Scope and Limitations of Medical Management of Ectopic Pregnancy: Comparison of Single versus Multiple Dose of Methotrexate

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ABSTRACT

The present study was a pilot study conducted at Nalanda Medical College and Patna Medical College, Patna, Bihar. The study included 120 women with ectopic pregnancy who were given single dose or multiple dose of methotrexate. In our study, the success rate in single dose group was 73.33% and in multiple dose group was 83.33% (p value 0.34) and the difference was statistically insignificant. The study showed that medical management of ectopic pregnancy with single dose IM methotrexate regimen is as effective as multiple dose regimen with lesser side effects and this option should be given to the women fulfilling the inclusion criteria.

Keywords: Ectopic pregnancy, methotrexate, single dose, multiple dose regimen

Ectopic pregnancy is a condition where the blastocyst implantation occurs at any site other than the usual endometrial lining of the uterine cavity. The most common ectopic implantation site is within the fallopian tube (95%).

The sites of tubal implantation in descending order of frequency are ampulla (73%), isthmus (12.5%), fimbrial (11.6%) and interstitial (2.6%). The remaining 5% of non-tubal ectopic pregnancies implant in the ovary, peritoneal cavity, cervix or prior cesarean scar or abdominal cavity.

An ectopic pregnancy can be 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 per vagina in early pregnancy.

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Reports of incidence from elsewhere shows an increase from 0.5% to 1-2%. There has been a rise of 3-5 in ectopic pregnancies from assisted reproductive technique (ART).

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.

Use of beta-human chorionic gonadotropin (β-hCG) and transvaginal ultrasound scan (TVS) has improved the accuracy of diagnosis. With early diagnosis and treatment, definite therapy for unruptured ectopic pregnancy is feasible even before the onset of symptoms.

Methotrexate (MTX) has been used successfully to treat ectopic pregnancy. MTX is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase and reduces the supply of tetrahydrofolate which is a cofactor in the synthesis of DNA and RNA and necessary for cell division.

MTX is currently administered either in a single or as a multiple dose regimen to treat ectopic pregnancy.

The purpose of this study was to compare the two regimens of medical management of ectopic pregnancy (single dose and multiple dose), their effectiveness and their side effects.

MATERIAL AND METHODS

This was a study conducted at Nalanda Medical College and Patna Medical College, Patna, Bihar which included 120 women from March 2012 to February 2018.

An informed consent was taken from each woman after explaining all treatment modalities and side effects of the drug. These women were given either single or multiple doses of MTX for ectopic pregnancy. Sixty women were given single dose and 60 were given multiple doses of MTX for ectopic pregnancy on the basis of computer generated random number. In the single dose regimen, MTX 50 mg/m^2 intramuscular (IM) was given on Day 1. Then β-hCG levels were measured on Day 7. If the difference was a fall of 15%, the test was repeated weekly until β-hCG level was ≤2 mIU/mL or undetectable. If difference was <15% between Day 1 and Day 7 levels, it was treated as a failure.

In multiple dose regimen, MTX 1 mg/kg body weight IM was given on days 1, 3, 5 and 7. Leucovorin 0.1 mg/m^2 was given on days 2, 4, 6 and 8. Then, weekly β-hCG levels were measured until β-hCG was ≤2 mIU/mL or undetectable. In case the fall was inadequate or the patient presented with pain in abdomen, medical management was discontinued and surgical intervention was sought.

For this study, the various inclusion and exclusion criteria were as follows:

Inclusion Criteria

- Unruptured ectopic pregnancy
- The woman should be hemodynamically stable
- Ectopic mass size ≤3.5 cm ultrasonographically
- No cardiac activity
- β-hCG level <5,000 mIU/mL.

Exclusion Criteria

- Lactating mother
- Immunodeficiency
- Alcoholism
- Blood dyscrasias
- Chronic hepatic, renal or pulmonary diseases
- Peptic ulcer diseases
- Heterotrophic pregnancy.

Statistical Methods

For all statistical tests, p value <0.05 was taken to indicate a significant difference.

OBSERVATION

In our study, no statistically significant difference was found between single and multiple dose MTX groups in terms of clinical and laboratory characteristics. Mean age of women, period of gestation, size of ectopic mass, pre-treatment β-hCG level and mean time of resolution of ectopic pregnancy were comparable in both groups (Table 1).

Of the 60 women who received single dose MTX 44 (73.33%) were successfully treated and of the other 60 women who received multiple dose MTX, 50 (83.33%) were successfully treated. This difference was statistically insignificant (p value 0.3479) (Table 2).

In our study, the most common side effect during the course of treatment was found to be gastric upset (Table 3). In the single dose group, gastrointestinal (GI)

Table 1. Patient Characteristics

	Multi-dose	Single dose	P value
Sample size	60	60	
Age (year)	30.53 ± 4.45	31.4 ± 4.41	0.52
Period of gestation	6.01 ± 7.78	5.75 ± 1.01	0.217
Pre-treatment β-hCG level	1507.2 ± 1184.82	1686.14±1217.33	0.301
Mean time of resolution (days)	5.76 ± 0.83	5.27 ± 0.88	0.061

Table 2. Success and Failure Rates with the Two Regimes

Group	Multi-dose	Single dose	Total	P value
Success	50 (83.33%)	44 (73.33%)	94 (78.33%)	0.347
Failure	10 (16.67%)	16 (26.67%)	26 (21.67%)	
Total	**60 (100%)**	**60 (100%)**	**120 (100%)**	

Table 3. Side Effects of MTX in Multi-dose and Single Dose Group

	Multi-dose	Single dose	Total	P value
GI upset	28 (46.67%)	10 (16.67%)	38 (31.67%)	0.26
LFT deranged	4 (6.67%)	0 (0.00%)	4 (3.33%)	0.491
Skin rash	2 (3.33%)	0 (0.00%)	2 (1.67%)	1.00
None	26 (43.33%)	50 (83.33%)	76 (63.33%)	0.003
Total	**60 (100%)**	**60 (100%)**	**60 (100%)**	

upset was seen in 16.67% (10/60) patients and in multi-dose group in 46.67% (28/60); this was found to be statistically significant (p = 0.026). Other side effects such as liver function test (LFT) alteration was seen only in the multi-dose group among 6.674% (4/60) patients.

Skin rashes were also seen only in multi-dose group in 3.33% patients (2/60); this showed no significant statistical difference.

DISCUSSION

Several studies report comparable rates of success with both regimens. However, Zargar et al recommended the single dose regimen in their comparative study because of greater chance of response with single dose than multiple dose management. Single dose regimen was associated with better results, patient tolerance and no need of hospitalization.

In present study, the most common side effect during the course of treatment was found to be gastric upset in single dose group (16.67%) and in multi-dose group (46.67%) and the difference was statistically significant (p = 0.026).

Other side effects such as LFT alteration was noted in 0% in single dose group and in 6.67% in multi-dose group. Skin rashes were seen in 0% in single dose regimen and in 3.33% in multi-dose group, which showed no significant statistical difference. Barnhart et al, in their study, showed that single dose regimen was associated with fewer side effects.

CONCLUSION

In treatment with MTX, the patient avoids surgery and anesthesia. This study showed that medical management of ectopic pregnancy with single dose IM MTX regimen is as effective as multiple dose regimen, with lesser side effects and this option should be given to those women who fulfill the inclusion criteria.

SUGGESTED READING

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Obesity

Rule of 30

- Take no more than 30 mL per kg of body weight liquids per day.
- It takes 30 calories per kg to maintain one's weight.

Smoking

Rule of 6: Smoking one cigarette takes away 6 minutes of your life.