

**Research Article****Comparison outcome in medical versus expectant management in patients with unruptured tubal pregnancy having  $\beta$ -hcg 1000-3000 IU/L****Maria Siddiquie, Usman Javed  
and Beenish**<sup>1</sup>House Officer, Bahawal Victoria Hospital, Bahawalpur<sup>2</sup>Medical Officer, BHU Gangran, Narowal<sup>3</sup>BHU Chauni Sulehrian, Sialkot**ABSTRACT**

**Objective:** To compare outcome in medical versus expectant management in patients with unruptured tubal pregnancy having  $\beta$ -hcg 1000-3000 IU/L.

**Materials & Methods:** A total of 82 patients with tubal ectopic pregnancy having  $\beta$ -hcg levels between 1000-3000 IU/L, 18 to 40 years of age were included. Patients with non-tubal pregnancy, ruptured ectopic pregnancy, heterotopic pregnancy, hypersensitivity to methotrexate were excluded. Then selected patients were placed randomly into Group A (expectant management) & Group B (medical management), by using lottery method. Outcome was measured after one week and considered successful if patient had  $\beta$ -hcg levels negligible i.e. <10 IU/L and complete resolution on ultrasonography (absence of adnexal mass, pelvic free fluid, gestational sac).

**Results:** The mean age of women in group A was  $30.90 \pm 5.95$  years and in group B was  $30.65 \pm 6.37$  years. The mean gestational age in group A was  $7.12 \pm 2.12$  weeks and in group B was  $7.63 \pm 2.41$  weeks. The mean  $\beta$ -hcg levels in group A was  $1584.63 \pm 515.81$  and in group B was  $1537.33 \pm 519.68$  IU/L. Outcome was successful in 90.24% in group A (expectant management) and 63.41% in group B (medical management) with p-value of 0.004.

**Conclusion:** This study concluded that expectant management is associated with better outcome as compared to medical management in women with tubal ectopic pregnancy having  $\beta$ -hcg between 1000-3000 IU/L.

**Keywords:** Ectopic pregnancy, methotrexate, expectant, resolution.

**INTRODUCTION**

A pregnancy in which the fertilized ovum implants outside the uterine cavity is known as ectopic pregnancy (EP).<sup>1</sup> EP is the most important cause of maternal mortality and morbidity in the first trimester.<sup>2</sup> Its global incidence varies from 0.5-2 per 100 pregnancies.<sup>2</sup> Ectopic pregnancy is 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 in early pregnancy.<sup>3</sup>

Early pregnancy units (EPUs) with their access to high resolution transvaginal ultrasonography (TVS) and the rapid immunoassay of serum hCG allow early diagnosis of pregnancy location. Currently over 90% of ectopic pregnancies can be visualized on TVS.<sup>4</sup> As a consequence, the clinical presentation of ectopic pregnancy has

changed from a life-threatening disease, necessitating emergency surgery, to a benign condition in frequently asymptomatic women for whom nonsurgical treatment options are available.<sup>5</sup> However, there is a group of women with ectopic pregnancy who can be managed non-surgically. One of the potential advantages of non-surgical treatment of ectopic pregnancy is the avoidance of any iatrogenic injury to the Fallopian tubes, which may decrease the risk of recurrent ectopic pregnancy and improve the chance of successful intrauterine conception.

Nonsurgical strategies, i.e. medical treatment and expectant management, have become a focus of research as laparoscopy is no longer used as gold standard for the diagnosis of ectopic pregnancy. Selecting the subset of ectopic pregnancies amenable for these strategies without putting the patient at risk is of the utmost importance.<sup>7</sup> Trio D et al<sup>8</sup> in his study has shown success rate (complete resolution) of 88% with expectant management in patients with ectopic pregnancy having  $\beta$ -hcg < 1000 IU/l while Dhar H et al<sup>2</sup> has shown this success rate of 65% with single dose of methotrexate.

In case of ruptured ectopic pregnancy, surgical therapy may be provided either via mini-laparotomy or via the laparoscopic route.<sup>9</sup> Laparoscopy has become the recommended approach in most cases. Laparotomy is usually reserved for patients who are hemodynamically unstable or patients with cornual ectopic pregnancies. It is also preferred for surgeons inexperienced in laparoscopy and for patients in whom a laparoscopic approach is difficult.<sup>10</sup> Multiple studies have demonstrated that laparoscopic treatment of ectopic pregnancy results in fewer postoperative adhesions than laparotomy. Furthermore, laparoscopy is associated with significantly less blood loss and a reduced need for analgesia.<sup>10,11</sup>

The aim of this study was to evaluate whether

single dose of methotrexate or expectant management is associated with successful outcome in un-ruptured tubal ectopic pregnancy having  $\beta$ -hcg between 1000-3000 IU/l and the better modality should be advised for these particular women. Furthermore, for the management of women with un-ruptured tubal ectopic pregnancy having  $\beta$ -hcg between 1000-3000 IU/L, evidence for selection of medical versus expectant management is scarce and no local data available on this in our general population, so this study would also give better management plan for our population in order to avoid tubal injury and improve fertility outcome.

#### **OPERATIONAL DEFINITIONS:**

- **Tubal Ectopic Pregnancy:** any pregnancy within the fallopian tubes and were diagnosed on ultrasonography as presence of a thick, brightly echogenic, ring like structure is located outside the uterus, with a gestational sac (thick, echogenic rim surrounding a sonolucent center corresponding to the trophoblastic decidual reaction surrounding the chorionic sac) without cardiac activity and also having  $\beta$ -hcg between 1000-3000 IU/L, was considered positive.
- **Medical Management:** All patients were given single intramuscular injection of methotrexate in a dose of 50mg/m<sup>2</sup>.
- **Expectant management:** In the **expectant management**, patients were monitored till one week. Monitoring consisted of serial  $\beta$ -hcg measurements and ultrasonography according to the local protocol.
- **Outcome:** was considered successful if patient had  $\beta$ -hcg levels negligibly reduced and complete resolution on ultrasonography (absence of adnexal mass, pelvic free fluid, gestational sac) within one week and was considered unsuccessful

if patient had  $\beta$ -hcg levels  $>3000$  IU/L and no complete resolution within one week.

## **MATERIAL AND METHODS**

**STUDY DESIGN:** Randomized controlled trial.

**SETTING:** Department of Obstetrics & Gynecology, Bahawal Victoria Hospital, Bahawalpur.

**DURATION OF STUDY:** 26<sup>th</sup> September 2014 to 25<sup>th</sup> March 2015.

### **Inclusion Criteria:**

- All patients with tubal ectopic pregnancy (as per-operational definition) having  $\beta$ -hcg levels between 1000-3000 IU/L.
- Size of ectopic mass  $<4$ cm.
- Patients 18-40 years of age.

### **Exclusion Criteria:**

- Patients with non-tubal ectopic pregnancy.
- Patients having  $\beta$ -hcg  $>1000$  IU/L and  $>3000$  IU/L.
- Ectopic mass  $>4$  cm.
- Patients with ruptured ectopic pregnancy assessed on ultrasound.
- Hemodynamically unstable patients.
- Presence of fetal cardiac activity.
- Coexistent viable intrauterine pregnancy (heterotopic pregnancy).
- Hepatic or renal failure.
- Known hypersensitivity to methotrexate.
- Patients not willing to be included in the study.

### **DATA COLLECTION PROCEDURE:**

After permission from Local Ethical Committee, 82 pregnant women who meet the selection criteria were included in the study. Before entry into the study, patients were informed about the aims, methods, reasonably anticipated benefits, and potential hazards of the study. Senior gynaecologist (with five year post fellowship experience) was available for more detailed information both for patients and researcher if required. After taking informed, written consent from

each patient for participation in the study, all patients were offered to pick up a slip from total mixed up slips (half-slips were contained letter 'A' and other half slips were contained letter 'B') and she was placed in that respective group. Group A included patients in which expectant management was done while Group B included the patients in which medical management (single intramuscular injection of methotrexate in a dose of  $50\text{mg}/\text{m}^2$ ) was done.

Outcome was measured after one week and was considered successful if patient had  $\beta$ -hcg levels negligible i.e.  $<10$  IU/L and complete resolution on ultrasonography (absence of adnexal mass, pelvic free fluid, gestational sac) and was considered unsuccessful if patient had  $\beta$ -hcg levels  $>3000$  IU/L and no complete resolution.

### **Statistical analysis:**

Statistical analysis was conducted by SPSS version 20.0. Age, gestational age and  $\beta$ -hcg levels were presented by mean  $\pm$  SD. Outcome (successful/unsuccessful) was presented by frequency and percentages. Comparison between the groups with respect to outcome (successful/unsuccessful) was analyzed by Chi-square. P value  $\leq 0.05$  was considered as statistically significant.

Control of confounding variables were done by making cross matched stratified tables for age of patients, gestational age and  $\beta$ -hcg levels and chi-square test was applied to see the effect of these on outcome. P value  $\leq 0.05$  was considered as statistically significant.

## **RESULTS**

Age range in this study was from 18 to 40 years with mean age of  $30.51 \pm 6.53$  years. The mean age of women in group A was  $30.90 \pm 5.95$  years and in group B was  $30.65 \pm 6.37$  years. Majority of the patients 47 (57.32%) were between 31 to 40 years of age as shown in Table I.

Mean gestational age was  $7.44 \pm 2.27$  weeks. The mean gestational age in group A was  $7.12 \pm 2.12$  weeks and in group B was  $7.63 \pm 2.41$  weeks. Majority of the patients 42 (51.22%) were >6 weeks of gestation as shown in Table II.

The mean  $\beta$ -hcg levels in group A was  $1584.63 \pm 515.81$  and in group B was  $1537.33 \pm 519.68$  IU/L as shown in Table III.

There was  $\beta$ -hcg levels negligibly reduced and complete resolution on ultrasonography (absence of adnexal mass, pelvic free fluid, gestational sac) within one week in 37 (90.24%) patients in Group A (expectant management) while in Group B (medical

management), it was seen in 26 (63.41%) patients as shown in Table IV. So, outcome was successful in 90.24% in group A (expectant management) and 63.41% in group B (medical management) with p-value of 0.004 as shown in Table IV.

Stratification of outcome with respect to age groups and gestational age in both groups was shown in Table V & VI respectively which showed statistically significant difference among both groups between 31-40 years of age and >6 weeks of gestational age. Stratification of outcome with respect to  $\beta$ -hcg levels has shown in Table VII.

**Table-I:** Age distribution for both groups (n=82).

Age (years)	Group A (n=41)		Group B (n=41)		Total (n=82)	
	No. of patients	% age	No. of patients	% age	No. of patients	% age
18-30	18	43.90	17	41.46	35	42.68
31-40	23	56.10	24	58.54	47	57.32
<b>Mean <math>\pm</math> SD</b>	<b>30.90 <math>\pm</math> 5.95</b>		<b>30.51 <math>\pm</math> 6.53</b>		<b>30.65 <math>\pm</math> 6.37</b>	

**Table-II:** %age of patients according to Gestational age in both groups.

Gestational Age (weeks)	Group A (n=41)		Group B (n=41)		Total (n=82)	
	No. of patients	% age	No. of patients	% age	No. of patients	% age
$\leq 6$ weeks	19	46.34	21	51.22	40	48.78
$> 6$ weeks	22	53.66	20	48.78	42	51.22
<b>Mean <math>\pm</math> SD</b>	<b>7.12 <math>\pm</math> 2.12</b>		<b>7.63 <math>\pm</math> 2.41</b>		<b>7.44 <math>\pm</math> 2.27</b>	

**Table III:** %age of patients according to  $\beta$ -hcg levels in both groups.

B-hcg levels	Group A (n=41)		Group B (n=41)		Total (n=82)	
	Frequency	% age	Frequency	% age	Frequency	% age
1000-2000	33	80.49	32	78.05	65	79.27
$> 2000-3000$	08	19.51	09	21.95	17	20.73
<b>Mean <math>\pm</math> SD</b>	<b>1584.63 <math>\pm</math> 515.81</b>		<b>1537.33 <math>\pm</math> 519.68</b>		<b>1565.45 <math>\pm</math> 517.89</b>	

**Table IV:** Comparison of Outcome between both Groups (n=82).

OUTCOME	Group A (n=41)		Group B (n=41)	
	Successful	Unsuccessful	Successful	Unsuccessful
	No. of Patients	37	04	26
% age	90.24	9.76	63.41	36.59

➤ P value is 0.004 which is statistically significant.

**Table V:** Stratification of outcome with respect to age groups.

Age of patients (years)	Group A (n=41)		Group B (n=41)		p-value
	Outcome		Outcome		
	Successful	Unsuccessful	Successful	Unsuccessful	
18-30	16 (88.89%)	02 (11.11%)	12 (70.59%)	05 (29.41%)	<b>0.176</b>
31-40	21 (91.30%)	02 (8.70%)	14 (58.33%)	10 (41.67%)	<b>0.010</b>

**Table VI:** Stratification of outcome with respect to gestational age.

	Group A (n=41)	Group B (n=41)	

Gestational age (in weeks)	Outcome		Outcome		p-value
	Successful	Unsuccessful	Successful	Unsuccessful	
≤6 weeks	18 (94.74%)	01 (5.26%)	18 (85.71%)	03 (14.29%)	<b>0.342</b>
>6 weeks	19 (86.36%)	03 (13.64%)	08 (40.0%)	12 (60.0%)	<b>0.002</b>

**Table VII:** Stratification of outcome with respect to  $\beta$ -hcg levels.

B-hcg levels	Group A (n=41)		Group B (n=41)		p-value
	Outcome		Outcome		
	Successful	Unsuccessful	Successful	Unsuccessful	
1000-2000	32 (96.97%)	01 (3.03%)	21 (65.63%)	11 (34.37%)	<b>0.001</b>
>2000-3000	05 (62.50%)	03 (37.50%)	05 (55.56%)	04 (44.44%)	<b>0.772</b>

## DISCUSSION

The increased incidence of ectopic pregnancy is partially attributed to improved ability in making earlier diagnosis. Ectopic pregnancies that previously would have resulted in tubal abortion or complete, spontaneous reabsorption and remained clinically undiagnosed are now detected. Some investigators have questioned the need for unnecessary surgical or medical intervention in very early cases and have advocated expectant management in select cases. However, distinguishing patients who are experiencing spontaneous resolution of their ectopic pregnancies from patients who have proliferative ectopic pregnancies could pose a clinical dilemma.<sup>12</sup>

In 1955, Lund was the first to practice expectant management in patients suspected of having an ectopic pregnancy who were not distressed on admission.<sup>11</sup> Expectant management has been advocated, based on the knowledge that the natural course of many early ectopic pregnancies is a self limiting process, ultimately resulting in tubal abortion or reabsorption. Since the work of these pioneers, only a few studies have been published describing expectant management in selected patients with small ectopic pregnancies without fetal cardiac activity, an upper limit for serum hCG concentration that continues to decline and/or a low serum progesterone concentration.<sup>12</sup> Close serum hCG monitoring is mandatory to detect inadequately declining serum hCG concentrations. Clear criteria for

therapeutic intervention have not been defined yet. One study described serum hCG dynamics during spontaneous resolution of ectopic pregnancy.<sup>13</sup>

Women with a visible ectopic pregnancy and low and plateauing serum hCG concentrations or a persisting PUL have thus far been offered medical treatment with methotrexate (MTX).<sup>14</sup> However, it may be that early ectopic pregnancies follow the natural course of a self-limiting process, resulting in tubal abortion or reabsorption. In several cohort studies, watchful waiting has been suggested as a safe alternative to treatment in this selected group of women with ectopic pregnancies,<sup>15</sup> but evidence from randomized studies is lacking. We have conducted this study to compare outcome in medical versus expectant management in patients with unruptured tubal pregnancy having  $\beta$ -hcg 1000-3000 IU/L.

In our study, there was  $\beta$ -hcg levels negligible i.e. <10 IU/L and complete resolution on ultrasonography (absence of adnexal mass, pelvic free fluid, gestational sac) within one week in 37 (90.24%) patients in Group A (expectant management) while in Group B (medical management), it was seen in 26 (63.41%) patients. So, outcome was successful in 90.24% in group A (expectant management) and 63.41% in group B (medical management) with p-value of 0.004. Trio Det al<sup>8</sup> in his study has shown success rate (complete resolution) of 88% with expectant management in patients with ectopic pregnancy having  $\beta$ -hcg <1000 IU/l while Dhar H et al<sup>2</sup> has shown this success rate of 65% with single dose of methotrexate.

The best predictor of success of medical therapy is the initial  $\beta$ -HCG level. Based on efficacy studies done by Lipscomb et al, success exceeded 90% for single-dose methotrexate when  $\beta$ -HCG levels were less than 5000 mIU/mL but dropped to about 80% when levels were 5-10,000 mIU/mL. Success was less than 70% with an initial  $\beta$ -HCG level of greater than 15,000 mIU/mL.<sup>13</sup> Srivichai et al. reported a success rate of 90.6% in 96 out of 106 patients were successfully treated with methotrexate though four required a second dose.<sup>16</sup> Success reached 90% (n=10) in patients out of 11 with single dose treatment in Merisio's series.<sup>17</sup> Literature published so far shows a success rate ranging from 67% to 100% in single versus multidose treatment for ectopic pregnancies.<sup>18</sup> Mahboob reported a success rate of 80% by treating 12 out of 15 women with single dose MTX with initial  $\beta$ -hcg levels equal to 5000 mIU/ml.<sup>19</sup>

Pertinent studies involving the expectant management of EP were identified using a Medline search of all data published between 1992 and 2004. Success rates of between 48 and 100% have been reported.<sup>20-21</sup> In the largest study to date, of 118 EPs managed expectantly, the overall success rate was 65.3% (77/118).<sup>81</sup> Women were reassessed every 1-3 days using TVS and serum hCG determinations until the hCG was less than 10 IU/L. The mean time to resolution was 20 (range, 4-67) days. In those with successful expectant management the initial hCG was much lower than in those who failed expectant management, 374 (range, 20-10762) IU/L compared to 741 (range, 165-14047) IU/L. The success rate for spontaneous resolution was 88% when the initial hCG level was <200 IU/L but only 25% at levels >2000 IU/L. Similar success rates have been shown in a recent study, with 96% success when the hCG was <175 IU/L.<sup>12</sup>

We found only one randomized controlled trial comparing expectant management to

another treatment (systemic methotrexate). It involved 60 hemodynamically stable women who were treated for 5 days with either 2.5 mg/day oral methotrexate or placebo.<sup>22</sup> The EPs were diagnosed using TVS and serum hCG determinations. The inclusion criteria were: mild symptoms, an hCG increase of <50% over 48 hours, an EP diameter of <40 mm, no signs of intra-abdominal bleeding and no secondary reasons for laparoscopy. The overall success rate was 77%, with no significant differences in primary treatment success between the two methods. However the median baseline hCG levels were low and the treatment used only low doses of methotrexate.<sup>22</sup>

## CONCLUSION

This study concluded that expectant management is associated with better outcome ( $\beta$ -hcg levels negligible i.e. <10 IU/L and complete resolution on ultrasonography (absence of adnexal mass, pelvic free fluid, gestational sac) within one week) as compared to medical management in women with tubal ectopic pregnancy having  $\beta$ -hcg between 1000-3000 IU/L. So, we recommend that expectant management should be preferred in women with tubal ectopic pregnancy having  $\beta$ -hcg between 1000-3000 IU/L in order to avoid tubal injury and improve fertility outcome.

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