

# Outcome with Methotrexate versus Expectant Management for Ectopic Pregnancy

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## ABSTRACT

**Background:** Patients with ectopic pregnancy and low serum  $\beta$ -HCG concentrations are commonly treated with systemic methotrexate.

**Aim:** To compare the outcome of methotrexate versus expectant management for females presenting with ectopic pregnancy.

**Study design:** Randomized controlled trial.

**Methodology:** Females with ectopic pregnancy (n=140) were enrolled in study. Blood sample was taken and beta-HCG was noted. Then females were randomly divided in two groups by using lottery method. In group A, females were given methotrexate. In group B, females were given expectant management and not received any specific treatment. Then females were followed-up for 24 hours for assessment of decline in HCG was labeled. If HCG was not declined or even increase, then females underwent surgical intervention. Data was evaluated by using SPSS v.24.

**Results:** The mean age of patients randomized to methotrexate group was  $31.24 \pm 8.85$  years while in expectant management group was  $29.94 \pm 8.02$  years. In methotrexate group, 67(95.7%) females had decline in beta-HCG while 3(4.3%) had no decline in beta-HCG. In expectant management group, 37(52.9%) females had decline in beta-HCG while 33(47.1%) had no decline in beta-HCG.

**Practical Implication:** As there is a high incidence of ectopic pregnancies among our pregnant females and there is lack of local data that specifically addresses this health issue thus current study was planned.

**Conclusion:** It was concluded that methotrexate is an effective way to treat ectopic pregnancy with less chances of complications. **Keywords:** Ectopic Pregnancy, Methotrexate, Beta-Human Chorionic Gonadotropin and Surgical Intervention.

## INTRODUCTION

Ectopic pregnancy is defined as presence of pregnancy outside the uterus. Various risk factors like PID, past history of miscarriages, age, previous ectopic pregnancy and intrauterine device usage contribute towards ectopic pregnancy<sup>1</sup>. The incidence of ectopic pregnancy is reported in Saudi Arabia as 0.58%<sup>2</sup>. In a Pakistani study, ectopic pregnancy represented the frequency of 0.6%<sup>3</sup>. Literature review revealed that ectopic pregnancy patients and low serum  $\beta$ -HCG levels are commonly treated with systemic methotrexate<sup>2,4</sup>.

Methotrexate is a common drug that is routinely used globally for various medical illnesses including tubal ectopic pregnancies. One study showed that it lacked superior effectiveness over expectant management. Although, that study go against the routine use of methotrexate for treatment of tubal ectopic pregnancies presenting with low serum hCG  $<1500$  IU/l<sup>5,6</sup>.

One trial showed that decline in  $\beta$ -HCG was achieved in 76% with methotrexate (n=41) while in 59% with expectant management (n=32). The difference was insignificant ( $p > 0.05$ ), showing that methotrexate and expectant management is almost equal in managing ectopic pregnancy. But the surgical intervention was very less (2%) with methotrexate as compared to expectant management (13%), but the difference was insignificant ( $p > 0.05$ ), showing that both methods have equal efficiency<sup>7</sup>. One more study also showed that decline in  $\beta$ -HCG was 83% with methotrexate and 76% with expectant management ( $p = 0.47$ )<sup>8</sup>.

One previous study enrolled 276 women diagnosed with ectopic pregnancy who received methotrexate as first-line treatment. Their results demonstrated that median beta-hCG levels were lower in the success than the failure group on days 0, 4 and 7 respectively,  $P < 0.001$  for all. The best cut-off for the change in beta-hCG level from day 0 to 4 was a 19% decrease whereas best cut-off for the change in beta-hCG level from day 0 to 7 was a 10% decrease. Thus they concluded that successful treatment with methotrexate for ectopic pregnancy lowers beta HCG levels<sup>8</sup>.

Literature showed that there was no difference in females given methotrexate or managed conservatively. Moreover, lack of local study regarding the treatment of ectopic pregnancy with

methotrexate in our population and its comparison with conservative management forced to plan present study. Its results added literature and insight to this health issue.

Aim of present study was to compare the outcome of methotrexate versus expectant management for females presenting with ectopic pregnancy.

## METHODOLOGY

It was a randomized controlled trial conducted at Jinnah Hospital-Lahore. Females with ectopic pregnancy (n=140) were enrolled randomly in present study. Blood sample was taken and beta-HCG was noted. In group A, females were given methotrexate 1 mg/kg body weight intramuscularly with a maximum of 100 mg, within 24 h of randomization. In group B, females were given expectant management and not received any specific treatment. Then females were followed-up in gynecology ward for 24 hours. After 24 hours, blood samples were again taken. All samples were sent to the laboratory of the hospital for assessment of bet-HCG. If HCG was not declined or even increase, then females underwent surgical intervention<sup>9</sup>. Included participants were aged 18-40 with  $<5$  parity while presenting with ectopic pregnancy at gestational age  $<10$  weeks (on LMP). Obese females with diabetes, viable ectopic pregnancy, signs of tubal rupture and active intra-abdominal bleeding were excluded. Informed consent was taken. Baseline investigations were done at start of study.

**Statistical analysis:** Data was evaluated by using SPSS v.24. Chi square was applied with P-value of  $<0.05$  was considered as significant. Quantitative variables like age, gestational age and BMI were calculated as mean  $\pm$  SD. Qualitative variables like decline in HCG, parity and surgical intervention were calculated as frequency and percentage. Data was stratified for age, gestational age and parity.

## RESULTS

Mean age of patients randomized to methotrexate group was  $31.24 \pm 8.85$  years while in expectant management group was  $29.94 \pm 8.02$  years. The mean gestational age of patients randomized to methotrexate group was  $7.74 \pm 1.15$  weeks while in expectant management group was  $7.57 \pm 1.11$  weeks as summarized in table-1.

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Figure-1: Frequency distribution of β-HCG decline

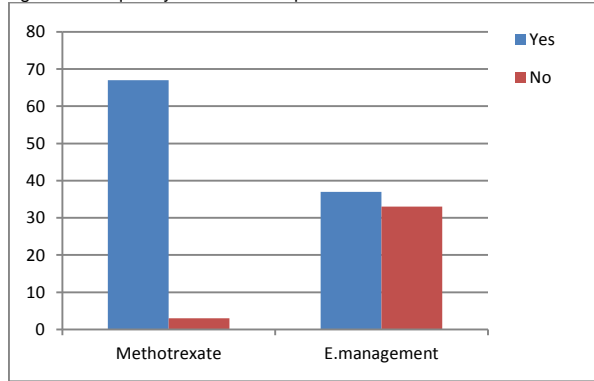


Table-1: Demographic Parameter of Enrolled Participants

Parameters	Categories	Mean ± SD
Age (years)	Methotrexate	31.24±8.85
	Expectant management	29.94±8.02
Gestational Age (weeks)	Methotrexate	7.74±1.15
	Expectant management	7.57±1.11
BMI (kg/m <sup>2</sup> )	Methotrexate	26.31±4.83
	Expectant management	25.52±5.17

In methotrexate group, there were 19(27.1%) primigravida, 10(14.3%) had parity 1, 17(24.3%) had parity 2 and 24(34.3%) had

Table-2: Distribution of parity

		Group		Total
		Methotrexate	Expectant management	
Parity	0	19 (27.1%)	18 (25.7%)	37 (26.4%)
	1	10 (14.3%)	19 (27.1%)	29 (20.7%)
	2	17 (24.3%)	22 (31.4%)	39 (27.9%)
	3	24 (34.3%)	11 (15.7%)	35 (25%)
Beta-HCG decline	Yes	67 (95.7%)	37 (52.9%)	104 (74.3%)
	No	3 (4.3%)	33 (47.1%)	36 (25.7%)
Surgical intervention	Yes	3 (4.3%)	21 (30%)	24 (17.1%)
	No	67 (95.7%)	49 (70%)	116 (82.9%)

Frequency distribution of β-HCG decline among enrolled participants was shown in figure-1.

Table-3: Comparison of decline in beta-HCG in both groups stratified for age

Age (years)	Beta-HCG decline	Group		Total	P-value
		Methotrexate	Expectant management		
16-30	Yes	34(97.1%)	22(56.4%)	56(75.7%)	0.000*
	No	1(2.9%)	17(43.6%)	18(24.3%)	
31-45	Yes	33(94.3%)	15(48.4%)	48(72.7%)	0.000*
	No	2(5.7%)	16(51.6%)	18(27.3%)	

\*Statistically Significant.

Table-4: Comparison of decline in beta-HCG in both groups stratified for gestational age

Gestational Age (weeks)	Beta-HCG decline	Group		Total	P-value
		Methotrexate	Expectant management		
6-8	Yes	48(96%)	27(51.9%)	75(73.5%)	0.000*
	No	2(4%)	25(48.1%)	27(26.5%)	
9-10	Yes	19(95%)	10(55.6%)	29(76.3%)	0.004*
	No	1(5%)	8(44.4%)	9(23.7%)	

\*Statistically Significant.

Table-5: Comparison of decline in beta-HCG in both groups stratified for parity

Parity	Beta-HCG decline	Group		Total	P-value
		Methotrexate	Expectant management		
Primi	Yes	18	9	27	0.002*
		94.7%	50.0%	73.0%	
	No	1	9	10	
Multi	Yes	5.3%	50.0%	27.0%	0.000*
		49	28	77	
	No	96.1%	53.8%	74.8%	
		2	24	26	
		3.9%	46.2%	25.2%	

\*Statistically Significant.

parity 3. In expectant management group, there were 18(25.7%) primigravida, 19 (27.1%) had parity 1, 22(3.14%) had parity 2 and 11(15.7%) had parity 3 as shown in table-2. In methotrexate group, 3(4.3%) females required surgical intervention while 67(95.7%) did not require surgical intervention. In expectant management group, 21(30%) females required surgical intervention while 49(70%) did not require surgical intervention. The difference was significant (p<0.05) as shown in table-2.

In females aged 16-30years, there was decline in beta-HCG in 34(97.1%) cases with methotrexate while in 22 (56.4%) cases with expectant management (p<0.05). In females aged 31-45 years, there was decline in beta-HCG in 33 (94.3%) cases with methotrexate while in 15 (48.4%) cases with expectant management (p<0.05) as shown by table-3.

Data was stratified for gestational age of females. In females presented during 6-8weeks, there was decline in beta-HCG in 48 (96%) cases with methotrexate while in 27(51.9%) cases with expectant management (p<0.05). In females presented during 9-10weeks, there was decline in beta-HCG in 19(95%) cases with methotrexate while in 10(55.6%) cases with expectant management (p<0.05) as shown by table-4.

In primigravida, there was decline in beta-HCG in 18(94.7%) cases with methotrexate while in 9(50%) cases with expectant management (p<0.05). In multigravida, there was decline in beta-HCG in 49(96.1%) cases with methotrexate while in 28(53.8%) cases with expectant management (p<0.05) as shown by table-5.

## DISCUSSION

Most difficult pregnancy is ectopic pregnancy as fertilized egg gets implanted outside the uterine cavity involving fallopian tubes most commonly<sup>9,10</sup>. Various risk factors like PID, past history of miscarriages, age, previous ectopic pregnancy and intrauterine device usage contribute towards ectopic pregnancy<sup>1</sup>.

With transformation in every field including medicine, undiscovered health issues are gaining attention. Due to its increasing incidence and huge impact on female fertility has highlighted ectopic pregnancy in recent past<sup>11,12</sup>. This disease is associated with various complications but the life-threatening issue is acute tubal rupture with massive intra-abdominal bleed leading to hypotension and first trimester high mortality<sup>3,13</sup>. However, literature review revealed that early ectopic pregnancies follow the natural course of a self-limiting process thus result in tubal abortion<sup>13</sup>. Few studies reported that watch and wait policy as a safe alternative treatment option among females with ectopic pregnancies<sup>14,15</sup>.

One previous study found that decline in beta-HCG was achieved in 76% with methotrexate (n=41) while in 59% with expectant management (n=32). The difference was insignificant (p>0.05), thus showing that methotrexate and expectant management were almost equal in managing ectopic pregnancy. But the surgical intervention was very less (2%) with methotrexate as compared to expectant management (13%), but the difference was insignificant (p>0.05), showing that both methods have equal efficiency<sup>7,16</sup>. Our results were in line with above mentioned study thus low surgical requirement in group treated with methotrexate. Present study showed that in methotrexate group, 3(4.3%) females required surgical intervention while 67(95.7%) did not require surgical intervention. In expectant management group, 21(30%) females required surgical intervention while 49(70%) did not require surgical intervention. The difference was significant (p<0.05).

One previous study enrolled 276 women diagnosed with ectopic pregnancy who received methotrexate as first-line treatment. Their results demonstrated that median beta-hCG levels were lower in the success than the failure group on days 0, 4 and 7 respectively, P<0.001 for all. The best cut-off for the change in beta-hCG level from day 0 to 4 was a 19% decrease whereas best cut-off for the change in beta-hCG level from day 0 to 7 was a 10% decrease. Thus they concluded that successful treatment with methotrexate for ectopic pregnancy lowers beta HCG levels.<sup>8</sup> Their results were in line with our findings that showed decline in beta HCG levels among patients who received methotrexate.

Another study also showed that decline in beta-HCG was 83% with methotrexate and 76% with expectant management (p=0.47)<sup>6</sup>. Results of above mentioned study were similar to our findings which showed that in methotrexate group, 67(95.7%) females had decline in beta-HCG while 3 (4.3%) had no decline in beta-HCG. In expectant management group, 37(52.9%) females had decline in beta-HCG while 33 (47.1%) had no decline in beta-HCG.

**Limitations of study:** Financial constrains and limited resources with no genetic workup and long follow-ups added to limitations. It was a single centre study.

## CONCLUSIONS

It was concluded that frequency of preterm birth in female residents having long duty hours was considerably high i.e. 17.18%. Hence pregnant doctors must be given relaxation in their duty hours especially in their 3<sup>rd</sup> trimester to minimize the risk of poor fetal and maternal outcome.

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