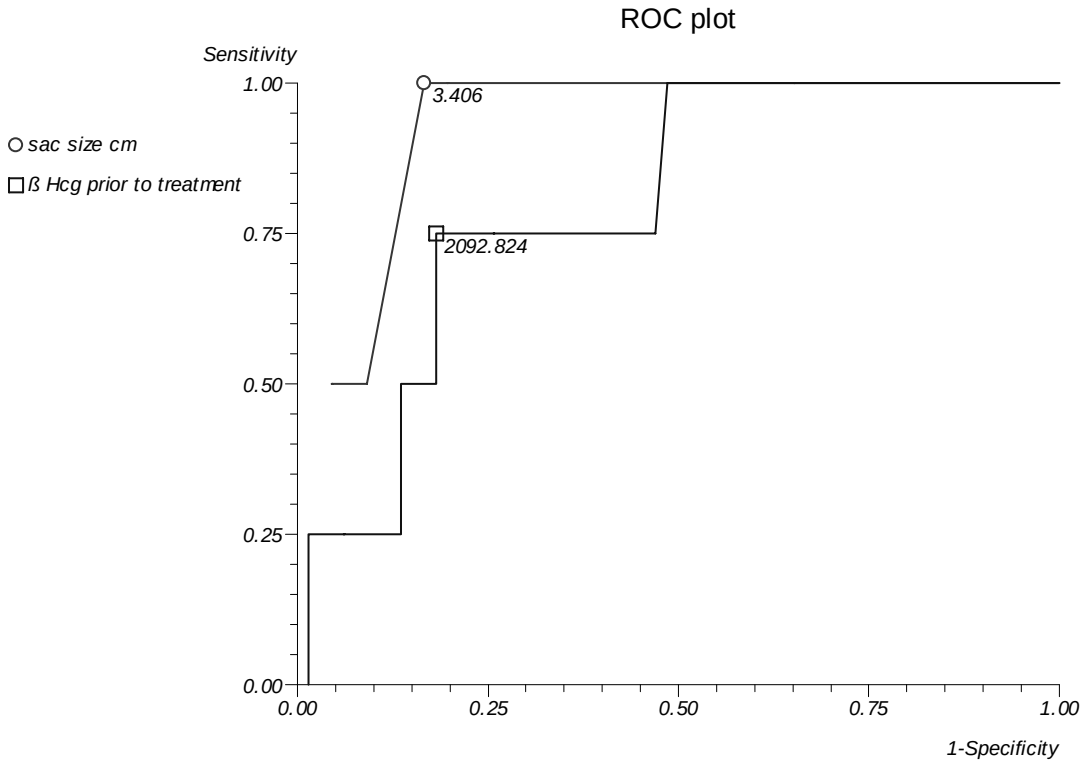

Figure 1. ROC curve analyses.

predictive value). Significance was determined as $P < 0.05$. Arcus Quickstat (1.0) statistical analysis program was used for data management and evaluations.

RESULTS

Table 1 shows the patient's demographics, the EP sac size, pre and post-treatment maternal HCG concentrations following success versus failed medical management. Maternal age, history of spontaneous abortions, sac size and initial ß-HCG measurement were all considered to statistically increased in the treatment failure group ($P < 0.05$). There was no difference with regards the women's parity between the two groups.

Multiple regression analyses confirmed that the sac size was the most important independent variable ($P = 0.039$). The other variables were not significantly different ($P > 0.05$).

Receiver operating characteristics curve (ROC) Analyses for sac size and initial BHCG measurements revealed that the optimum cutoff point for sac size is 3.406 cm [Area under ROC curve by trapezoidal rule = 0.91; Sensitivity = 1, Specificity = 0.83, Positive Predictive Value = 0.27, Negative Predictive Value = 0.83]. For the ß-HCG measurement, it was 2092.82 [Area under ROC curve by trapezoidal rule = 0.79; Sensitivity = 0.75, Specificity = 0.82, Positive Predictive Value = 0.2, Negative Predictive Value = 0.82] (Figure 1).

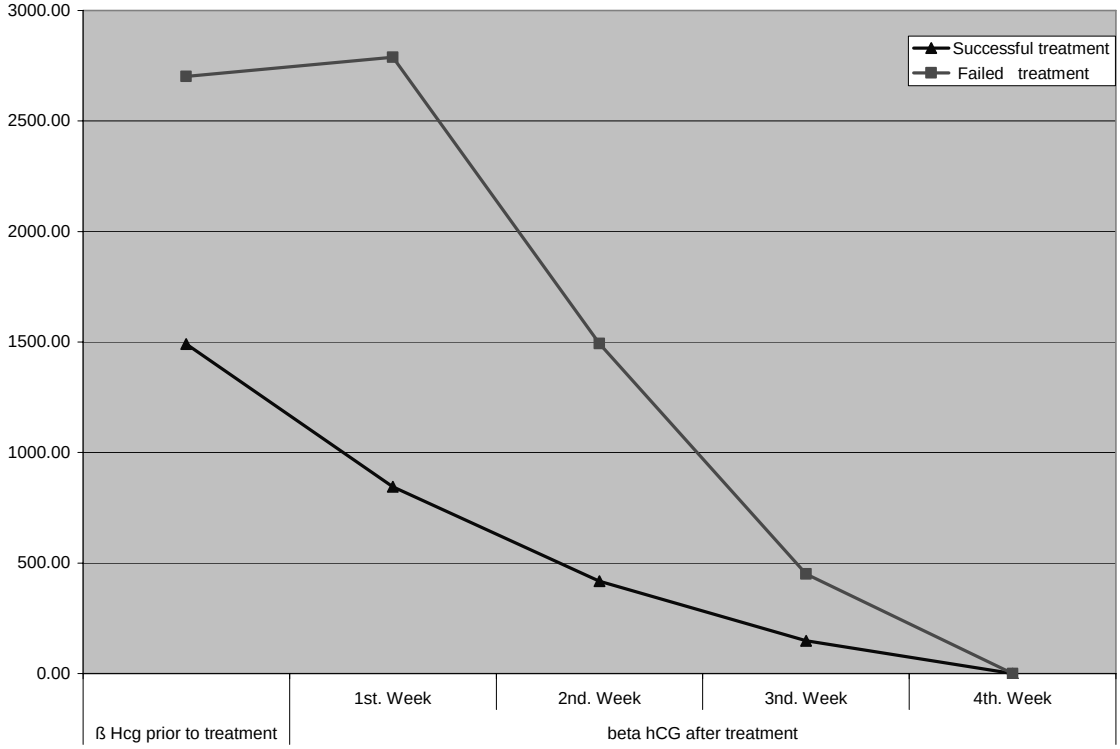

Figure 2. Post-treatment follow-up ß-HCG measurements.

DISCUSSION

Ectopic embryo implantation outside of the uterine cavity is a serious and sometimes life-threatening condition affecting about 1% of all pregnancies. It occurs when the fertilized oocyte implants outside the uterine cavity. The most common site of ectopic pregnancies is the ampullary part of the fallopian tube, but other sites have been documented including the ovary, peritoneum and abdominal wall. If not properly diagnosed and managed, affected women are at risk of ectopic disturbance and tubal rupture leading to internal hemorrhage, maternal cardiovascular collapse, shock and possibly death. (17).

The fertilized oocyte normally transcends the fallopian tube from the ovary to the cavity of the uterus where it implants on post-fertilization day 6-7. The most common reason for an ectopic pregnancy is damage to the fallopian tube, causing a blockage or narrowing of the tube. Conditions such as pelvic inflammatory disease (PID) and endometriosis have been shown to increase the chances of ectopic pregnancies in women due to tubal pathology, adhesions and inflammation. (18).

Today, proper diagnosis is provided by the lack of presence of a fetal sac in the uterine cavity and an associated rise in β-HCG levels. The diagnosis is confirmed by the presence of an ectopic fetal sac outside the uterine cavity. Laparoscopy may be needed for confirmation in difficult cases, especially if the ectopic pregnancy is present in an extra-ordinary site (e.g. the abdomen).

Methotrexate is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Chemically methotrexate is N-[4-[[(2, 4-diamino-

6-pteridinyl) methyl] methylamino] benzoyl]-L-glutamic acid and a molecular weight of 454.45. Since its introduction in the management of ectopic pregnancies, systemic methotrexate administration has been proven to be successful in the treatment of undisturbed ectopic pregnancies.

In a recent study performed by Barnhart and co-workers, only 0.5–1% of patients who received single dose MTX developed these side effects (6, 8, 19 – 21). The single dose regimen was associated with fewer side effects (1, 19). Medical treatment proposal to the patients needs some objective criteria proven to predict tubal rupture during nonsurgical management (20, 22).

Possible serious side effects of methotrexate administration include bone marrow suppression, dermatitis and stomatitis to the patients are proportionate to the length and amount of treatment. Arguably the greatest risk to women receiving MTX for an ectopic gestation is tubal rupture. Even so, the need to determine patients that will also fail using a single-dose regimen of methotrexate is of great importance. The current literature on the topic of ectopic pregnancy includes multiple papers identifying predictors of MTX success (21 – 23).

Predictors of treatment failure for ectopic pregnancy have been studied in previous studies. Tawfig et al. emphasized vaginal bleeding and pelvic pain as most reliable predictors for predicting medical treatment failure of ectopic pregnancy and they did not recommend MTX use for treatment when β-hCG was >4000IU/ml (22).

Elito et al. evaluated peritrophoblastic Doppler blood flow to predict medical treatment failure beside β hCG value, aspect and size of the ectopic pregnancy image. They recommended using Doppler in association with the other parameters that constitute predictive score grading system. They established a cut-off grade of 5 to select patients for medical treatment (20).

Lipscomb et al. (24) stated that the initial level of hCG is the best prognostic indicator of MTX success. Of the 350 women they studied, the investigators found a 94% success rate when the initial hCG level was less than 10,000 mIU/mL, and a 75% success rate when the initial hCG level was above 10,000 mIU/mL. This observation led them to conclude that an initial hCG value above 10,000 mIU/mL was a risk factor for treatment failure. More recent literature has questioned this cut-point, suggesting that the level above which MTX may prove to be less effective should be lowered to between 2000 mIU/mL (23). Our present study is in accordance with the more recent guidelines. In addition, we have demonstrated a marked difference in initial HCG levels in patients that will respond to one dose of MTX and patients that will not respond (Table 1, Figure 2).

Efforts for determining the most reliable and useful clinical criteria for ectopic pregnancy patients will probably give chance to both physicians and patients to decide the appropriate treatment strategy in the light of objective criteria. A clinical predictive test must be reproducible and easy to perform especially for an acute disease like tubal pregnancy. Sophisticated diagnostic studies for predicting tubal rupture like transvaginal Doppler sonography need expensive tools and experienced staff. This study has demonstrated that simple and readily available ultrasound and HCG determinations can effectively determine patients with increased chance of treatment failure. We demonstrated that ß-HCG of 2000 mIU/mL is an optimum cutoff value for selecting potential cases for medical failure using the single-dose approach. In addition, it is important to note that embryonic sac size was also found to be an important independent variable, as confirmed by the ROC and multiple regression analyses.

In conclusion, single-dose methotrexate treatment could be confidently offered to most stable patients undergoing medical management of an ectopic pregnancy. In cases with an initial ß-HCG of >2000 mIU/mL and/or an embryonic sac of >3.4 cm, treatment failure should be closely monitored.

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Received on August 8, 2006; revised and accepted on November 2, 2006