



ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY WITH METHOTREXATE

**KEY WORDS:** Methotrexate, maternal mortality, ectopic pregnancy

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ABSTRACT

**Objective:** The aim of this study is to determine the efficacy of methotrexate treatment for ectopic pregnancies in our settings, which will in-turn help us reduce maternal mortality and morbidity.

**Material and methods:** This was a prospective study of 40 cases of unruptured ectopic pregnancy treated with methotrexate in v.s.general hospital, Ahmedabad. Clinical presentation, treatment, progress, outcome, side effects were analyzed using database from December 2015 to June 2017.

**Results:** The success rate of methotrexate therapy in our study was 85% (n = 35) and 15% (n = 06) required surgical intervention compared to reported success rate of 67-100% published in various studies. The mean average time of resolution of ectopic pregnancy was 32 days for a single dose and 58 days for repeat doses.

**Conclusion:** Methotrexate treatment of ectopic pregnancies is safe and effective with no major side effects. Intramuscular methotrexate has the advantage of tubal conservation and saves patients from surgical intervention. Our study showed single dose methotrexate to be an effective treatment option for selected patients with unruptured tubal ectopic pregnancy.

Introduction

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. It is an important diagnosis to exclude when a woman presents with bleeding in early pregnancy. A report of the incidence from elsewhere is showing arise from 0.5% to 1.2%. The clinical presentation of ectopic pregnancy has changed from a life-threatening disease to a more benign condition for which nonsurgical treatment options are available with systemic methotrexate or expectant management. Medical management with methotrexate fulfilling the criteria in selected cases were tried and found to be equally successful as surgical management. Medical management was found to be equally effective as surgical management particularly taking consideration of future fertility

Methotrexate can be administered systemically as a single dose regimen; this was introduced to minimize side effects, to improve patient compliance and to reduce the overall costs. Methotrexate has been shown to be safe with virtually no adverse effects reported on reproductive outcome. Careful follow-up and assessment are required for all women presenting with pain in the few days following methotrexate therapy before assuming that the treatment has failed and if there is need for surgical intervention.

Material and Methods

Between December 2015 and June 2017, (n = 40) patients of diagnosed ectopic pregnancy treated as in patients with methotrexate regimen were included in study in v.s. general hospital, Ahmedabad. The diagnosis of ectopic pregnancy was made using both transvaginal ultrasound and measurement of B-human chorionic gonadotropin (b-hCG). All cases selected for medical management gave their informed written consent before starting the treatment.

The selection criteria for patients who were hemodynamically stable with B-hCG level of  $\leq 10,000$  mIU/mL and if clinically feasible  $>10,000$  mIU/mL, adnexal mass  $\leq 4$  cm and if clinically feasible  $>4$  cm, absent cardiac activity. Baseline investigations such as full blood count, b-hCG, renal and liver functions tests and blood group, RH factor were done on Day 1 and single dose of 50 mg/m<sup>2</sup>. Methotrexate was administered intramuscularly. Serial b-hCG was repeated on Days 4 and 7. If b-hCG on Day 7 was at least 15% lower than that on Day 4, the patient was discharged and followed up as an outpatient. If the b-hCG level on Day 7 was the same or higher than that on Day 4, the patient received a second dose of 50 mg/m<sup>2</sup> methotrexate.

Follow-up serum b-hCG was performed weekly. Single dose methotrexate treatment was considered successful when b-hCG levels became negative without further administration of methotrexate dose or surgery. The ultrasound examination was performed. Second dose of methotrexate was installed in both cases of either increasing b-hCG or plateauing b-hCG. Follow-up b-hCG was performed weekly until negative with value of b-hCG  $<5$  mIU/mL. For patients with hemodynamic instability, signs of tubal rupture, increasing abdominal pain, falling hemoglobin level surgical intervention were considered. The toxicity of methotrexate treatment was evaluated by noting side effects such as lower abdominal pain, vaginal bleeding, mouth ulcers, sore throat, gastrointestinal side effects or complaints of any rashes. Nonsensitized Rhesus negative women received anti-D immunoglobulins 250  $\mu$ g as per the department protocol. Women treated with methotrexate were advised to refrain from sexual intercourse until serum b-hCG was negative, and not to conceive within 3 months of treatment.

Results

In this study, the majority of patient (45%) were between 20-25 years (n = 18) (Table 1). The success rate of methotrexate decreased as maternal age increased. Gravidity was between one and six with 40% (n = 12) primipara. The majority of patient with gestation age at diagnosis was  $<6$  weeks 62.5% (n = 25) (Table 2). The success rate of methotrexate decreased with increasing gestational age. Adnexal mass ranged from 2 to 4 cm. In patients with adnexal mass  $>4$  cm, the success rate was less. In women with 2-3 cm adnexal mass success rate is 82.1% (n = 28) (Table 3). There was no marked difference in the site of ectopic gestation. The average value of b-hCG on Day 1 in patients treated with single dose of methotrexate was 3,000 mIU/mL (range 100-8,847) and those treated 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).

The average time of resolution for serum b-hCG level was 32 days for single dose of methotrexate and 58 days for those receiving two doses. Time of resolution for serum b-hCG was defined as the total number of days from the beginning of treatment until b-hcg level became negative ( $<5$  mIU/mL). The total number of women treated with single dose was 87.5% (n = 35) and (n = 5) 12.5% received two doses. Success rate in group of patient given single dose methotrexate was 82.85% and in patients with two dose methotrexate it was 100%. The overall success rate of treatment in our study was 85% (n = 34). Surgical intervention was required for 15% (n = 6) of patients with tubal rupture and abdominal pain (Table 6). One patient complained of lower abdominal pain between Days 2-7 and early surgical intervention by laparotomy

followed by salpingectomy. Two cases were managed by laparoscopic salpingotomy.

Mild vaginal bleeding, not more than the initial bleeding was noted with no reported case of gastrointestinal sideeffects. Fifteen percent (n = 6) women had history of previous ectopic pregnancy, three women had history of pelvic tuberculosis and 40% (n = 16) had history of miscarriages.

**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. 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 hCG measurement. Single dose methotrexate appears effective and has better patient compliance. Treatment success is inversely correlated to  $\beta$ -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 85% (n = 34), 12.5% (n = 5) were treated with two doses of methotrexate 15% and (n = 6) required surgical intervention. Patients with small unruptured ectopic pregnancies achieved a success rate of 82.1% with five 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. 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  $\beta$ -hcg values and complaints of abdominal pain were taken early for surgical intervention for fear of rupture of the ectopic pregnancy.

**Table 1.** Age of Patients

Age(years)	No.of patient	Percentage(%)
20-25	18	45
25-30	15	37.5
31-35	4	10
35-40	3	7.5
	40	100

**Table 2.** Month of Amenorrhoea

Month of amenorrhea	No. of patients	Percentage(%)
<1.5 MA	25	62.5
>1.5 MA	9	22.5
NO MA	6	15

**Table 3.** Size of Ectopic Mass and Outcome

Size of mass	No. of patients	Percentage (%)	No. of successful patient	Success rate%
<4 cm	28	70	25	85.7
>4 cm	12	30	9	75.0

**Table 4.** b-hcg Level on Day 1

On admission b-hcg level	No. of Patients	Percentage (%)	No. of successful patients	Success rate (%)
< 10,000	35	87.5	32	80
> 10,000	5	12.5	2	40

**Table 5.** Fall in b-hcg Level on Days 4 and 7 and Outcome

b-hcg level	Total No. of Patients	Percentage (%)	No. of successful patients	Success rate (%)
> 15%	32	80	29	96

< 15%	8	20	5	62.5
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**Table 6.** Success Rate

	No. of patients	Percentage (%)
Successful	34	85
Unsuccessful	6	15

**Table 7.** Cardiac activity

	No. of patients	Percentage(%)
Present	1	2.5
Absent	39	97.5

With more experience of using the drug the success rate improved. Treatment failure based strictly on a high increase in  $\beta$ -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 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  $\beta$ -hcg levels equal to 5,000 mIU/mL. In the same series, an increase in the treatment failure group with advanced maternal age  $\geq 35$  years and history of spontaneous abortions was noted corresponding to our study where success rate of methotrexate treatment decreased as maternal age increased. In our study, nine women aged over 30 years had a failure rate of

(n = 4). Lee reported a success rate of 96% with  $\beta$ -hcg < 6,000 mIU/mL and 58% when  $\beta$ -hcg was > 6,000 mIU/mL. He noted that initial  $\beta$ -hcg is the only predictor of success for repeated injection of methotrexate in single dose regimen.

Erdem reported the mean time of resolution as 26.5 (10-37) days in patients who were successfully treated with methotrexate. 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  $\beta$ -hcg

follow-up to avoid complications such as delayed hemorrhage owing to persistent trophoblast. In our study, cardiac activity was absent in 97.5% (n = 39) patients and 2.5% (n = 1) patient cardiac activity was present, which required surgical intervention (Table 7). In our study, 37.5% (n = 15) of women complained of lower abdominal pain and 15% (n = 6) 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. Methotrexate therapy was associated with high rates (80%) of subsequent fertility compared to our study, successful

intrauterine pregnancy following methotrexate was observed in three women

### Conclusion

Methotrexate has proven to be an effective medical management for ectopic pregnancies in a society where tubal conservation is of utmost 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 methotrexate side effects making compliance important in patient selection. The predictors of success in our study are low  $\beta$ -hcg and adnexal mass <4 cm. Single dose methotrexate offers a safe and effective nonsurgical method of treating selected patients and one important advantage of medical therapy is the potential for considerable savings in treatment costs.

### References

1. Thia EW, Loi K, Wang JJ, Siow A. Methotrexate treatment for ectopic pregnancy at the KK Women's and Children's Hospital, Singapore. *Singapore Med J* 2009;50(11):1058-61.
2. Merisio C, Anfuso S, Berretta R, Gualdi M, Pultrone DC, Melpignano M. Single-dose methotrexate for ectopic pregnancy treatment: preliminary data. *Acta Bio Med* 2005;76(1):33-6.
3. Zargar M, Razi T, Barati M. Comparison of single and multidose of methotrexate in medical treatment of ectopic pregnancy. *Pak J Med Sci* 2008;24:586-9.
4. Kirk E, Condous G, Bourne T. The non-surgical management of ectopic pregnancy. *Ultrasound Obstet Gynecol* 2006;27(1):91-100.
5. Hajenius PJ, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. *Cochrane Database Syst Rev* 2007;(1):CD000324.
6. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. *Obstet Gynecol* 2003;101(4):778-84.
7. Lipscomb GH, Puckett KJ, Bran D, Ling FW. Management of separation pain after single-dose methotrexate therapy for ectopic pregnancy. *Obstet Gynecol* 1999;93(4):590-3.
8. Cho GJ, Lee SH, Shin JW, Lee NW, Kim T, Kim HJ, et al. Predictors of success of repeated injections of single-dose methotrexate regimen for tubal ectopic pregnancy. *J Korean Med Sci* 2006;21(1):86-9.
9. Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, et al. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. *Am J Epidemiol* 2003;157(3):185-94.
10. Fernandez H, Gervaise A. Ectopic pregnancies after infertility treatment: modern diagnosis and therapeutic strategy. *Hum Reprod Update* 2004;10(6):503-13.
11. Erdem M, Erdem A, Arslan M, Oc A, Biberoglu K, Gursoy R. Single-dose methotrexate for the treatment of unruptured ectopic pregnancy. *Arch Gynecol Obstet* 2004;270(4):201-4.
12. Tawfiq A, Agameya AF, Claman P. Predictors of treatment failure for ectopic pregnancy treated with single-dose methotrexate. *Fertil Steril* 2000;74(5):877-80.
13. The management of tubal pregnancy. Royal College of Obstetricians and Gynaecologists Guidelines 2004;21:1-10.
14. Slaughter JL, Grimes DA. Methotrexate therapy. Nonsurgical management of ectopic pregnancy. *West J Med* 1995;162(3):225-8.
15. Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. *Obstet Gynecol* 1991;77(5):754-57.
16. Stovall TG, Ling FW, Gray LA, Carson SA, Buster JE. Methotrexate treatment of unruptured ectopic pregnancy: a report of 100 cases. *Obstet Gynecol* 1991;77(5):