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Original Research Article

Role of methotrexate in ectopic pregnancy

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ABSTRACT

Background: Ectopic pregnancy is an acute emergency in obstetric if not timely diagnosed and timely treated. Ectopic pregnancy is leading cause of death in first trimester. Ectopic pregnancy can be managed surgically or medically. Medical management with Methotrexate administration avoids anesthesia in surgery, is cost effective and also offers success rate comparable to surgical management. Aim and objectives were to study the role of methotrexate in ectopic pregnancy

Methods: This will be a retrospective observational study conducted in Obstetrics and Gynecology department of AMC MET medical college. Study group constitutes of 30 females with ectopic pregnancy. Preliminary blood investigations, ultrasonography and beta-human chorionic gonadotropin (b-hcg) level will be tested. Patients will be treated with single dose of methotrexate 50 mg/M². Follow up b-hcg level will be done after 48 hours. Response and tolerance to methotrexate will be monitored.

Results: The success rate of methotrexate therapy in our study was 83.33% (n=25) and 16.66% (n=5) required surgical intervention with tubal ruptured and abdominal pain.

Conclusions: Methotrexate treatment of ectopic pregnancies is safe and effective with no major side effects. It has the advantage of tubal conservation and saves patients from surgical intervention.

Keywords: Ectopic pregnancy, Methotrexate, b-hcg

INTRODUCTION

Ectopic pregnancy is a pregnancy in which the fertilized ovum implant outside the uterine cavity. its incidence 2 per 100 pregnancy.^{1,2} Risk of ectopic pregnancy is 3-fold in IVF cycle.³ Ectopic pregnancy is an acute emergency if not timely diagnosed and treated. Timely diagnosis and appropriate treatment can reduce the risk of maternal mortality and morbidity related to ectopic pregnancy. Greater awareness of risk factors and improved technology allow ectopic pregnancy to be identified before development of life-threatening events.⁴ Ectopic pregnancy is still the leading cause of maternal death in the first trimester of pregnancy, accounting For 6-13% of pregnancy related death.⁵ EP most common occur in young woman and the commonest presenting symptom is

abdominal pain.⁶ Early diagnosis of EP is now possible by serum beta HCG and ultrasound. This increase the chance of success of medical treatment and avoid the morbidity of anesthesia and surgery. Medical treatment of EP with methotrexate (MTX) has been effective and safe in selected patients.⁷ Methotrexate can be systemically as a single dose (MTX 1.0 mg/kg or 50 mg/m² IM without folinic acid) or as a multi dose regimen (MTX 1.0 mg/kg I.M daily 0,2,4,6 alternated with folinic acid 0.1 mg/kg orally on day 1,3,5,7).

A single dose regimen was introduced to minimize side effects, improve the patient's compliance and to reduce the cost. Carefull follow-up and assessment are required women treated with MTX therapy.

METHODS

A retrospective observational study of 30 patients diagnosed ectopic pregnancy was conducted from period of one year from June 2018 to May 2019 at L.G hospital, Ahmedabad. Patients was diagnosed ectopic pregnancy by trans vaginal ultrasound and measurement of beta human chorionic gonadotropin(beta-Hcg). A detailed history and informed consent were taken of all patients. Thirty patients included the study inclusion criteria for conservative management was hemodynamically stable, ectopic mass size<4 cm in trans vaginal ultrasound, serum beta Hcg level<15000.Those with ruptured ectopic pregnancy, visualization of fetal cardiac activity in ectopic mass and heterotopic pregnancy. Baseline investigation CBC, b-hcg, RFT, LFT and blood group were done in all patients.

Single dose of MTX (1 mg/kg or 50 mg/m2) intramuscular injection was given to selected patient. Repeat beta hcg level were taken on day 4 and 7. Those patients with not decline beta hcg level by<15% from day

4-7 second dose of MTX was given. Other patients with beta hcg level decline at least 15% on 7th day than 4th day. These patients were discharged and weekly follow up for serum b-hcg level. Single dose MTX treatment was considered successful when b-hcg level became negative without further administration of MTX dose or surgery. Sign of MTX toxicity like leucopenia, thrombocytopenia, raised hepatic enzyme, raised blood urea and creatinine level were noted carefully.

Statistical analysis

All the data was entered and analysed in to Microsoft excel sheet.

RESULTS

Thirty patients with the diagnosis of EP and single dose MTX treatment were included in to the study. out of 30 patients twenty-five patients (83.33%) were successfully treated.

Table 1: Maternal age in years

S. no.	Age in years	Case(n)	Case (%)	Successful (n)	Successful (%)
1	15-25	6	20	4	66.66
2	25-35	20	66.6	18	90
3	35-45	4	13.13	3	75

Table 2: Parity wise distribution.

S. no.	Parity	Case(n)	Case (%)	Successful (n)	Successful (%)
1	0-1	18	60	15	83.33
2	2-5	9	30	8	88.88
3	>5	3	10	2	66.66

Table 3: Adnexal mass size.

S. no	Adnexal mass (cm)	Case (n)	Case (%)	Successful (n)	Successful (%)
1	0-2	6	20	4	66.6
2	2-3	22	73.33	20	90.9
3	3-4	2	6.6	1	50

Table 4: Beta-hcg level on day 1.

On admission b-hcg level	No of patients	Percentage (%)	No of successful patient	Success rate (%)
<10000	26	86.66	24	92.30
>10000	4	13.33	1	25

Table 5: Fall in beta-hcg level on days4 and 7 and outcome.

	Total No. of patient	Percentage (%)	No. of successful patient	Success rate (%)
>15%	24	80	22	91.66
<15%	6	20	3	50

In this study majority of patient (66.6%) were between 25-35 years (n=20). The success rate of methotrexate decreased as maternal age increased. Gravidity was

between one and six with 60% (n=18) primipara. Adnexal mass ranged from 2-4 cm. In patients with adnexal mass >3 cm, the success rate was less. In women

with 2-3 cm adnexal mass success rate is 90.9% (n=22) (Table 3). There was no marked difference in the site of ectopic gestation. The average value of β -hcg on Day 1 in patient treated with single dose of methotrexate was 3,000 mIU/ml (range 100-8,847) and those with two doses or more was 10,000 mIU/ml (Table 4). An increase in the day 4 value was observed in some cases, mainly due to the trophoblastic tissue breakdown releasing the hormone (Table 5).

Table 6: Success rate.

	No. of patient	Percentage (%)
Successful	25	83.33
Unsuccessful	5	16.66

The average time of resolution for serum β -hcg level was 32 days for single dose of methotrexate and 58 days for those receiving two doses. Time of resolution for serum β -hcg was defined as the total number of days from the beginning of treatment until β -hcg level became negative (<5 mIU/ml). The total number of women treated with single dose was 86.66% (n=26) and (n=4)13.33% received two doses. Success rate in group of patients given single doses MTX was 80.7% and in patient with two dose MTX it was 100%. Overall, the success rate of treatment in our study was 83.33% (n=25). Surgical intervention was required for 16.66% (n=5) of patients with tubal ruptured and abdominal pain (Table 6). Two patients of unsuccessful group underwent emergency laprotomy. One patient was managed by laparoscopic salpingotomy.

DISCUSSION

Ectopic pregnancy occurs in around 1% of pregnant women and may seriously compromise women's health and future fertility. With increase in the use of artificial reproduction technique and increase in pelvic inflammatory disease due to increased sexual promiscuity incidence of ectopic pregnancy has increased. It will help this community as a whole in preserving future childbearing function. Ectopic pregnancy can be diagnosed before the patient's condition has deteriorated and the cornerstone of diagnosis is the use of transvaginal ultrasound and serum β -hcg measurement. Single dose methotrexate appears effective and has better patient compliance. Treatment success is inversely correlated to β -hcg concentration. The most important selection criteria for medical management is the absence of pain and the prediction that the pregnancy will not rupture before its resolution. Surgery and medical management are the two ways to treat ectopic pregnancy. Both are effective and the choice depends on clinical situation, site of ectopic mass and access to technology. Systemic single dose methotrexate seems to offer the greatest benefits in terms of efficacy and tolerability. It has proved to be a good alternative to laparoscopy in selected cases. The success rate of systemic methotrexate in our study was 86.66% (n=26), 13.33% (n=4) were treated

with two doses of MTX 6.66% and (n=5) required surgical intervention. Patients with small unruptured ectopic pregnancies achieved a success rate of 90.9% with four women requiring a second dose. Srivichai et al reported a success rate of 90.6% in 96 out of 106 patients who were successfully treated with methotrexate though four required a second dose.⁸ In all comparative studies, the success rate was found to be same as in our study. The reason being that at the beginning of starting the methotrexate regimen in our institution women with increasing β -hcg values and complaints of abdominal pain were taken early for surgical intervention for fear of rupture of the ectopic pregnancy. With more experience of using the drug the success rate improved. Treatment failure based strictly on a high increase in β -hcg level from day 4 to 7 may be a hasty judgment. Pain after methotrexate treatment could be due to tubal abortion or stretching of the tube by hematoma contributing to increased failure rate in most of the medical management. Differentiating 'separation pain' due to tubal abortion from pain due to tubal rupture can be difficult and may lead to early surgical intervention. Mahboob reported a success rate of 80% by treating 12 out of 15 women with single dose methotrexate with initial β -hcg levels equal to 5,000 mIU/ml.⁶ In the same series, an increase in the treatment failure group with advanced maternal age ≥ 35 years and history of spontaneous abortions was noted corresponding to our study where success rate of methotrexate treatment decreased as maternal age increased. Lee reported a success rate of 96% with β -hcg 6,000 mIU/ml. He noted that initial β -hcg is the only predictor of success for repeated injection of methotrexate in single dose regimen.⁹ The incidence of infertility as a risk factor reported in literature was 30% for ectopic pregnancy. However, it accounted for 15% (n=9) in our study (primary-7 and secondary-2). Many studies have identified the risk factors for ectopic pregnancy. A third of cases are associated with tubal damage caused by infection or surgery and another third with appendectomy, which is a rare factor. No cause can be established for the remaining third. Techniques of assisted reproduction increase the risk of ectopic pregnancy by 2-4%. Multiple dose regimen for hemodynamically stable women with an unruptured tubal ectopic pregnancy with serum hcg concentrations <3,000 mIU/ml and a single-dose methotrexate for serum hcg <1,500 mIU/ml is recommended. Women with a pretreatment β -hcg level of 3,000-4,000 mIU/ml have a greater probability of surgery or multiple dose treatment. The time of resolution of serum β -hcg in our study was 32 days with a single dose and 58 days with two doses of methotrexate as compared to 27.3 days and 35 days, respectively in other series. Thia noted the time of resolution was 33 days with one dose and 55 days with two doses, similar to our study. Erdem reported the mean time of resolution as 26.5 (10-37) days in patients who were successfully treated with Methotrexate.¹⁰ These results are consistent with other studies. Methotrexate regimen reduces the incidence of persistent trophoblast. Persistent trophoblast is detected by the failure of serum hcg levels to fall as expected after initial treatment, often

a problem occurring after salpingostomy rather than salpingectomy. In 12 cases treated with laparoscopy, one case of persistent trophoblast was observed and this could have been prevented with medical management of ectopic pregnancy and β -hcg follow-up to avoid complications such as delayed hemorrhage owing to persistent trophoblast. In our study, 36.6% (n=11) of women complained of lower abdominal pain and 16.66% (n=5) were treated surgically due to increasing hemoperitoneum. Most studies showed increased lower abdominal pain between 2-7 days after treatment. This complication of methotrexate is disturbing in an outpatient with an ectopic pregnancy. No other side effect of methotrexate was observed in our study. In Thia's series, 40% (n=4) of patients were hospitalized for pelvic pain 2 days after treatment and their pain regressed without surgery. One patient developed mild rash in light exposed skin areas. No such complaint was observed in the studied patients managed as in-patients. In the same study, 28.2% (n=9) of patients complained of abdominal pain between Days 4 and 8 and one patient was found to have a ruptured cornual ectopic pregnancy at laparoscopy. Minor side effects reported in the same series were mucositis in 19.1% (n=21) and 10.9% (n=12) of the patients suffered gastric pain and diarrhea. No side effects were reported with single dose treatment in a series of 30 patients with a success rate of 97%. Increased abdominal pain on Days 5-10 after medical management of ectopic pregnancy has to be closely monitored for possible rupture. MTX therapy was associated with high rates (80%) of subsequent fertility compared to our study, successful intrauterine pregnancy following methotrexate was observed in three women.¹¹

Limitations

Absolute contraindication of MTX includes chronic liver disease, pre-existing blood dyscrasias, pulmonary disease, peptic ulcer disease and immunodeficiency. Additionally, patients who have sensitivity to MTX.

CONCLUSION

Methotrexate has proven to be an effective medical management for ectopic pregnancies in a society where tubal conservation is of at most importance. The medical management by methotrexate seems to offer several benefits over surgical treatment. It is less invasive, less expensive and does not need expertise like laparoscopy. Future reproductive expectations are better with methotrexate with higher intrauterine pregnancy rates and lower ectopic rates subsequently. However, the risk of tubal rupture after medical treatment combined with a prolonged follow-up for an ectopic pregnancy to resolve requires monitoring for rupture and MTX side effects

making compliance important in-patient selection. The predictors of success in our study are low β -hcg and adnexal mass <4 cm. Single dose methotrexate offers a safe and effective nonsurgical method of treating selected patient and one important advantage of medical therapy is the potential for considerable saving in treatment costs.

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