Original Article

Medical Management of Ectopic Pregnancies with Injection Methotrexate

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Abstract

Objective: to determine success rate in medically managed ectopic pregnancies with Injection Methotrexate.

Setting and Duration: this case series study was conducted from May 2012-Mar 2013 in Maternal and Child Care Centre, Pakistan Institute of Medical Sciences, Islamabad.

Methodology: this study included 57 patients with ectopic pregnancy (EP). Ultrasound was performed for confirmation of ectopic pregnancy. Serum beta hCG levels were determined at the time of presentation and then at day 4 and day 7. Systemic methotrexate at the dose of 1mg/kg body weight was administered. A second dose was given to those cases in which more than 10 – 15% fall of beta-hCG level did not occur after day 4. The outcome of interest was success rate.

Results: the mean age of the patients was 28.79 ± 5.06 years. The mean beta hCG levels in the study sample at day 1, 3, 5 and 7 were 3149 ± 978.49 mIU/ml, 2108 ± 1195.76 mIU/ml, 1101.96 ± 1246.79mIU/ml and 16.25 ± 31.33 mIU/ml respectively. There were 44 (77.2%) patients who were treated with a single dose of methotrexate, while in 13 (22.8%) patients, two doses were needed. There were 48 (84.2%) patients in whom the treatment remained successful, and the failure of the treatment was seen among 9 (15.8%) patients, who were managed with surgery.

Conclusions: the success rate of treatment of ectopic pregnancy with Methotrexate is high hence, it should be considered as first line therapy among patients with ectopic pregnancy.

Key Words: ectopic pregnancy, Success, Methotrexate.

Authorship Contribution: [1] Data collection, Methodology and writing the article, [2]Concept and idea, reviewed the study, [3]Data analysis, [4]Randomization of study.

Introduction

EP is an important diagnosis to be excluded when a woman presents with bleeding in early pregnancy. This is because ectopic pregnancy remains a leading cause of maternal mortality in the first trimester.[1]

Clinical signs and symptoms of ectopic pregnancy are not sensitive or specific [2] but a 5.5 weeks gestation, a corresponding human chorionic gonadotrropin (hCG) level of 2000 mIUml (discriminatory zone), and sensitivity of ultra-sound approach 100 %. [3] In some situations, it has been proposed that a uterine curettage (dilation and curettage {D&C} be performed to distinguish between an ectopic pregnancy and a miscarriage. [4] Once the possibility of a miscarriage is ruled out, medical or surgical management for entopic pregnancy is pursued.[5]

The incidence of ectopic pregnancy appears to be rising from 0.5%, 30 years ago to the current rate of 1%–2%. In pregnancies from assisted reproductive techniques, the incidence can be as high as 3%–5%. [6]

Once the diagnosis of ectopic pregnancy has been made, options include surgical, medical, or expectant management. The goal of treatment is to minimize disease and treatment related morbidity with maximizing reproductive potential.[7]

As a consequence, the clinical presentation of EP has changed from a life threatening disease, necessitating emergency surgery, to a more benign condition in frequently asymptomatic patients for whom non-surgical treatment options are available, i.e. medical treatment with systemic methotrexate (MTX) treatment or expectant management.

Methotrexate is further metabolized to MTX polyglutamates, which are long-lived metabolites, inhibiting other folate dependent enzymes. It is generally used to treat cancers, psoriasis, and rheumatic diseases, as well as obstetric or gynaecologic conditions, including extra uterine pregnancy (EUP), first trimester terminations, and gestational trophoblastic disease.[8]

MTX can be administered systemically in a multiple dose regimen (MTX 1.0 mg/kg intramuscularly (IM) day 0, 2, 4, 6, alternated with folinic acid 0.1 mg/kg orally day 1, 3, 5, 7) or in a single dose regimen (MTX 1.0 mg/kg or 50 mg/ m2 IM without folinic acid). [9,10]

A single dose regimen was introduced to minimize side effects, to improve patients' compliance and to reduce overall costs. MTX has been shown to be safe with virtually no adverse effects reported on reproductive outcome.[11] Usually there is no side effect of the treatment, but lower abdominal pain after a few days, occasionally other side effects occur such as nausea and vomiting, diarrhoea, sore throat, indigestion or tiredness. [12-14]

Limited data is available on national scale in our country. The purpose of this study is to assess the efficacy of medically treated ectopic pregnancy so that modification of standards for medical treatment of ectopic pregnancy in terms of beta hCG levels and size of the gestational sac would be possible, which can avoid unnecessary surgical intervention for the ectopic pregnancy, which is directly related to future fertility.

Methodology

The study was conducted at Pakistan Institute of Medical Sciences (PIMS) in Maternal and Child health Centre (Outpatient and Inpatient).Sample size of 57 cases was calculated by using WHO sample size calculator taking confidence level 95%, population proportion 82% with absolute precision required 10%.

All ectopic pregnancies with serum beta hCG levels less than 5000 IU/L, who had gestational sac measuring less than 5 cm, with no evidence of fetal cardiac activity and who were haemodynamically stable were included in this study. Patients who had ectopic

pregnancies with deranged renal and liver function tests, thrombocytopenia and leucopenia were excluded from the study.

Approval of the study was taken from hospital ethical committee. An informed written consent was taken from all the patients included in the study. Ultrasound (transabdominal/ transvaginal) was performed for confirmation of ectopic pregnancy, size of sac, fetal cardiac activity, and fluid in the pouch of Douglas. Serum beta hCG levels were performed at the time of presentation and then at day 4 and day 7 from the specific laboratory reported by three consultant pathologists. Complete blood picture, LFTs, RFTs of every patient were performed at admission. Systemic methotrexate at the dose of 1mg/kg body weight was administered to the patients with ectopic pregnancy, were monitored after 48 hours. A second dose was given to those cases in which more than 10 – 15% fall of beta-hCG level did not occur after day 4 or size of the mass further increased after a lapse of seven days. Patients on methotrexate were warned that therapy might fail in 5 – 10% cases. Moreover, the failure of medical therapy could results in surgery, which might be elective or emergency. Data was collected on specially designed performa. Patients were followed up daily and final result with regard to the success of intramuscular injection methotrexate was recorded by trainee researcher.

Results

There were a total of 57 patients of ectopic pregnancy who were included in the study.The mean age of the patients was 28.79 ± 5.06 years [range 19 – 41]. Majority of the patients 14 (24.6%) belonged to age range of 21- 25 years and 22 (38.6%) to age range of 26 – 30 years followed by 14 (24.6%) patient of age range of 31 – 35 years (Table I).

Table I. Distribution of patients by age (n=150)

Age (years)	No. of patients	Percentage
18 – 20	2	3.5
21 – 25	14	24.6
26 – 30	22	38.6
31 – 35	14	24.6
36 – 40	4	7
41 – 45	1	1.7
> 45	0	0
Mean + SD	28.79 ± 5.06	
Range	19 – 41	

The mean beta HCG levels in the study sample at day 1, 3, 5 and 7 were 3149 ± 978.49 mIU/ml, 2108 ± 1195.76 mIU/ml, 1101.96 ± 1246.79mIU/ml and 16.25 ± 31.33 mIU/ml respectively (Table II).

Table II. Distribution of beta HCG level in study sample (n= 57)

Days	Beta HCG (mIU/ml)	
	Mean	Stand deviation
Day 1	3149	978.49
Day 3	2108.23	1195.76
Day 5	1101.96	1246.79
Day 7	16.25	31.33

There were 44 (77.2%) patients who were treated with a single dose of methotrexate, while in 13 (22.8%) patients, two doses were needed. There were 48 (84.2%) patients in whom the treatment remained successful, and the failure of the treatment was seen among 9 (15.8%) patients, who were managed with surgery.

Discussion

Methotrexate is a treatment for EP. However, in the literature, there are few studies that have described the outcome of treatment with methotrexate.

Shahab M, et al. [15] conducted a cross sectional study at Royal Medical Services Hospitals (RMS, Jordan)

over a two years a period and included 112 patients with ectopic pregnancy. The diagnosis was based on Human Chorionic gonadotrophin (hCG) and ultrasound. Like the present study, methotrexate was administered in single oral dose of 70-90 mg in association with folic acid. The success of treatment was seen in 85.7% patients. Single dose was successful in 84.82% patients and 15.17% required two doses. The results of this study are important, as in this study, the parameters of success were similar to that of ours i.e. beta hCG levels. The success rate was high i.e. 85.7% which is also similar to ours. In their study, single dose was successful in 84.4% while in ours it was successful in 77.4% patients.

In a study by Thia EWH, et al. [16] medical treatment was offered to the patients with ectopic pregnancy by giving intramuscular injection of methotrexate. In this study, prospective data on 110 patients treated with intramuscular methotrexate for ectopic pregnancy was reviewed. The mean age was 30 (range 17–44) years. The mean HCG level of the 110 patients at Day 1 was 1,414.7 (range 18.3–10,073.0) IU. The success rate after single-dose methotrexate was 79.1%, and after two doses of methotrexate, 84.5%. Out of 110 patients, 14.5% required surgery. In another study, the success rate of methotrexate was detected as 82% when beta hCG level was between 2000 – 5000 IU/L.[17]

Similarly in another study by Fletcher, et al. [18] a total of 24 patients with ectopic pregnancy treated with methotrexate were compared to surgery. In their cohort, medical treatment was done for 19 pregnancies while surgery was offered to women with 5 such pregnancies. In the medically treated group the success rate was 68% while in the surgically treated groups success was 100%. The success rate of medical treatment was lower than this present study, but surgery was successful in all the patients. The higher failure rate seen for medically managed patient, in that study may have been because the criteria for medical management were not strictly adhered to in that study as 13 of 19 patients and 10 of 19 patients medically treated had abdominal pain and abdominal tenderness (respectively) which may have been inherent signs of rupture.

Liu YL, et al. [19] performed a study in which different doses of methotrexate (single dose, or multiple dose and combination with mefiprestone) were tested. In this study, the success rate of single dose methotrexate was very high, i.e. 92.68% which is much higher than any other study.

In our study, we offered medical treatment to the patients who had gestational sac size of up to 5 cm. With regard to the gestational size of ectopic pregnancy, Shalev et al. [20] found a success rate of 76% when the gestational sac was smaller than 2 cm, and 52% when it was larger than 2 cm.

In different clinical trials, various authors have documented various frequencies of success ranging as low as 68% to as high as 92.68%. However, in majority of trials, including ours, a high rate of success has been observed which is encouraging.

This study has certain limitations. Firstly, lack of our experience in such regime and second, selection and the type of the patients, because in our society our patients prefer surgical treatment.

Conclusion

The rate of success of treatment with methotrexate for the management of ectopic pregnancy is quite high. So it is recommended that every patient with a gestational sac of < 5 cm diameter should be offered medical management with methotrexate as a first line treatment. Failure of which may need surgery.

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