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Original Article

Systemic methotrexate: An effective alternative to surgery for management of unruptured ectopic pregnancy

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ABSTRACT

Background: Medical management of an unruptured ectopic pregnancy with intramuscular methotrexate is a common and cost-effective alternative to surgery. Early diagnosis and timely institution of methotrexate has resulted in a dramatic decline in the morbidity, mortality and financial burden associated with ectopic pregnancy. The objective of our study was to evaluate the efficacy of medical management in a series of patients with unruptured ectopic pregnancy meeting the strict inclusion criteria.

Methods: Multiple dose methotrexate regimen was utilized for the management of the cases. Parenteral methotrexate 1 mg/kg was administered on Day 1, Day 3, Day 5 and Day 7 whereas rescue dose of injection leucovorin 0.1 mg/kg was given on Day 2, Day 4, Day 6 and Day 8. Monitoring for the resolution of the ectopic was carried out with β -hCG, done on Day 1, Day 3, Day 5, and Day 7. Any value showing a decline of >15% of the baseline value led to the termination of treatment and only surveillance was carried out. If the decrease was <15%, treatment was continued.

Results: Total 43 patients with ectopic pregnancy were diagnosed over a period of 1 year, conceived during infertility evaluation and treatment. 11 cases went directly for surgery whereas 32 were subjected to medical treatment. 75% of the patients got successfully treated and rest 25% required surgery following failed medical management.

Conclusions: Methotrexate therapy is a safe and effective alternative for the management of unruptured ectopic pregnancies with minimal or no side-effects and associated advantage of avoiding invasive surgery.

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Introduction

Ectopic pregnancy (EP), accounting for 2% of all pregnancies is a major cause of maternal morbidity and mortality in the first trimester.¹ It has also been seen that with the advent of

Assisted Reproductive Technology (ART), the incidence of ectopic pregnancy has shown a rising trend.²

Early diagnosis using a combination of high index of clinical suspicion, trans vaginal sonography and hormonal estimation has led to a timely intervention and prevention of

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complications of ectopic pregnancy. Once a definitive diagnosis of ectopic pregnancy is made, the patient may be either treated expectantly or with surgical or medical management. Medical management apart from avoiding the inherent morbidity of anesthesia and surgery is also cost-effective and offers the success rates comparable to surgical management, with no loss in future potential fertility.³

Several drugs have been suggested in literature for medical treatment. Among them, methotrexate (MTX) systematically administered has demonstrated the greatest benefits in terms of efficacy and tolerability. Methotrexate, a folic acid antagonist, highly toxic to rapidly replicating trophoblastic cells has been the mainstay of the medical management of ectopic pregnancy.⁴ Currently there are two commonly used protocols for the administration of this drug. It can be given using a “multidose” regimen of 1 mg/kg intramuscularly, alternating with 0.1 mg/kg of leucovorin (LEU) intramuscularly for up to four doses of each drug. Alternatively, methotrexate can be administered using a “single dose” method, based on body surface area, at 50 mg/m² without the need for leucovorin rescue.⁵ The follow up of the medical management is carried out with estimation of serum beta human Chorionic Gonadotropin (β -hCG) values. Methotrexate therapy is continued until β -hCG falls by 15% from its peak concentration. The results achieved using medical management in appropriately selected ectopic pregnancies is comparable to surgery. Surgery is specifically indicated in cases that does not fall within the purview of medical management, like suspected tubal rupture and when MTX is contraindicated. This study was carried out to analyze the efficacy of MTX in the medical management of unruptured ectopic pregnancy.

Materials and methods

The study was carried out in a tertiary care hospital having Assisted Reproductive Technology (ART) centre as well as an advanced laparoscopic surgical unit. All cases of ectopic pregnancies diagnosed between Sep 2009 and Sep 2010 and meeting the strict inclusion and exclusion criteria were included in the study. The study group included patients undergoing treatment for infertility who had conceived either spontaneously or by ART.

The inclusion criteria for medical management were

- Hemodynamic stability
- No severe or persistent abdominal pain
- Commitment to follow-up until ectopic pregnancy has resolved

The patients were excluded from the study if they had a concomitant intrauterine pregnancy, deranged liver or renal function tests, embryonic cardiac activity detected by Trans vaginal sonography (TVS), high initial β -hCG concentration (>5000 mIU/ml), ectopic pregnancy >4 cm in size as imaged by TVS or inability to participate in follow up. The multi-dose MTX treatment protocol was advocated after an informed consent was taken from the subjects (Table 1). Prior to the commencement of the treatment protocol, a baseline β -hCG value, complete blood count, liver function test, renal function test and blood grouping was carried out. Patients who were

detected to be Rh negative were administered 50 μ g Rh immunoglobulin to prevent Rh sensitization.

The patients were instructed to avoid intercourse and refrain from taking food and multivitamins containing folic acid. Repeated pelvic examination and Trans vaginal sonography was also not resorted to, until the β -hCG was undetectable during surveillance.⁷

The success of the medical management of EP was defined as β -hCG levels becoming negative after administration of one or more MTX doses. Medical management was considered to be failed whenever there were signs or symptoms suggestive of rupture, including hemodynamic instability, increasing abdominal pain regardless of the trend in β -hCG concentration or rapidly increasing β -hCG values. Such patients were taken up for surgery.

Results

A total of 43 cases of ectopic pregnancy reported in the study period of one year at the ART centre. The age of the patients were in the range of 23–45 years however, the maximum patients were in the age group of 25–30 years (Table 2). Out of the 43 patients, 32 of them were subjected to medical management and 11 of them went directly for surgery as they did not fulfill the inclusion criteria for MTX administration.

In all the study subjects, ultrasound imaging suggested EP with an average pregnancy diameter smaller than or equal to 3.5 cm. A yolk sac was visible in four cases. No embryonic cardiac activity was detected in any of the patients who were administered MTX.

Out of the 32 patients who underwent medical management, 24 (75%) got successfully treated. Whereas, the rest 8 (25%) required surgical management following failed medical management (Fig. 1). 4 out of the 8 subjects had rapidly rising β -hCG values (more than 53%) over two days, 2 had persistent abdominal pain and 2 had suspected rupture with features of shock.

Table 1 – Multi-dose MTX treatment protocol.

Treatment day	Laboratory evaluation	Intervention
1	β -hCG (baseline)	Methotrexate 1.0 mg/kg IM
2		Leucovorin 0.1 mg/kg IM
3	β -hCG	MTX 1.0 mg/kg IM if β -hCG $<15\%$ decline from day 1 to day 3. If β -hCG $>15\%$, stop treatment and start surveillance.
4		Leucovorin 0.1 mg/kg IM
5	β -hCG	MTX 1.0 mg/kg IM if β -hCG $<15\%$ decline day 3–day 5. If β -hCG $>15\%$, stop treatment and start surveillance.
6		Leucovorin 0.1 mg/kg IM
7	β -hCG	MTX 1.0 mg/kg IM if β -hCG $<15\%$ decline day 5–day 7. If β -hCG $>15\%$, stop treatment and start surveillance.
8		Leucovorin 0.1 mg/kg IM

Table 2 – Age wise distribution of the patients.

Age group	Number of cases
<25	7
25–30	21
30–35	9
35–40	2
40–45	4

As all the subjects in the study were patients undergoing treatment for infertility it was observed that 84.6% cases had conceived following in-vitro fertilization (IVF) (Table 3). It was also seen that of the patients who were successfully treated through medical management, the ones with lower β -hCG values required less dosages as compared to the subjects with comparatively higher values (Table 4).

Discussion

Once the diagnosis of ectopic pregnancy is made, the options for management include surgical, medical, or expectant. However the goal of treatment for all options remains the same: to minimize disease and treatment related morbidity while maximizing reproductive potential. Various clinical prediction tools have been developed to aid management and decision making, incorporating factors like gestational age, β -hCG level, progesterone level, abdominal pain or presence of hemoperitoneum.⁶ In our study eligibility for methotrexate administration was as per the American society of Reproductive Medicine guidelines⁷ which were taken as the inclusion and exclusion criteria.

With the classic presentation of a 'collapsed woman' with an ectopic pregnancy becoming less common due to the availability of facilities for early diagnosis, there has been a drift toward non-surgical management with minimal or no intervention, less morbidity and lower cost implications. Therefore diagnosing the condition earlier in its natural history has changed the principle of management, as early ectopic pregnancies tend to be smaller and have lower baseline β -hCG levels, have more time available for conservative

Fig. 1 – Distribution of the patients in the study groups.**Table 3 – Mode of conception in patients who underwent medical management.**

Total cases	Spontaneous conception	IUI conception	IVF conception
32	4	1	27 (84.6%)

management and comparable outcomes to that of surgical treatment.

Methotrexate has been found to be an ideal drug for the medical management. It depletes tetrahydrofolate cofactors required for DNA and RNA synthesis and cell replication, and thereby inhibits the rapidly growing trophoblasts. Apart from treating the primary ectopic gestation, methotrexate can also be used for persistent ectopic pregnancy following tubal sparing surgery, as prophylaxis to reduce persistent ectopic pregnancy following salpingostomy, and in cornual and cervical pregnancies.³ However we aimed to study the efficacy of this drug only in unruptured ectopic pregnancy.

The trend of ectopic pregnancies has been shown to be on a rising trend both because of better diagnostic modalities and increased use of assisted reproductive technologies.⁸ We found that, of the 32 cases of EP who were systemically administered MTX, 27 had conceived after an in-vitro fertilization.

Although there are two regimens for institution of methotrexate, superiority of one over the other continues to be unresolved. A meta-analysis combining the results of 26 studies with 1067 women treated with a single-dose regimen and 267 women treated with a multidose regimen found that the multidose regimen was slightly more effective. The success rate for women with multidose treatment was 92.7% vs. a single-dose treatment success rate of 88.1%.⁹ A recent retrospective study comparing the multidose and single-dose

Table 4 – Number of methotrexate injections administered to the treated group.

No of MTX doses	Number of patients	Base line β -hCG values (mIU/ml)	
1	10	<1000	6
		1001–2000	1
		2001–3000	2
		3001–4000	1
		4001–5000	0
2	5	<1000	2
		1001–2000	0
		2001–3000	1
		3001–4000	1
		4001–5000	1
3	4	<1000	0
		1001–2000	1
		2001–3000	0
		3001–4000	1
		4001–5000	2
4	5	<1000	1
		1001–2000	1
		2001–3000	0
		3001–4000	1
		4001–5000	2

regimens in 643 patients with ectopic pregnancy from a single database also showed slightly better success with the multi-dose regimen.¹⁰ We had advocated only the multidose protocol and our success was 75% which is however, lower than the overall success rates of 89% documented in a review of the studies published so far on the efficacy of MTX.⁴ It has also been elucidated in literature that if the criteria for medical management are strictly fulfilled, treatment with MTX yields success rates comparable to those achieved with conservative surgery.¹¹

Conclusion

Thus, the treatment of a woman with a small unruptured ectopic pregnancy with intramuscular methotrexate is a successful and non invasive modality of management. Strict selection criteria for treatment, especially, a low β -hCG concentration and absence of fetal cardiac activity enhances the success of medical management.

Intellectual contributions of authors

Study concept: Col Pankaj Talwar, vsm, Lt Col Sandeep K

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Conflicts of interest

All authors have none to declare.

REFERENCES

1. Tay JJ, Moore J, Walker JJ. Ectopic pregnancy. *BMJ*. 2000;320:916.
2. Chatterjee S, Dey S, Chowdhury RG, et al. Ectopic pregnancy in previously infertile women – subsequent pregnancy outcome after laparoscopic management. *Al Ameen J Med Sci*. 2009;2:67–72.
3. Barnhart KT, Esposito M, Coutifaris C. An update on the medical management of ectopic pregnancy. *Obstet Gynecol Clin North Am*. 2000;27:653–667.
4. Barnhart KT, Gosman G, Ashby R, et al. The medical management of ectopic pregnancy: a meta-analysis comparing “Single dose” and “Multidose” regimens. *Obstet Gynecol*. 2003;101:778–784.
5. Stovall TG, Ling FW, Gray LA, et al. Methotrexate treatment of unruptured ectopic pregnancy: a report of 100 cases. *Obstet Gynecol*. 1991;77:749–753.
6. Ramakrishnan K, Scheid DC. Ectopic pregnancy: expectant management or immediate surgery? *J of Fam Pract*. 2006;55:517–523.
7. ASRM Practice Bulletin. Treatment of ectopic pregnancy. *Fertil Steril*. 2008;90:S206–S213.
8. Weigert M, Gruber D, Pernicka Bauer P, et al. Previous tubal ectopic pregnancy raises the incidence of repeated ectopic pregnancies in in-vitro fertilization-embryo transfer patients. *J Assist Reprod*. 2009;26:13–17.
9. Barnhart KT, Gosman G, Ashby R, et al. The medical management of ectopic pregnancy: a meta-analysis comparing “single dose” and “multidose” regimens. *Obstet Gynecol*. 2003;101:778–784.
10. Lipscomb GH, Givens VM, Meyer NL, et al. Comparison of multidose and single-dose methotrexate protocols for the treatment of ectopic pregnancy. *Am J Obstet Gynecol*. 2005;192:1844–1847.
11. Lipscomb GH, Stovall TG, Ling FW. Non surgical treatment of ectopic pregnancy. *N Engl J Med*. 2000;343:1325–1329.