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Management of Unruptured Ectopic Pregnancy by Low Dose Methotrexate – Four Years Experience

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Summary

Objective of this study was to review our experience with low dose methotrexate for medical management of ectopic pregnancy. The study included 25 patients in whom ectopic pregnancy was diagnosed and treated with methotrexate. All these patients were treated with single dose (50mg/M^2) intramuscular methotrexate. Surgical intervention was done in case of rupture of ectopic pregnancy or haemodynamic instability. **Results :** 21 patients (84%) treated successfully with methotrexte. 4 patients were treated surgically after medical treatment had failed. Success rate was higher if size of ectopic pregnancy measured by TVS was <2.5cm (92.7%) or β hCG was <2500miu/ml (92.3%). The time of initiation of treatment and resolution of β hCG was 25 days (mean). Tubal patency rate after methotrexate therapy was confirmed in five out of six patients subjected to hystero-salpingography. **Conclusion :** Low dose systemic methotrexate is a simple, safe and effective method of treating ectopic pregnancy in selected patients.

Introduction

The modern management of ectopic pregnancy is one of the medicine's greatest success stories. Before the first successful operative treatment of tubal pregnancy reported by Lawson Tait in 1884, the patients suffering from ectopic pregnancies were managed expectantly by observation only, carrying 70% mortality. Thereafter the surgery became the main form of treatment. However in past few years the management has changed dramatically. With the availability of high-resolution transvaginal sonography (TVS) and highly sensitive human chorionic gonadotrophin (hCG) assay, it has now become possible to detect ectopic pregnancy at very early stage. The diagnosis of unruptured ectopic offers number of therapeutic options such as – conservative surgery by laparoscopy or medical management.

Medical treatment of ectopic pregnancies is appealing for several reasons: less tubal damage, less cost and hopefully enhanced potential for future fertility. Methotrexate a folic acid antagonist has been used for quite some time against gestational trophoblastic disease with remarkable success. Tanaka first used it for ectopic pregnancy in 1982.

We are presenting a study of 25 cases of ectopic pregnancies, who were managed conservatively by single dose methotrexate as primary treatment.

Material and Methods

Between 01 January 1995 and 31 July 1999, 71 patients of ectopic pregnancy were treated in Naval hospital INHS Asvini. 25 of these patients were initially selected for medical management. This study is conducted to review our experience with low dose methotrexate for medical management of ectopic pregnancy.

Criteria for patients selection

1. Patient should be haemodynimically stable.
2. Ultrasonography (USG) should fail to find intrauterine pregnancy.
3. The ectopic pregnancy should measure 4 cm or less in its greatest diameter.
4. There should be no evidence of rupture of ectopic pregnancy.
5. Serum βhCG titre should be less than 10,000 miu/ml or βhCG negative in 1:200 dilution of urine. (sensitivity of the test 25-50 miu/ml).

Treatment protocol

A common treatment protocol was followed in all 25 cases. Only in three of our cases repeat injection of methotrexate was required after 7 days of initiating the treatment because of inadequate fall in β hCG values.

Day-1 Baseline Hb, TLC, DLC, platelet count, serum Creatinine, liver function test.
Injection methotrexate 50 mg/M2 IM.
Day-4 hCG titre.
Day-7 hCG titre, complete blood count, platelet count, serum creatinine, liver function test.
Weekly hCG titre till it becomes negative.

Results

Medical management was started for 25 patients, who fulfilled the selection criteria. 21 of these patients (84%) had a successful outcome. Size of ectopic pregnancy, measured by TVS effected the outcome of treatment. 93.3% success rate was obtained in the patients who had ectopic pregnancy less than 2.5 cm in size, compared to 66.6% where size was more than 2.5 cm (Table-I).

In this study we could not do quantitative assay of β hCG in all patients. Twenty of the 25 patients had quantitative serum β hCG before the commencement of the treatment. In rest of the five patients a rough guide for initial β hCG levels was confirmed by doing urinary β hCG by semiquantitative method. Positive β hCG in 1:200 dilution or more were excluded from the study. Follow-up in these patients was also done by dilution method. 20 patients who had quantitative β hCG estimation, 13 had levels <2500miu/ml and 12 of these patients had successful outcome of medical treatment (success rate 93.3%). In remaining seven patients the dilution method was used. Patients having urinary β hCG +ve in <1/50 dilution (4 patients) had successful outcome (success rate 100%). The only patientt, who had initial urinary β hCG positive in more than 1/100 dilution, required surgical management (table II). β hCG values touched normal after 15 to 38 days of giving methotrexate, average being 25 days. As far as anatomical regression is concerned transvaginal sonography (TVS) had shown regression of ectopic tubal pregnancy takes about 25 days to 6 months, average being 60 days. A total of 11 patients who were desirous of future pregnancies were followed-up. Five patients conceived (intrauterine pregnancy) within 3-12 months of ectopic pregnancy. Out of the remaining six, who were subjected to hystero-salpingography (HSG), tubal patency on the side of tubal pregnancy was present in five. Side effects of methotrexate – nausea, vomiting, stomatitis were present in 3(12%) of our patients (Table III)

Table I : Size of ectopic pregnancy and outcome of treatment

Size of pregnancy	No. of patients	Successful medical Treatment	Patients needing surgical intervention
Equal or <2.5cm	16(64%)	15(93.7%)	1 (6.3%)
>2.5 cm	9(36%)	6(66.6%)	3(33.4%)
Total	25 (100%)	21 (84%)	4 (16%)

Table – II
Initial β hCG levels and outcome of medical treatment

Initial β hCG	No. patients	Successful medical Treatment	Patients needing surgery
Equal or <2500miu/ml	13(100%)	12(92.3%)	1(7.7%)
>2500 miu/ml	7(100%)	5(71.4%)	2(28.6%)
+ve in <1/50 dilution	4(100%)	4(100%)	Nil
+ve in >1/50 dilution	1(100%)	Nil	1(100%)

Table III – Outcome variables

Anatomical regression (by TVS)	25 days to 6 months, average 60 days
Regression of β hCG to normal	15 to 38 days, average 25days
Pregnancies after methotrexate treatment	4 pregnancies within 3-12 months of treatment by methotrexate. No congenital abnormality in newborn
Tubal patency after treatment (HSG)	Tubes were found patent in 5 out of 6 patients subjected to HSG (83.3g%)
Side effects of the drug	Minor side effects 3 patients (12%).

Discussion

[illegible] 33 cases of tubal ectopic pregnancy [illegible] protocol [illegible] gold standard [illegible] was [illegible] as [illegible] success rate [illegible] between [illegible] to 91.7% [illegible] (Stovall et al, 1991, Stika et al, 1996, Glock et al, 1994) [illegible] In our study [illegible] success rate was [illegible] which is comparable with [illegible] other studies.

Size of ectopic pregnancy was found to have some effect on the outcome of treatment. [illegible] in whom the size of ectopic pregnancy at the time of initiation of treatment was less than 3.5 cm, 93.7% success rate was obtained compared to 66.6% in the patients with size between 3.5 and 5 cm. Rajan (1997) reported a failure in 3 cases where size of ectopic pregnancy was 5 cm. Selecting smaller ectopic pregnancies for medical management can reduce failure of the treatment. The time for resolution of mass is variable and often it takes several months to disappear. In our study, [illegible] mass persisted for 15 days to 6 months. Brown et al (1991) observed that persistent mass [illegible] treatment failure.

βhCG levels at the time of initiating the treatment was another factor associated with prognosis. [illegible] between 3000-10,000 [illegible] were associated with higher failure rate. In the group where β hCG was less than 2000 [illegible] pregnancy, which required surgical intervention, was in [illegible] treatment. Stika et al (1996) also observed [illegible] relationship between initial β hCG levels and outcome of pregnancy. They concluded that if β hCG levels are more than 3000 [illegible], there is greater probability of surgical intervention. [illegible] detection of β hCG levels in the urine was used [illegible] [illegible] actual levels could not be obtained. All the patients having β hCG levels less than [illegible] had successful outcome [illegible] pregnancy [illegible] the patients with β hCG [illegible] more than [illegible] [illegible] for detection of β hCG [illegible] actual levels cannot be obtained. The average time taken for resolution of β hCG was 25 [illegible] which is consistent with work of other authors (Glock & [illegible]).

There has been a concern about possible teratogenic effect of methotrexate [illegible] to Walden and Bagshawe (1979) who reported [illegible] incidence of [illegible] anomalies in the patients treated for [illegible] tumors. Five of our patients who conceived within [illegible] months of the treatment did not have any abnormality in the newborn.

[illegible] patients constitute large percentage [illegible] for ectopic pregnancy [illegible] remains major concern [illegible] subsequent [illegible] rate of [illegible] has been reported (Lindblom et al, 1987; Mitchell et al 1987; [illegible] 1993). In [illegible] of our patients [illegible] tubal patency was present [illegible].

[illegible] side effects of methotrexate were noticed [illegible] other authors have [illegible] side effects like stomatitis, nausea, [illegible] were present in [illegible] of our patients. Other authors [illegible] complication rate [illegible] (Stovall et al 1991, [illegible]).

Conclusion

[illegible] means of diagnosis such as [illegible] and TVS has changed the clinical picture of ectopic pregnancy from an emergency [illegible] condition. It is only due to early diagnosis that newer forms of treatment modalities have been [illegible]. Medical management with single dose methotrexate [illegible] effective.

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