Original Article

COMPARISION OF SINGLE AND MULTIDOSE OF METHOTREXATE IN MEDICAL TREATMENT OF ECTOPIC PREGNANCY

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ABSTRACT

Objective: The purpose of this study was to compare the efficacy and safety of two regimens of methotrexate for medical treatment of ectopic pregnancy.

Methodology: In this prospective randomized clinical trial 100 women clinically suspected to have un ruptured ectopic pregnancy were randomly (One by one) treated with single (50mg/m2) and multi dose (1mg/kg MTX+ 0.1mg/kg folinic acid) Methotrexate (50 cases in each group). Results of two groups were compared.

Results: The overall success rate of treatment was 94%. The use of single dose was associated with a greater chance of response to medical management than multi dose. (97% versus 91%). The single dose regimen was associated with greater side effects. Women who experienced side effects were more likely to have successful treatment regardless of regimen. Three percent of patients had serum B hCG >10000IU/ml and in 5% of cases fetal heart reported in adnexal mass. Both these groups were much more responsive to single dose treatment.

Conclusions: Efficacy of single dose in medical treatment of Ectopic pregnancy is better than multi dose regimen.

KEY WORDS: Ectopic pregnancy, Vaginal sonography, Methotrexate.

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INTRODUCTION

Ectopic pregnancy is one of the most important causes of death during the first trimester of pregnancy and about 1% of all pregnancies are ectopic. Ectopic pregnancy is more threatening for women than normal vaginal delivery and induced abortion.[1] The number of ectopic pregnancies (EP) has increased dramatically over the last few decades.

There are different risk factors for E.P. The most important high risk factors include: Tubal surgery & tubal Ligation, previous EP, IUCD use, tubal pathology, morning after pill, assisted reproductive techniques, salpingitis, genital tract infection.[1,2] With improving the diagnostic methods and suitable treatment,

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mortality rate from ectopic pregnancy has decreased dramatically.[3]

Clinical manifestations are variable and depend on whether rupture has occurred or not. Earlier presentation and more precise diagnostic technology have enabled identification before rupture in most cases.[1] Because modern diagnostic methods now permit early recognition of most ectopic pregnancies, attention has shifted from emergency surgery for the control of life-threatening hemorrhage to medical treatments aimed at avoiding surgery and preserving reproductive anatomy and fertility. At times, identification of an early unruptured tubal pregnancy may be difficult, but clinical suspicion diagnostic methods and careful evaluation are the best way to reach a correct diagnosis.[4]

Due to direct visualization of the fallopian tubes and pelvis, laparoscopy is a standard method for ectopic pregnancy diagnosis, but sometimes lead to false negative or false positive results.[2] Laparoscopy usually is performed when on the basis of noninvasive tests, the diagnosis of ectopic pregnancy is fairly certain and medical therapy is not planned. Medical management avoids the inherent morbidity of anesthesia and surgery and reduces costs.

There are two ways to treat ectopic pregnancy: Surgery and medical management. Both methods are effective and the choice depends on clinical situation, site of ectopic and access to technology. Early diagnosis leads to considerable reduction in maternal morbidity and mortality from this disease. Also there is enough time to choose therapeutic treatment. Methotrexate, potassium chloride, hypersmolar glucose, actinomycine D and prostaglandins all have been used successfully to treat ectopic pregnancy (direct local ingection or systemic).[5,6] MTX has been established as an effective first line medical therapeutic alternative to surgical treatment. Methotrexate is a folic acid antagonist and with inactivation of enzyme didydrofolate reductase, thereby, depleting available stores of tetrahydrofolate, an essential cofactor in DNA and RNA synthesis during cell multiplication. Because of side effects, if needed higher dose can be used for longer period with leukoverin.[1]

In patient selection for medical management, stable homodynamic status, the size of ectopic mass less than 4cm in sonography report, unruptured ectopic pregnancy, no contraindications for MTX use, and informed consent is also essential. bhCG levels more than 10000mIU/mL and fetal heart activity are relative contraindications for medical management. According to American College of Obstet. & Gynecologist other contraindications include: breast feeding, immune deficiency status, alcohole abuse, hepatic or renal disease, blood dyscreasia, active pulmonary disease and peptic ulcer.[1]

MTX is administered by single or multidose regimen. Single dose regimen was introduced in efforts to simplify treatment, improve compliance and reduce side effects and costs. The main aim of present study was to compare both regimens and estimate of success and failure rate and side effects of these treatments.

METHODOLOGY

In this randomized clinical trial one hundred patients with un ruptured ectopic pregnancy were evaluated at Dept. of Obstetrics and Gynaecology, Ahwaz University of Medical Sciences of Iran. The diagnosis was confirmed by measurement of bHCG and vaginal sonography. The patients were randomized to either single or multiple dose of methotrexat.

Singl dose regimen: Informed consent was obtained in all patients after explaining the effectiveness and side effects of treatment. In the single dose regimen, 50mg /m2 intramascular methotrexat was given on day one and hCG level was measured on day four and seven. If the hCG level did not decrease by 15% between day four and seven, a second dose of methotrexate was injected on day seven. If more than 15% decline was achieved between day four and seven, hCG level was measured weekly until a normal level of 10mIU/ml was obtained.

Multidose regimen: Intramuscular methotrexate (1mg/kg/day) and citrovoram factor

(0.1mg/kg/day) were administered for four days or after a decline of hCG level by two consecutive days.

RESULTS

The average age of the patients was 32, but ranged from 23-41 years old. Most patients were gravid two. Fifty three percent of patients had past history of vaginal discharge. Other risk factors in this study were: Infertility, use of assited reproductive technology (30%) history of recurrent abortion, history of pelvic or abdominal surgery and ectopic pregnancy. The most common symptoms included: Missed period, abnormal uterine bleeding and pelvic pain.

An adnexal mass was noted in only 9% of the patients. There was no pelvic tenderness in most of the patients. ßhCG level was less than 10000mIU/ml in 97% of the patients. An adnexal mass was noticed in 80% of the patients and in 5% of them fetal heart was present. The success rate with medical treatment in both groups, single and multidose were 97% and 91% respectively. Three out of five patients with an adnexal mass and fetal heart beat were in single dose group. In two of those patients single dose of methotrexate was repeated two times and the third patient needed third doses of MTX to respond. The other two patients, who were randomly assigned to multiple dose treatment, had complication with ruptured tube and underwent salpingectomy.

In 80 patients with adnexal mass who had medical treatment, adnexal mass was detected by ultrasonography in 13 patients six weeks after treatment. Side effects of medical treatment, included transient increase in liver enzymes, gasteroenteritis, hair loss in 7% of the patients was present. Positive findings at sonography was seem in 80% of cases

DISCUSSION

In this study, the success rate in single dose group was 97% and in multidose group was 91%. In other studies the success rate of single and multidose has been 90-97% and 95-97% respectively.[7,8]

The best protocol for MTX treatment for ectopic pregnancy remains controversial. In a meta analysis performed 2003 showed that single dose was used more frequently but multidose has been associated with more success.[3] So far there has not been a randomized, prospective clinical trial of MTX for the medical treatment of ectopic pregnancy and most studies were retrospective. In only one prospective study done at Tennessee University in 2005, two protocol of treatment has been studied which showed similar rate of success (Multidose 95% and single dose 90%) It needs to be mentioned that those who are treated with single dose regimen may have other relative contraindication for medical therapy, such as fetal heart activity of larger ectopic mass.[9]

In some studies presence of fetal heart or ßhCG >10000mIU/ml has been reported as a relative contraindication for multidose regimen of MTX.[3] In other studies, the presence of fetal heart activity has been reported to be associated with decrease of response (about 80%). In our study the presence of fetal heart activity and high hCG level has not been considered in decision making and the patients were randomly assigned to the two groups. Overall the success rate in single dose was higher. Some patients, who were assigned to multidose due to failure of medical treatment and tubal rupture, needed surgical intervention.

In 88% of cases in the single dose group the success rate was achived with only one dose and in 12% of cases they needed more than one dose (2 doses in 6% and 3 dose in 6% cases). On the other hand 22% of cases in multidose group responded to only one dose of MTX whereas other patients needed three or four dose of treatment. Tennessee university finding showed 76% success with single dose and 24% need more than one dose for treatment. (20.7%, 2.9% and 0.4%, two, three and four dose respectively) and in multidose group 17.5% of the patients needed only one dose for treatment. These findings show that the appropriate treatment may require 2-7 dose of

methotrexate.[9] Side effects of MTX is mild but relatively common. In different studies their incidence ranged between 3-4% in multidose and 1% in the single dose regimen.[7,8] In the present study, incidence of side effects was 9% in single dose and 6% in multidose group, with no significant difference statistically. Those who achieved recovery with only one dose in single dose group had no complication. When medical treatment is successful, the rate of regression is dependent on intial level of ßhCG concentration; the average time is five weeks.[2] In this study, inspite of fall in serum ßhCG, tubal ruptured occurred in a patient.

Tubal rupture may be seen as long as six weeks after initiation of medical treatment.[2] Abdominal pains commonly occurs or increases in the first few days following MTX treatment (66% and 26% in single and multidose in this study). The cause is not known but most likely reflects tubal abortion or stretching of peritoneum over the formed hematoma. Although tubal rupture is also a possibility, but is not an indication for immediate surgery. We noticed that patients in single dose groups had more abdominal cramps, but they had lower rate of rupture.

In some studies the persistent of adnexal mass has been a treatment failure,[1] but this study showed that gestational mass may persist for weeks (up to 6 weeks) and does not mean treatment failure.

In conclusion, we recommend the single dose regimen of MTX for medical treatment of ectopic pregnancy because of similar rate of success and failure (P=0.303) and even better result in single dose regimen, patient tolerance and no need of hospitalization.

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