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## **A study on success of methotrexate in single or two doses for medical management of ectopic pregnancy**

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**Abstract**---Background: The treatment of ectopic pregnancy in conservative manner in order to preserve the subsequent fertility is important. Methotrexate can be effectively used in termination of ectopic pregnancy. This study compares the single dose versus double dose approach for the conservative management of pregnancy. Material and Methods: A prospective study was conducted in a tertiary care centre. About 70 women with ectopic pregnancy were administered with single or double dose of methotrexate were followed up. The second dose of MTX was administered when there was no 15% decrease in  $\beta$ -hCG levels between day 4 and 7. The data thus obtained was compiled and analysed. Results: The mean age was comparable in single and double dose groups. The mean gestational age in single dose group was 7.1 weeks and double dose group was 7.48 weeks. The termination of ectopic pregnancy was successful in 80.8% of the single and 33.3% of the two dose groups. The mean EP diameter in single dose group was 24.03 and double dose group was 33.7 mms. The length of stay was significantly lower in double dose groups. Conclusion: The single dose protocol of methotrexate was superior when compared with the double dose protocol.

**Keywords**---methotrexate, ectopic pregnancy, failure, beta hCG, ectopic mass diameter.

## Introduction

Ectopic pregnancy accounts for 2% of all pregnancies and is a major cause of maternal morbidity and mortality during first trimester.<sup>1</sup>The ciliated epithelium of uterus is known to be damaged especially in pelvic inflammatory diseases including chlamydia infections and also forms adhesions predisposing to entrapment of the zygote and the resultant ectopic implantation of the blastocyst and also assisted reproductive technologies in subfertile women can also result in ectopic pregnancy.<sup>2, 3, 4</sup>

Conservative surgical and non-surgical methods are available for the conservative management of the ectopic pregnancy in order to prevent subsequent fertility. Medical management is becoming increasingly popular in the treatment of ectopic pregnancy. Systematically administered methotrexate is shown promising approach for the treatment of ectopic pregnancy with efficacy and tolerability.<sup>5, 6</sup>

Methotrexate can be administered by using two approaches, one is multidose regimen of intramuscular injection and single dose protocol. Two dose protocol had shown better success rates, well tolerated treatment and most of other side effects will be mild and transient. This study mainly examines the success rate of methotrexate and predictors of success like serum  $\beta$ -hCG and EP diameter in the medical management of ectopic pregnancy.

## Material and Methods

A prospective study was carried in the three allied hospitals of JJM Medical College, Davanagere in the department of Obstetrics and Gynaecology. The diagnosis of ectopic pregnancy was made using non-laparoscopic approach including a thorough medical history, physical examination, ultrasound and serum  $\beta$ -hCG levels. Ethical clearance was obtained before the study was started and an informed consent was obtained from all the patients before including them in to the study.

The calculated sample size was 70 and hemodynamically stable patients, gestational adnexal mass of  $\leq 4$  cm, serum  $\beta$ -hCG levels of  $< 5000$  IU/L and absent cardiac activity in gestational sac or minimal hemoperitoneum on ultrasound assessment were included in to the study. The patients with adnexal mass  $> 4$  cm in greatest dimension, disturbances in LFT, KFT, leucopenia, thrombocytopenia or patient inability to comply with treatment protocol were excluded from the study.

The patients thus admitted were monitored in the ward. The baseline investigations including complete blood count, blood group, renal and liver function tests, viral markers, urine routine, urine pregnancy test,  $\beta$ -hCG levels and Ultrasonography were done. The size of the gestational mass was its maximal diameter in any dimension were measured by USG and the maximal diameter of the entire mass was used if the mass was not differentiated from tubal hematoma. The patients received first dose of  $50 \text{ mg/m}^2$  methotrexate IM on day 1. The serum  $\beta$ -hCG level was measured on day 4 and 7 and if the  $\beta$ -hCG level decreased by at least 15%, the treatment was deemed to be successful and also

follow weekly follow up showing decreasing and subsequently negative serum  $\beta$ -hCG.

Second dose of MTX was administered when there was no 15% decrease in  $\beta$ -hCG levels between day 4 and 7. Weekly follow up and treatment of  $\beta$ -hCG levels performed and the treatment considered successful if  $\beta$ -hCG levels became negative. The data thus obtained was collected by using a predesigned proforma. The data was compiled by using Microsoft excel sheet and analysed using Statistical Package for Social Services ver 20.

## Results

Table 1. Distribution of the study group according to demographic characteristics

Demographic characteristics	One dose Mean $\pm$ SD	Two doses Mean $\pm$ SD	T value	P value, Sig
Age in years	26.7 $\pm$ 4.5	27.7 $\pm$ 6.67	-0.707	0.482, NS
Gestational age (in weeks)	7.1 $\pm$ 1.35	7.48 $\pm$ 1.18	-0.973	0.334, NS

The mean age of the women with ectopic pregnancy who had taken single dose of methotrexate was 26.7 years and two doses was 27.7 years which was statistically not significant. The mean gestational age in one dose was 7.1 weeks and two doses was 7.48 weeks in two doses group which was also not statistically significant.

Table 2. Distribution of the study group according to Obstetric score

Obstetric score	One dose n (%)	Two doses n (%)	$\chi^2$ value	P value, Sig
Multigravida	35 (67.3)	12 (66.7)	0.002	0.96, NS
Multipara	41 (78.8)	16 (88.9)	0.892	0.345, NS
Abortion > 1	42 (80.8)	18 (100)	4.038	0.044, Sig

About 67.3% in single dose group and 66.7% in two dose group were multigravida which was not statistically significant. About 78.8% of the one dose group and 88.9% in two dose group were multipara. About 80.8% of the women in single dose group and all the women in the two-dose group had abortion more than 1. This difference was not statistically significant.

Table 3. Distribution of the study group according to free fluid

Free fluid	One dose n (%)	Two doses n (%)
No	42 (80.8)	6 (33.3)
Yes	10 (19.2)	12 (66.7)
Total	52 (100)	18 (100)

$\chi^2$  value= 13.961

df=1

p value, sig=0.000, Sig

The free fluid was found in 19.2% of the pregnant women with ectopic pregnancy in one dose group and 66.7% of the women in two dose group had free fluid. This difference was statistically significant between the two groups.

Table 4. Distribution of the study group according to outcome

Outcome	One dose n (%)	Two doses n (%)
Fail	10 (19.2)	12 (66.7)
Success	42 (80.8)	6 (33.3)
Total	52 (100)	18 (100)

$\chi^2$  value= 13.961                      df=1                      p value, sig=0.000, Sig

The abortion was successful in 80.8% of the study group in one dose group and 33.3% of the cases in two dose group. This difference was statistically significant between the two groups.

Table 5. Distribution of the study group according to EP diameter

EP diameter	One dose Mean $\pm$ SD	Two doses Mean $\pm$ SD	T value	P value, Sig
Mean $\pm$ SD	24.03 $\pm$ 29.73	33.7 $\pm$ 11.71	-1.339	0.185, NS

The EP diameter in one dose methotrexate group was 24.03 mm and 33.7 mm in two doses group. This difference was not statistically significant between the two groups.

Table 6. Distribution of the study group according to Length of stay

Length of stay	One dose Mean $\pm$ SD	Two doses Mean $\pm$ SD	T value	P value, Sig
Mean $\pm$ SD	4.02 $\pm$ 1.57	6.28 $\pm$ 2.14	-4.785	0.000, Sig

The length of stay in one dose methotrexate group was 4.02 days and 6.28 days in two doses group. This difference was statistically significant between the two groups.

Table 7. Beta HCG levels in the study groups at various follow up periods

Beta HCG levels (Mean $\pm$ SD)	One dose Mean $\pm$ SD	Two doses Mean $\pm$ SD	T value	P value, Sig
Day 1	2250.02 $\pm$ 1166.7	5015.0 $\pm$ 2088.9	-6.958	0.000, Sig
Day 4	1451.2 $\pm$ 2403.3	4750.2 $\pm$ 1889.8	-5.278	0.000, Sig
Day 7	470.5 $\pm$ 534.5	3082.3 $\pm$ 1139.4	-13.011	0.000, Sig
Day 14	262.96 $\pm$ 418.9	3616.7 $\pm$ 7946.8	-3.074	0.003, Sig

The beta HCG levels were significantly lower on all days of follow up. The levels of Beta HCG decreased in both the groups during different time intervals of follow up. In single dose group the levels reduced from 2250.2 to 262.96 and in two dose group, the levels reduced from 5015.0 to 3616.7 IU.

## **Discussion**

This study was mainly undertaken to study the efficacy of single dose and two dose Methotrexate in termination of ectopic pregnancy in terms of success rate, serum  $\beta$ -hCG levels and EP diameters. The mean age was comparable between the single dose and two dose Methotrexate groups. In a study by Saleh et al, the mean age in single dose group was 21.3 years and double dose group was 31.6 years unlike the results of this study.<sup>7</sup> Song et al also noted higher age compared to the results of this study.<sup>8</sup>In a study by Mergenthal et al, the mean age in single dose MTX group was 30.6 years and two dose group was 30.1 years.<sup>9</sup>

The gestational age in one dose group was 7.1 weeks and 7.48 weeks in two dose group. Song et al reported that, the mean duration of gestation was 46.6 days in single dose group and 48.9 days in two dose group.<sup>8</sup>A study by Mergenthal et al reported that, the mean gestational age was 6 weeks in one dose group and 6.3 weeks in two dose group.<sup>9</sup> Majority of the women in both the groups were multigravida, multipara and had abortion of more than 1. In contrary to these study results, majority of the women with ectopic pregnancy were nulliparous in a study by Song et al.<sup>8</sup>In a study by Mergenthal et al, many women were multigravida but primipara or nullipara. This study had noted a significant difference in the free fluid between the two groups.<sup>9</sup>

Majority of the women in single dose methotrexate group had successful termination of ectopic pregnancy and two group had failure which was statistically significant. In a study by Song et al, the mean success rate was 82.6% in single dose group and 87.0% in two dose group.<sup>8</sup> There was no statistically significant difference in EP diameter between the single dose methotrexate group and two dose methotrexate groups. In a study by Song et al, the maximal diameter of ectopic mass was 2.59 cm in single dose group and 2.62 cms in two dose group.<sup>8</sup>

The length of stay was significantly lower in single dose group than the two-dose group in this study. A study by Alur Gupta et al had reported that, the length of follow up was 7.9 days shorter for two dose protocol.<sup>10</sup> The beta HCG levels was significantly lower in single dose group than the two groups at all follow intervals in this study. The beta HCG levels reduced significantly at different follow intervals in both the groups but markedly in single dose group. A study by Song et al reported that, the mean resolution time of beta HCG was 31.9 days in single dose group and 25.7 days in two doses group.<sup>8</sup> In a study by Mergenthal et al, the initial hCG was 1684 mIU in single dose group and 1839 mIU in double dose group.<sup>9</sup>In a study by Alur Gupta et al, two dose protocol was more successful in women with high hCG and in women with a large adnexal mass.<sup>10</sup>

## Conclusion

This study had shown that, the single dose protocol of methotrexate was superior than the two-dose protocol in treating the ectopic pregnancy.

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