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Original Research Article

Medical management of ectopic pregnancy

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ABSTRACT

Background: Ectopic pregnancy is a commonest cause of maternal morbidity and mortality in the first trimester of pregnancy. Clinical presentation of ectopic pregnancy has changed from life threatening disease to a more benign condition for which nonsurgical treatment options are available with methotrexate administered systemically or locally. The study was done to evaluate the outcome of medical management of ectopic pregnancy with single regimen methotrexate.

Methods: A cohort study was conducted over 18 months on 60 unruptured ectopic pregnancies who were treated with methotrexate injection.

Results: Out of 60 unruptured ectopic pregnancies, 53 (88.3%) were successfully treated with methotrexate. Failure rate was 11.7% (7/60) patients who underwent laparotomy. Success of medical treatment was dependent on pretreatment β -hCG (≤ 4102.5 mIU/mL), period of gestation (≤ 5 weeks), size of gestational sac (≤ 3 cm) above which the failure rate increases. No correlation was seen between fall of β -hCG from day 4 to 7 and the success rate. Mean time to resolution of β -hCG seen was 4.3 ± 1.25 weeks. Mean duration of hospital stay was 8.85 ± 1.603 days. Single dose regimen of methotrexate was given to all patients and only 1/60 patients required second dose of methotrexate for suboptimal decrease of β -hCG.

Conclusions: The result showed that pretreatment β -hCG level and period of gestation were good predictors for success of medical treatment.

Keywords: Ectopic pregnancy, Methotrexate, β -hCG

INTRODUCTION

Ectopic pregnancy occurs when fertilized ovum gets implanted in tissue other than the endometrium. It is a common life-threatening emergency in the developing world and the commonest cause of maternal morbidity and mortality in the first trimester of pregnancy.¹

According to centre for disease control and prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancy.² Fallopian tube being the most common site of ectopic implantation, accounting for more than ninety percent.³

Risk factors include prior ectopic pregnancy to be the commonest, followed by prior tubal surgery, pelvic inflammatory disease (PID), smoking, prior medical or surgical abortion, infertility and its treatment, prior intra uterine contraceptive device (IUCD) use in case of failure.⁴ Currently early high suspicion, serial hormonal assays and transvaginal sonography (TVS) facilitates the early diagnosis and treatment of ectopic pregnancy before it ruptures. This has resulted in a dramatic decline in mortality rate.⁵

The management for an ectopic pregnancy includes surgery, medical or rarely expectant management. Over

the time the clinical presentation of ectopic has changed from life threatening disease to a more benign condition for which nonsurgical treatment options are available, with methotrexate (MTX) being the most commonly given drug for a medical management of ectopic pregnancy. It is a folic acid analogue that inhibits dihydrofolate reductase and thereby prevents synthesis of DNA.

Multiple dose regimen which was traditionally used has now been replaced by single dose regimen protocol which were easier with better patient compliance, less expensive, requiring less monitoring and treatment results and prospects for future fertility were comparable.⁶ The overall effectiveness of methotrexate therapy ranges from 78-96%.⁷ High pre-treatment serum β -human chorionic gonadotropin (hCG) levels has shown to be the most important predictor for medical treatment failure, although which treatment modality is appropriate for specific range of pre-treatment serum β -hCG level still remains unclear.¹⁰

The decision for medical or surgical management of ectopic pregnancy should be guided by the initial clinical, laboratory and radiological data using specific criteria as well as patient informed choice based on discussion of benefits and risk of each approach.

The purpose of this study is to evaluate the outcome of medical management of ectopic pregnancy using a single dose regime of methotrexate.

METHODS

Prospective cohort study conducted in the department of Obstetrics and gynecology RIMS, Imphal from 1st September 2016 to 28th February 2018. Sixty patients with confirmed diagnosis of unruptured ectopic pregnancy who were hemodynamically stable and fulfilling the inclusion and exclusion criteria were recruited for the study.

Inclusion criteria

Patients included with hemodynamically stable, adnexal mass <4 cm, β -hCG <5000 mIU/mL, no fetal cardiac activity on USG, hemoperitoneum <100 ml were included in this study.

Exclusion criteria

Patients with sensitivity to methotrexate, liver, hematological and renal impairment, presence of fetal activity, breast feeding, inability to participate in follow-up were excluded from the study.

After obtaining informed written consent, a detailed history was taken from the patients i.e., age, parity, last menstrual period, period of amenorrhoea, lower abdominal pain, bleeding per vagina and past history to

rule out risk factors i.e., previous ectopic pregnancy, PID, infertility, contraception, abdomino-pelvic surgery, abortions. After detailed history patient were examined thoroughly including abdomino-pelvic examination for tenderness, guarding, rigidity, distension, cervical excitation.

Investigations such as complete hemogram, blood grouping, liver function test, kidney function test, serum β -hCG were done. All patients were administered a single dose of 50 mg/m² MTX on day 1 and measured β -hCG level on day 4 and 7. If the decrease in β -hCG level was >15% we considered treatment successful and followed weekly until it reaches non pregnant level. If the decrease in β -hCG level on day 4 and 7 was <15%, second dose of methotrexate was administered. If β -hCG level did not decrease after two doses, authors considered surgical management.

Statistical analysis

All details were entered in a pre-designed performa and analysed using SPSS 21 IBM. Descriptive statistics like mean, percentage and standard deviation were used. For differential statistics, Chi square, Fisher's exact test and independent t-test were utilized and p-value <0.05 was taken significant.

RESULTS

After screening for inclusion and exclusion criteria 60 unruptured ectopic pregnancy who came during the study period were included.

Table 1: Distribution of cases according to outcome of treatment.

Outcome	No. of cases	Percentage
Success	53	88.3
Failure	7	11.7
Total	60	100.0

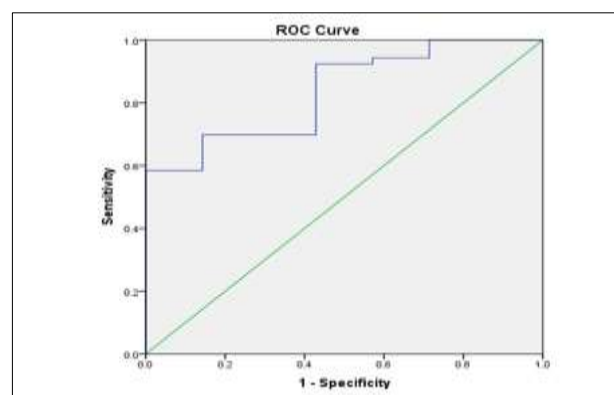


Figure 1: Receiver operating characteristic (ROC) curves for initial β -hCG concentration on successful outcome. β -hCG area under curve=0.836, SE=0.069, p=0.04.

The cut off hCG value which determined the failure of MTX treatment with sensitivity of 92.5% and specificity of 57.1% in ROC curve analysis was found to be >4102.50 mIU/mL.

Table 2: Correlation of level of β -hCG on day 1 with treatment outcome.

Level of β -hCG	Outcome		P value*
	Success n (%)	Failure n (%)	
≤ 4102.5	49 (94.2)	3 (5.8)	0.004
> 4102.5	4 (50)	4 (50)	

*Fisher's exact test.

Table 3: Correlation of fall in β -hCG level on day 4 and 7 with treatment outcome.

% fall in β -hCG	Outcome		P value*
	Success n (%)	Failure n (%)	
< 15	0 (0)	1 (100)	0.117
≥ 15	53 (89.3)	6 (10.2)	

*Fisher's exact test.

Maximum number of patients (59/60) had fall of β -hCG value more than equal to 15% between day 4 and day 7. In spite of fall of β -hCG between day 4 and day 7, there was a failure rate of 10.2% (6/60) cases. There was no significant relation between fall of β -hCG between day 4 to day 7 and treatment outcome ($p=0.117$).

Table 4: Correlation of size of ectopic with treatment outcome.

Size of ectopic	Outcome		P value*
	Success n (%)	Failure n (%)	
≤ 3 cm	26 (96.3)	1 (3.7)	0.116
4 cm	27 (81.8)	6 (18.2)	

*Fisher's exact test.

Failure rate was found to be 3.7% when size of ectopic pregnancy was less than equal to 3 cm and above its failure rate was 18.2%. Here, p value is 0.116. Therefore, the association was found to be insignificant.

Table 5: Correlation of period of amenorrhea with treatment outcome.

Period of amenorrhoea (in weeks)	Outcome		P value*
	Success n (%)	Failure n (%)	
≤ 5	23 (100)	0 (0)	0.037
> 5	30 (81.1)	7 (18.9)	

*Fisher's exact test.

A total 9 (15%) out of 60 cases were admitted again despite of fall in hCG level from day 4 to day 7 (Table 7).

Table 6: Distribution of cases according to reason for failure.

Reason for failure	No. of cases	Percentage
Haemodynamic instability	3	42.9
Severe pain	3	42.9
Persistent pain abdomen	1	14.2
Total	7	100

Table 7: Distribution of cases according to need for readmission.

Readmission	No. of patients	Percentage
No	51	85.0
Yes	9	15.0
Total	60	100.0

Table 8: Distribution of cases according to reason for readmission.

Reason for readmission	No. of cases	Percentage
Moderate pain	5	55.6
Severe pain	3	33.3
Sub-optimal decrease in hCG	1	11.1

Table 9: Distribution of cases according to management after readmission.

Management	No. of cases	Percentage
Conservative	6	66.7
Surgery	3	33.3
Total	9	100.0

Table 10: Distribution of cases according to resolution time of β -hCG.

Time to resolution (in weeks)	No. of cases	Percentage
3-4	18	33.9
4-6	32	60.4
> 6	3	5.7
Total	53	100.0
Mean \pm SD		4.36 \pm 1.25

Maximum number of cases 60.4% had a resolution time of 4-6 weeks, followed by 33.9% of cases with resolution time of 3-4 weeks and 5.7% of cases with resolution time more than 6 weeks. Mean time to resolution of β -hCG was 4.36 \pm 1.25 weeks.

DISCUSSION

One of the known factors associated with MTX treatment success is the pretreatment β -hCG levels, but threshold

reported in the literature vary from 1000 mIU/mL to as much as 5000 mIU/mL. In the present study, we found that cut off β -hCG value by using ROC curve to predict MTX failure was 4102.50 mIU/mL with 92.5% sensitivity and 57.1% specificity. In patients with β -hCG level >4102 mIU/mL, the failure rate was 50% whereas in patients with lower β -hCG levels, failure rate was 5.8%. Hence positive correlation was seen between β -hCG and success rate. The study conducted by Vaswani et al revealed the cut off β -hCG level for success as 6000 mIU/mL and to be good predictors for success rate.⁸ In the study conducted by Menon S et al, a cut off of pretreatment β -hCG value was 5000 mIU/mL and substantial increase in failure was noted when β -hCG value was >5000 mIU/mL.⁹

In study, patients with ectopic size ≤ 3 cm had 96.3% success rate and with 4 cm size 81.1% success rate. No significant relationship was found between ectopic size and treatment success. Vaswani et al in their study showed size ≤ 3 cm to be a good predictor of success.⁸

In the present study, patients with period of gestation ≤ 5 weeks have 100% success rate and above the level have 81.1% success. The correlation between period of gestation and success rate was significant. Similar study was conducted by Vaswani et al where period of gestation <6 weeks to be a good predictor for success of medical management of ectopic pregnancy.⁸

The fall of β -hCG value >15% from day 4 to day 7 was 87.9%. There was no correlation with fall of β -hCG value from day 4 to day 7 with the success rate. This can be due to unequal distribution of patients for fall of β -hCG value.

In the present study, 9 (15%) patients were readmitted after successful decrease of β -hCG from day 4 to day 7. Out of which 3 patients underwent laparotomy for severe pain and termed as treatment failure, 5 readmitted patients were managed conservatively for moderate pain and one patient was given second dose of methotrexate and was successful.

Mean time to resolution of β -hCG seen in my study was 4.3 ± 1.25 weeks which was similar to time to resolution shown by Lee et al which was 27.4 ± 11 days.¹⁰ Shah et al in their study stated the time to resolution was 32 days.¹¹

Success rate of medical management with single dose methotrexate for ectopic pregnancy in my study was 88.3% with no side effects. It was comparable with studies conducted by Shah et al where success rate was 85% and Krik et al where success rate was 91%.^{11,12}

Failure rate was (11.7%) 7/60 patients. Among which 3 patients (42.9%) had hemodynamic instability, 1 patient (14.2%) had persistent pain abdomen and 3 (42.9%) of them were readmitted for severe pain abdomen after successful decrease of hCG from day 4 to day 7. One case of cervical pregnancy with hemodynamically

unstability underwent hysterectomy. Rest 6 patients underwent laparotomy out of which 5 had ruptured ectopic pregnancy.

CONCLUSION

Treatment of an ectopic pregnancy with methotrexate is safe and effective in carefully selected cases. Although methotrexate treatment is beneficial in that it allows one to avoid surgery in a patient, there are certain disadvantages. Medical treatment requires extended follow-up of patients, which can be cumbersome and difficult at times. The need to follow patients clinically until the serum β -hCG is undetectable requires multiple visits, which takes valuable time of both patient and clinician. It is appropriate for clinicians to select suitable candidates for treatment of ectopic pregnancy with methotrexate. It is imperative to confirm diagnosis to avoid unnecessary administration of a chemotherapy, such as in a completed miscarriage or early intrauterine pregnancy, that can have severe consequences for both mother and fetus. There is usually no indication that methotrexate has to be administered at the first presentation of the patient, especially if she is clinically stable. If a woman is not stable or is in significant pain, she is not a candidate for medical management. Follow-up hCG or ultrasound can often avoid unnecessary or contraindicated administration of methotrexate. Moreover, patients should have appropriate counselling, willingness for follow-up and no absolute contraindications to methotrexate treatment. The choice between two acceptable treatments, medicine or surgery, should be an informed, not reflective decision.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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