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Original Research Article

Analysis of risk factors and treatment outcome following methotrexate therapy in ectopic pregnancy

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ABSTRACT

Background: Ectopic pregnancy is a significant cause of morbidity and mortality in first trimester of pregnancy. Awareness regarding risk factors for ectopic pregnancy aids in early diagnosis and timely medical intervention before tubal rupture occurs. This study was undertaken to analyze the risk factors for ectopic pregnancy and to study the treatment outcome following methotrexate therapy.

Methods: In this prospective study, 34 women with unruptured ectopic pregnancy selected for medical therapy were enrolled women with ectopic pregnancy who were hemodynamically stable with initial beta-human chorionic gonadotropin (β hCG) values of <5000 mIU/L, ectopic gestation mass size <5 cm and with no contraindication for methotrexate use were included in the study. Risk factors for ectopic pregnancy were studied and treatment outcome following single dose or 2 dose methotrexate regimen were analyzed.

Results: The mean age of the study group was 26.88 ± 4.5 years. Highest incidence of ectopic pregnancy was noted in 26-30 years and in second gravidas. Successful treatment outcome was observed in 61.8% with single dose methotrexate (MTX) and in 23.5% with 2 doses. Overall success rate of MTX therapy was 85.3%. Surgical intervention was instituted in 14.7% when pretreatment β hCG levels were <1500 mIU/ml. Single dose MTX was successful in 91.7% and with 2 doses it was 100%. None developed any major side effects to methotrexate therapy.

Conclusions: MTX therapy is safe and effective in carefully selected women with ectopic pregnancy. Success rate of MTX therapy was 85.3%. MTX was most effective when pretreatment β hCG levels were less than 1500 mIU/ml.

Keywords: Ectopic pregnancy, Risk factors, Methotrexate

INTRODUCTION

Despite advances in diagnosis and management, ectopic pregnancy (EP) is one of the significant causes of maternal mortality in early weeks of pregnancy.¹ The incidence of EP in India ranges from 1-2%.² Maternal mortality due to EP varies from none to 3.5 % and reflects the variable quality of medical infrastructure facilities available in the country.³ Late diagnosis and delay in accessing medical care are important causes of deaths due to EP.

Nearly about 50 % of women diagnosed with EP do not have any known risk factors.⁴ However, those with

significant risk factors should be evaluated for possible EP even in the absence of symptoms.⁵ Clinical presentation and serum beta-human chorionic gonadotropin (β hCG) levels along with reliable sonographic findings like adnexal mass with features of early pregnancy such as a gestational sac with yolk sac or fetal pole with or without cardiac activity should be used to confirm or rule out EP.⁶ However, most pregnancies do not progress to this stage.⁷ Women with confirmed or high clinical suspicion of EP who are hemodynamically stable with unruptured ectopic mass and who do not have any absolute contraindications to methotrexate (MTX) are ideal candidates for medical therapy. The decision for medical therapy should be

guided by clinical, laboratory and radiological data as well as by patient informed choice.⁵

This study was undertaken to have a better understanding of risk factors for EP in our population and to analyze the outcome of medical therapy in a carefully selected group of women with EP.

METHODS

This prospective study was conducted in Government Medical College Hospital, Pudukottai in South India between January 2021 and December 2021. All women diagnosed with EP and selected for medical management were enrolled in the study. Women enrolled were counselled about the benefits and risks involved and informed consent was obtained. EP was diagnosed based on specific clinical features, ultrasound findings and serial β hCG values.

Women who were hemodynamically stable, with no evidence of hemoperitoneum, adnexal mass of <5 cm, absent fetal cardiac activity, β hCG level of <5000 mIU/ml and mild abdominal pain were included in the study.

Exclusion criteria were non-tubal EP, hemodynamic instability, evidence of intraperitoneal bleeding, moderate to severe anaemia, hepatic or renal dysfunction, sensitivity to MTX, blood dyscrasias, pulmonary disease, thrombocytopenia, immuno-compromised state, adnexal mass of >5 cm and β hCG level of >5000 mIU/ml. Details of risk factors for EP were noted. Baseline blood investigations like complete blood count, liver function tests and renal function tests were done.

All women received injection MTX 50 mg/m² intramuscularly. Serial β hCG estimations were done on day 1, 4 and 7. Post administration, women were monitored for symptoms and signs of rupture of EP and side effects of MTX. Ultrasound examination was done if any woman became symptomatic with increasing abdominal pain or if there is suboptimal decline (<15%) of β hCG on day 7. If the decline in β hCG level on day 7 was >15%, then weekly estimations were done until it was <15 mIU/ml. Those with suboptimal fall in β hCG levels on day 7 were either given a 2nd dose of MTX after excluding ectopic fetal cardiac activity and hemoperitoneum or taken up for surgical intervention based on the trend of β hCG and ultrasound findings. Those given a second dose of MTX were followed up with repeat β hCG estimation on day 11. Side effects of MTX if any were noted.

Statistical analysis

Data were entered in the excel spreadsheet and variables were coded accordingly. The statistical analyses were performed using Graph pad Prism version 5 software. Data were presented as frequency with proportion n (%) for categorical data.

RESULTS

The mean age of the study group was 26.8±4.5 years with a range of 17-36 years (Table 1). Maximum incidence (41.2%) of EP was noted in the 26-31 years age group and in second gravidas (Table 2) which was statistically significant (Table 3). In 26.5% (n=9) EP was the first conception.

Table 1: Ectopic pregnancy in relation to age.

S. no.	Age category (years)	n=34	%
1	≤20	3	8.8
2	22–25	10	29.4
3	26–30	14	41.2
4	31–35	6	17.6
5	>35	1	2.9

Data are expressed as n with proportions (%), total n=34

Table 2: Distribution of cases based on parity.

S. no.	Parity	n=34	%
1	Nullipara	9	26.5
2	Para 1	14	41.2
3	Para 2	9	26.5
4	Para 3	2	5.8

Data are expressed as n with proportions (%), total n=34. On review of previous reproductive performance, incidence of ectopic gestation (41.2 %) was higher in second gravidas

On analysis of risk factors, 19 out of 34 (55.9%) women had 1 or more risk factors for EP. Four women had undergone tubal surgeries and 5 non tubal pelvic surgeries, 4 had been treated for infertility, 1 had a prior medically managed ectopic gestation, 3 had prior abortions, 2 had history of prior intra uterine device (IUD) use and 2 gave history of pelvic inflammatory disease (Table 4). Fifteen women had no identifiable risk factor for EP.

On analyzing the initial β hCG level and treatment outcome (Table 5), 91.7 % (11/12) responded to single dose of MTX when β hCG levels were <1500 mIU/ml. In women with β hCG levels between 1500 and 3000 mIU/ml, 80% (8/10) responded to single dose and only 20% (2/10) required an additional dose of whom 1 required surgery. On the contrary, in those with β hCG levels more than 3000 mIU/ml, 83.3% (10/12) required an additional dose, of whom 4 (33.3 %) had to undergo surgery. The success rate of MTX therapy was 100 % when β hCG levels were <1500 mIU/ml, 90% when β hCG levels were between 1500 and 3000 mIU/ml and it dipped to 66.7% when β hCG levels were above 3000 mIU/ml.

On analysis of factors favoring successful treatment outcome, 28 had an adnexal mass of <3.5 cm and in 6 it was >3.5 cm. Twenty one out of 28 (75%) with an adnexal mass of <3.5 cm were successfully treated with single dose MTX while 5 (17.9%) responded to an additional dose and

2 (7.1%) required surgery. All 6 women (100%) with adnexal mass of >3.5 cm required an additional dose of MTX of whom 50% (n=3) required surgical intervention. The success rate of MTX therapy for EP was 93% when the adnexal mass was <3.5 cm and it fell to 50% in those with adnexal mass of >3.5 cm (Table 6).

The overall success rate of MTX therapy in our study was 85.3% (29/34). Five women (14.7%) needed emergency surgical intervention of whom 1 had developed intra-peritoneal haemorrhage and 4 had plateauing/increasing levels of β hCG after the additional dose of MTX.

Table 3: Correlation of the cases by age and parity.

S. no	Gestational age category (years)	Primigravida (n=9)		Gravida-2 (n=14)		Gravida-3 (n=9)		Gravida-4 (n=2)	
		N	%	n	%	n	%	n	%
1	≤20	3	33.3	0	0	0	0	0	0
2	21–25	5	55.6	5	35.7	0	0	0	0
3	26–30	1	11.1	7	50	5	55.6	1	50
4	31–35	0	0	2	14.3	3	33.3	1	50
5	>35	0	0	0	0	1	11.1	0	0

Chi square value=23.47; df=12 and p value=0.024*, data are expressed as n with proportions (%), total n=34, *p<0.05 is significant

Table 4: Risk factors for ectopic pregnancy observed in study population.

S. no	Risk factors	Break up of risk factors	n	%
1	Prior ectopic gestation	Medically treated ectopic gestation – 1 Surgically managed ectopic gestation – 1	2	5.9
2	Prior abortions	Spontaneous first trimester abortions – 3	3	8.8
3	Tubal surgery	Laparoscopic sterilization – 1 Tubal sterilization – 1 Tubal re-canalisation – 1 Partial salpingectomy for adnexal torsion -1	4	11.8
4	Non tubal pelvic surgeries	Caesarean section – 4 Appendicectomy – 1	5	14.7
5	Infertility	Ovulation induction – 1 Ovulation induction and artificial insemination – 1 Assisted reproductive technique – 1 Untreated infertility – 1	4	11.18
6	Intrauterine device use	Prior multiload Cu T use – 2	2	5.9
7	Pelvic inflammatory disease		2	5.9

Data are expressed as 'n' with proportions (%). 19/34 women were identified to have 1 or more risk factors

Table 5: Analysis of initial β -hCG level and treatment outcome.

S. no.	Initial β -hCG level on admission (mIU/ml)	No of cases n=34	Single dose n=21	Multiple dose n=13	Success rate n=29	MTX treatment success %	MTX treatment failure 14.7% (n=5)
1	<1500	12	11	1	12	100	-
2	1500 to 3000	10	8	2	9	90	1
3	3000 to 5000	12	2	10	8	66.6	4

Data are expressed as 'n' with proportions (%)

Table 6: Correlation between size of ectopic gestation mass and treatment outcome.

S. no	Size of the mass on TVS (cm)	n=34	Single dose (n=21)	%	Multiple dose (n=13)	%	Treatment success (n=29)	%	Treatment failure (n=5)	%
1	<3.5	28	21	75	7	25	26	92.9	2	7.14
2	3.5-5	6	0	-	6	100	3	50	3	50

Data are expressed as 'n' with proportions (%)

DISCUSSION

EP is a life threatening emergency and could adversely affect the future reproductive potential of the affected women. Awareness regarding the risk factors of EP will aid in early diagnosis and management and those risk factors could serve as potential targets for intervention and modification.⁸

Various studies have documented that incidence of EP increases with maternal age.⁹⁻¹² The mean age of our study group was 26.8±5 years. Various other trials in their assessment of age as a risk factor for EP have reported contradicting results. Bouyer et al in a case control study had reported older age to be a significant risk factor for EP and that it was unlikely that the higher risk was due to higher probability of exposure to most other risk factors for EP in older women.¹² It was hypothesized that age related changes in tubal function may delay ovum transport and cause tubal implantation.¹³

Three women (8.8%) had prior spontaneous abortions in our study. The association between prior spontaneous abortion and risk of EP has been variably reported.^{12,14,15} It was observed that risk of EP was considerably high in women with 3 or more abortions and this could possibly be attributed to infections secondary to spontaneous abortions.^{12,14} Higher risk could also be due to other risk factors common for EP and spontaneous abortions such as chromosomal abnormalities or hormonal factors.^{16,17} Prior medically induced abortion was also observed to be a risk factor for EP and could be due to lack of routine antibiotic prophylaxis in such group of women.¹² But Banhart et al have reported no such association.⁴

Infertility as a risk factor was observed in 4 (11.8%) women in our study of whom 1 had undergone assisted reproductive techniques (ART). ART have traditionally been believed to increase the risk of EP.^{1,18} Though rapid advances in ART over the years have considerably decreased the incidence of EP following ART, techniques such as multiple embryo transfer can lead to increased risk.¹⁹ Fresh nondonor cycles had the highest EP rates compared to donor cycle and frozen thawed cycles.^{19,20} In vitro fertilization and embryo transfer has also been identified to be a risk factor for EP specifically in women with tubal infertility.^{21,22}

Two out of 34 women (5.9 %) had history of prior IUD use in the current study. Prior IUD usage was reported to have a direct etiological role in EP and also through an association with infection, but Barnhat et al found no evidence to link prior IUD use with risk of EP.^{4,12,23,24} IUD does not inhibit ovulation and hence it is not effective in preventing extrauterine pregnancies. Risk of EP increased following failure of most contraceptives including IUD used in current cycle.²¹

In this study, 5.9% were treated for PID in the past and 11.8 % had undergone tubal surgeries. Several trials have

reported an association between pelvic infection and EP.^{10,12,21,25} probably due to a causal link. This was also evidenced in a study in Sweden which reported that declining rates of chlamydial infections were accompanied by a fall in rates of EP.²⁶ Many studies have also reported that factors like prior EP, prior tubal surgery, documented tubal pathology, in- utero exposure to DES to be strongly linked to risk of EP.^{4,12,15,21} Recurrence of EP may be due to persistent tubal pathology and the risk of repeated EP increases in direct proportion to the number of previous ectopic pregnancies.⁴

Medical management of EP

Major advances in the diagnosis and management of EP in the last 2 decades has led to early diagnosis, enabling a subset of women with EP to be treated with medical therapy thereby preserving future fertility. It is imperative that diagnostic and management strategies are clearly documented, keeping in mind the risk of ruptured EP.²² MTX is a folic acid antagonist, which prevents proliferation of cytotrophoblasts and reduces cell viability and β hCG secretion.

In our study, 61.8% of women were successfully treated with single dose MTX and 23.5% with 2 doses. The overall success rate of MTX therapy was 85.3% and this was consistent with several other trials.²⁷⁻²⁹ Single dose MTX has been recommended to be most appropriate for women with relatively low pretreatment β hCG levels and the 2 dose regimen in those with high pretreatment β hCG levels.^{5,27,30} The 2 dose regimen minimizes the number of injections and surveillance methods compared to multiple dose regimen. The cut off value for pretreatment β hCG which predicted treatment success has been variably reported and there is no consensus on it.^{5,31-34} In our study the success rate of MTX was 100% when β hCG levels were <1500 mIU/ml and 90% when β hCG levels were between 1500 and 3000 mIU/ml and it declined to 66.7% when β hCG levels exceeded 3000 mIU/ml. The commonly identified predictors of MTX treatment failures are the presence of fetal cardiac activity, size of ectopic gestational mass of >4 cm, initial β hCG concentration of >5000 mIU/ml, increase in β hCG concentration of >50% in 48 hours before MTX, and continued rapid increase in β hCG concentration during MTX therapy.³⁰ The change in β hCG levels between day 1 and day 4 was also found to be an early and effective predictor of success of MTX therapy by Zhang et al.³⁵ Single dose regimen was found to be less expensive, requires less intense monitoring and does not require citrovorum rescue.²⁷ We found MTX therapy to be successful in 93% when the ectopic mass was <3.5 cm, while it was only 50% when the ectopic mass was >3.5 cm and it was consistent with that reported by Dhar et al.³⁶ Single dose MTX protocol was stated to be associated with fewer side effects.²⁷ In our study 4 women (11.8%) developed minor side effects like nausea and vomiting and none developed any serious side effects. Some trials comparing single versus multiple fixed dose regimen found no significant difference in either treatment

success or rates of serious side effects³² while some others found multiple fixed dose regimen to be more effective.^{27,29,30,32,37,38}

The significance of association between the risk factors detected in our study and EP cannot be commented upon as ours was not a case control study and that was a limitation.

CONCLUSION

MTX therapy in carefully selected unruptured tubal ectopic pregnancies is safe and effective. The success rate of MTX therapy was 85.3% with our management protocol. MTX was most effective when pretreatment β hCG levels were less than 1500 mIU/ml. Need for surgical intervention should be anticipated when pretreatment β hCG levels are high.

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

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