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# Outcomes of medical management of ectopic pregnancy with a combination of mifepristone and methotrexate

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**Abstract**
**Aim:** Ectopic pregnancy can be treated either by surgical intervention or also by medical and expectant management if the patient is haemodynamically stable. The current study aims to determine the outcomes and safety of the combination of mifepristone and methotrexate in the medical management of ectopic pregnancy and evaluate the relation between the baseline serum progesterone and success rate(resolution) in the combination agent (study) group.
**Materials and Methods:** The study was an observational longitudinal follow up study of a cohort of women with ectopic pregnancy in the study period of February 2010 to November 2011 at Fernandez Hospital - Bogulkunta, a tertiary referral centre, in Hyderabad, AP.
40 women satisfying the inclusion criteria after due consent were registered into the study group of oral mifepristone plus systemic methotrexate. The patients with an ectopic pregnancy between January 2008 and December 2009, who met the same inclusion criteria for medical treatment and were treated with 50 mg/m$^2$ methotrexate alone, were used as historical controls to compare outcomes.
**Outcomes:** A successful resolution of the ectopic pregnancy was achieved in 35 (85.36%) women who received the combination (cases) and 23 (69.6%) women who received only methotrexate (controls). Although clinically significant, this difference was not statistically significant (p=0.10). The median resolution time taken for β HCG to fall to 10 MIu/ml in the combination group was significantly lower compared to the methotrexate group. All of the cases resolved within 6 weeks while 6 of the control took more than 6 weeks to resolve (p=0.001). The most common side effect seen in the combination group was the separation pain (65%) which subsided with nonopiate analgesics. The mean serum progesterone was 8 ng/ml and it ranged from 0.7 to 29.5 ng/ml. The mean time taken for normalization of β hCG levels in women with serum progesterone > 10 ng/ml was 30.6 days versus 20.4 days in those with serum progesterone <10ng/ml.
**Conclusion:** Our prospective observational study has proved that the combination of methotrexate and mifepristone did better in terms of faster and cost effective resolution of ectopic pregnancy. Absence of any adverse effects related to the above combination appears to confirm the safety of mifepristone in combination of methotrexate. Serum progesterone was not helpful in predicting the success of medical treatment though ectopic pregnancy with higher progesterone levels required more days for resolution.

**Keywords:** Medical management, unruptured tubal pregnancy, ectopic pregnancy, mifepristone, methotrexate, serum progesterone

## Introduction
An estimated 3.12 per 1000 pregnancies in India are ectopic and account for 10% of all pregnancy related deaths. For nulliparous women, conceptions after one year of unprotected intercourse are 2.6 times more likely to be tubal (reference). About 1.1-4.6% of conceptions associated with ovulation induction are ectopic pregnancies and about 2-8% of IVF conceptions are tubal (references). After an ectopic pregnancy, there is a 7 to 13 fold increase in the risk of a subsequent ectopic pregnancy [1]. The chance that a subsequent pregnancy will be intrauterine is 50% to 80%, and the chance that the pregnancy will be tubal is 10% to 25%; the remaining patients could be infertile [2, 3].
Ectopic pregnancy can be treated either by surgical intervention and/or medical and expectant management if the patient is haemodynamically stable. Conventionally the most widely used protocol is single dose of methotrexate given IM at a dose of 50mg/m$^2$, with subsequent doses given if required. Success rates of 90% with single dose regimen have been cited [5, 6]. The combination of mifepristone with methotrexate has been reported to be more beneficial than methotrexate alone in the faster resolution of ectopic pregnancy [4].

The current study aimed to determine the outcomes and safety of the combination of mifepristone and methotrexate in the medical management of ectopic pregnancy in a population of pregnant women in south India.

## Methods

The study was an observational longitudinal follow up study of a cohort of women with ectopic pregnancy in the study period of February 2010 to November 2011 at Fernandez Hospital, a tertiary referral centre, in Hyderabad, India. The study protocol was reviewed and approved by the Institutional Review Board of the study institute.

Pregnant women presenting to the outpatient or the emergency unit with clinical features of amenorrhoea with pregnancy test positive, abdominal pain, vaginal bleeding, syncopal episodes, and a referred shoulder tip pain were investigated for potential ectopic pregnancy. Ectopic pregnancy was diagnosed by transabdominal or transvaginal ultrasound using 3.5 & 6.5 Mhz probes by a certified radiologist in the obstetric ultrasound department. Serum β hCG levels were assessed using chemiluminiscence assay. Serum creatinine and serum transaminases were evaluated prior to the administration of medical management.

The study included haemodynamically stable women without active intraperitoneal bleeding, with absent intra uterine gestational sac on ultrasound, Serum β hCG levels ≤ 3500 mIu/ml, a sub-optimal rise in serial serum β hCG Level in 48 hrs (< 66% increase or <15% decrease in β hCG), an extra uterine gestational mass measuring < 3.5 cm with minimal fluid collection on ultrasound, informed consent for participation and serial follow ups, and who had no contraindication to methotrexate or mifepristone. The study excluded women with heterotopic pregnancy, significant decrease in β hCG level (>15%) within 48 hr after initial level of β hCG ≤ 3500 mIu/ml, hepatic derangement (Raised serum aminotransferase concentration > 2 fold), renal dysfunction (serum creatinine > 1.5 mg/dl), hematological dysfunction (leucopenia, thrombocytopenia), supra renal gland dysfunction, active pulmonary disease / peptic ulcer disease, overt biological evidence of immunodeficiency, presence of cardiac activity in the ectopic gestation and known sensitivity to mifepristone / methotrexate.

Women enrolled in the study received a single intramuscular dose of 50 mg/m$^2$ of methotrexate with a single oral dose of mifepristone 600 mg (on day 1) after hemogram, RFT (Serum creatinine), and liver enzymes were found to be normal. They were reviewed on days 4 and 7 with β hCG values (on outpatient basis). Significant fall in β hCG levels was defined as a fall in serum β hCG levels of more than 15% between days 4 and 7. If significant fall was observed, the frequency of β hCG testing was changed to a weekly interval till it became negative. If the decrease in β hCG was not significant, (less than 15% drop in levels between days 4 - 7, second injection of methotrexate 50mg/m$^2$ was administered after re-evaluating liver and renal function (transaminases + creatinine). Evaluation of β hCG was done on days 4 and 7 after second dose of Methotrexate. Studies evaluating medical management with single dose methotrexate in women with serum beta HCG less than 5000 Iu/ml,found 100% success with serum levels less than 3600Iu/ml [7, 8]. We chose a threshold value of 3500 Iu/ml of serum β hCG level which is close to the median value of β hCG our population treated with methotrexate.

The regimen was offered on outpatient basis, but some of the patients were admitted for reasons like residence far away from the hospital with no transport, reassurance, and pain relief. The women eligible for the medical management were educated about the warning symptoms which should alert them to immediately attend the hospital for review such as increased abdominal pain, giddiness, separation pain, irregular vaginal bleeding and also the patterns of β hCG levels - possibility of day four flare followed by drop in the levels and the need for follow up till negative β hCG levels. Patient was advised to refrain from alcohol, intercourse, folic acid till complete resolution of ectopic. Use of oral contraceptives or barrier contraception for three months post therapy with methotrexate was strictly advised.

Patient was explained about the follow up of medical management, side effects of the treatment, and told to report back to the hospital if there was abdominal pain or giddiness. The woman was assessed clinically for blood pressure, pulse rate, pallor, abdominal tenderness and distension at enrolment, day 4, day 7 and weekly thereafter. Complete blood counts, liver function tests, serum creatinine were done prior to administering methotrexate. Serum β hCG was done at enrollment, day 4, day 7, and weekly till negative. Follow up with a repeat ultrasound was done when β HCG became negative to confirm success of therapy (resolving mass), β hCG increased significantly (> 50%) during the treatment course, or there was increase in pain severity with clinical suspicion of rupture.

The patients with an ectopic pregnancy between January 2008 and December 2009, who met the same inclusion criteria for medical treatment and were treated with 50 mg/m$^2$ methotrexate alone, were used as historical controls to compare outcomes. Primary outcome of the study was a comparison of successful or complete resolution of the ectopic pregnancy defined as return of beta hCG to normal non pregnant levels. The secondary outcomes of the study were the mean time period for resolution of the ectopic pregnancy, i.e the time taken from the drug administration to the normalisation of β hCG levels compared to historical controls, the proportion of women requiring emergency surgical interventions, need for the second dose of methotrexate, number of ultrasound scans required in each group and proportion of women requiring hospital admission during treatment. Failed medical management was considered as severe pain not manageable by non-opiate analgesics or signs suggestive of rupture (acute drop in blood pressure, anemia, or hemoperitoneum visible on ultrasound), inadequate fall of serum β hCG levels i.e the β hCG level had not decreased sufficiently by day 14 (<15% fall from day 4 to 7 level) (in spite of 2nd dose of methotrexate), or a rapid significant rise in serum β hCG levels (eg near doubling). The decision to convert to a surgical intervention was taken after a review of the case by two consultants.

Statistical analysis was performed using SPSS statistical software version 14.0 (SPSS inc). Categorical variables were compared using the chi-square test and continuous variables were compared using the Students t-test. A p value <0.05 was considered statistically significant.

## Results

This study was conducted in 41 women eligible for medical management of ectopic pregnancy with mifepristone and methotrexate for a period from February 2010 to November 2011 both inclusive. The data was compared with 33 out of 42 historical controls between January 2008 and December 2009 who met the same inclusion criteria set for the study and had been treated with only methotrexate. There was no significant difference in the characteristics of cases and controls (see Table-

1). The most common site for ectopic pregnancy was tubal (n=41, 100.00% and n=30, 90.91% respectively) in cases and controls.

A successful resolution of the ectopic pregnancy was achieved in 35 (85.36%) women who received the combination (cases) and 23 (69.6%) women who received only methotrexate (controls). Although clinically significant, this difference was not statistically significant (p=0.10). Six (14.63%) cases and 3 (9.09%) controls underwent surgical intervention. The most common cause for surgical intervention was an increasing titre of βHCG (2 cases and 1 control), rupture (2 cases and 2 controls), a drop in hemoglobin (1 case) and woman requesting surgery for an immediate resolution (1 case).

All of the cases resolved within 6 weeks while 6 of the control took more than 6 weeks to resolve (p=0.001). The median resolution time taken for β HCG to fall to 10 MIu/ml in the combination group was significantly lower compared to the methotrexate group (see Table-2). During the analysis of the β hCG levels, a day 4 flare during the course of treatment was found in 36.5% of cases. The drop in between the day 4 to day 7 levels and day 7 value of β HCG post treatment when compared between groups was found to be significantly high in the combination group (p=0.04). The proportion of women requiring a second dose of methotrexate was lower in the combination group; this difference was not statistically significant (see Table-2). Women in the control group had significantly more ultrasound scans compared to those who received the combination therapy (see Table-2). The regimen was offered on outpatient basis, however 63% of the patients were admitted for reasons such as residence far away from the hospital, reassurance and pain relief. The mean duration of admission did not differ significantly between cases and controls (see Table-2).

The size of adnexal mass after normalization of β HCG level was compared with pre-treatment size. In 12 of the 41 cases the mass resolved completely, where as in 25 women it showed a decreasing trend. However in 4 cases there were no follow up scans available. In 15 of 33 controls mass decreased in size on follow up scans while in others there was no appreciable change and the mass took longer time to resolve completely.

The most common side effect seen in the combination group was the separation pain (65%) which subsided with nonopiate analgesics. Other side effects included fever and nausea in two women, which were treated symptomatically. In patients requiring second dose of methotrexate there was no derangement seen in the SGPT, Serum creatinine and complete blood picture post methotrexate and mifepristone. However, in the control group 5 women had irregular vaginal bleeding, one complained of nausea, one had gingival ulcer and one had dysuria and constipation. Separation pain remained the commonest complaint during follow up assessments.

Serum progesterone values were available only for the cases and hence a comparison of combination therapy and methotrexate alone was not possible. The mean serum progesterone was 8 ng/ml and it ranged from 0.7 to 29.5 ng/ml. Thirty two (78.1%) of the cases had serum progesterone < 10 ng/ml. All of the cases had resolved in 6 weeks irrespective of the serum progesterone levels, however, the mean time taken for normalization of β hCG levels in women with serum progesterone > 10 ng/ml was 30.6 days versus 20.4 days in those with serum progesterone <10ng/ml. Women with progesterone levels > 10 ng/ml required more mean number of scans on an average as they took longer time to resolve(p=0.14) and a few more hours during the hospital stay (p value =0.37), which were statistically insignificant. (See Table 3).

## Discussion

Results of this study suggest that combination therapy led to a faster resolution of ectopic pregnancy, a more rapid decrease of β hCG levels, and lower number of ultrasound scans. The duration of admission in the hospital was significantly lower in the group of women that received combination therapy; however, admissions were often based on request from the women rather than a medical need. To the best of our knowledge, this is the first study from India that has explored the benefits from combination therapy for the medical management of ectopic pregnancies.

Perdu M *et al* [4] in their preliminary nonrandomized phase II study that managed patients with ectopic pregnancy with 50 mg/m$^2$ of methotrexate IM and 600 mg of oral mifepristone compared results with a previous group who received only 50 mg/m$^2$ of IM methotrexate. They reported only one failure among the 30 patients treated with the combination whereas medical treatment had failed for 11 of 42 patients treated with methotrexate alone. Song HD *et al* [2] in their meta-analysis of 1,706 patients from 23 randomized control trials reported that combined use of methotrexate and mifepristone was better than exclusive use of methotrexate [combined odds ratio (OR) 2.84, 95% confidence interval [CI] (2.18, 3.69), Z = 7.79, P<0.00001]. The additional therapeutic efficacy of mifepristone could be due to a luteolytic effect (Somell *et al*., 1990; Telleria *et al*., 2001) [9, 10] particularly useful in the case of active corpus luteum. Our study findings are similar to the observations of Gazvani *et al* [11] where the median resolution (hCG, 12 IU/l) time of14 days in the combination group was significantly lower than the 21 days in the methotrexate group. Similar to the results from the trial conducted by Rosenberg *et al*, this study did not find a statistically significant difference in complete resolution between the two groups. However, the higher rates of complete resolution achieved with combination therapy was clinically significant.

There were several limitations to this study. The relatively smaller sample size can be considered a limitation although the numbers may appear large for a single center study. The comparison with a historical control can be considered a limitation. However, this was a pragmatic consideration based on the shift towards combination therapy as a departmental policy. Additionally, the controls were selected based on the same eligibility criteria and for the two years preceding the study. The characteristics of the historical controls and the cases did not show any significant differences. The lack of data on serum progesterone for the controls is another pragmatic weakness that limited the comparison of combination therapy and serum progesterone levels. A multicentre trial with a larger sample size may help to provide more evidence on benefits from combination therapy.

## Conclusion

In conclusion the prospective observational study has proved that the combination of methotrexate and mifepristone could improve the outpatient medical management of ectopic pregnancy as it did better in terms of faster resolution of ectopic pregnancy

Absence of any adverse effects related to the above combination appears to confirm the safety of mifepristone in combination of methotrexate. It also proved to be cost effective in terms of requiring lesser number of visits to the hospital, fewer days of hospital stay and requiring lesser number of investigations and the surgical interventions were not found to be different.

Serum progesterone was not helpful in predicting the success of

medical treatment. It could be used to identify patients at risk of ectopic pregnancy who need further evaluation but its discriminative capacity is insufficient to diagnose ectopic with certainity. Ectopic pregnancy with higher progesterone levels required more days for resolution.

We agree that efforts should be made for early diagnosis and nonsurgical management of ectopic and it should run in parallel with new modes of management.

**Table 1:** Comparison of the characteristics of cases and controls

| | Cases (n=41) | Controls (n=33) | P Value |
|---|---|---|---|
| Mean Age | 27.34 (3.46) | 26.39 (3.27) | 0.33 |
| Primigravid | 19 (46.34%) | 15 (45.45%) | 0.94 |
| Nulliparous | 28 (68.29%) | 20 (60.61%) | 0.86 |
| Previous ectopic | 7 (17.50%) | 2 (6.06%) | 0.17 |
| Pain abdomen | 31 (77.50%) | 23 (69.70%) | 0.59 |
| Bleeding | 26 (65.00%) | 15 (45.45%) | 0.10 |
| Dizziness | 5 (12.50%) | 1 (3.03%) | 0.21 |
| Mean ET (mm) | 12.02 (4.89) | 9.48 (3.09) | 0.05 |
| Mean Haemoglobin | 11.42 (1.45) | 11.63 (1.23) | 0.51 |
| Mean SGPT | 41.95 (12.37) | 40.70 (7.29%) | 0.61 |
| Mean S Creatinine | 0.78 (0.06) | 0.79 (0.06) | 0.38 |

**Table 2:** Comparison of outcomes between women who received combination therapy (cases) and women who received only methotrexate (controls)

| | Cases (n=41) | Controls (n=33) | P Value |
|---|---|---|---|
| >42 days | 0 (0.00%) | 6 (25.93) | 0.001 |
| Median duration for bhcg to become normal | 21.85 (6.95) | 34.50 (15.44) | 0.0001 |
| Laparoscopy | 6 (14.63%) | 3 (9.09%) | 0.72 |
| Second dose of methotrexate | 4 (9.75%) | 7 (21.20%) | 0.17 |
| Mean Number of USG | 1.93 (0.68) | 2.64 (1.19) | 0.002 |
| Mean duration of admission | 1.34 (1.62) | 1.91 (1.33) | 0.11 |

**Table 3:** Comparision of mean number of USG and duration of admission

| Serum Progesterone | Mean no of USG | Mean duration of admission in days |
|---|---|---|
| More than10 ng/ml | 2.22 | 1.78 |
| Less than 10 ng/ml | 1.84 | 1.22 |

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