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Research Article

## How important is serum $\beta$ -hCG in the management of ectopic pregnancy?

Sandya M. Renukesh, Lavanya Rai\*, Shripad Hebbar

Department of Obstetrics and Gynaecology, Kasturba Hospital, Manipal University, Manipal-576104, Karnataka, India

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**\*Correspondence:**

Dr. Lavanya Rai,

E-mail: menal20@yahoo.co.in

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### ABSTRACT

**Background:** Objective: To investigate whether serum  $\beta$ -hCG levels may influence presentation & management of ectopic pregnancy.

**Methods:** A total of 176 women diagnosed with ectopic pregnancy were divided into 4 groups based on initial serum  $\beta$ -hCG values; group 1 - <1000 mIU/ml, group 2 - 1001-3000 mIU/mL, group 3 - 3001-5000 mIU/ml, group 4 - >5000 mIU/ml. The clinical presentations, ultrasound findings, mode of management & success of medical management in relation to serum  $\beta$ -hCG values were recorded.

**Results:** There were no significant correlations between Serum  $\beta$ -hCG values and ultrasound findings. Ectopic pregnancies with values less than 1000 mIU/ml could also present with rupture, requiring surgical management. A falling trend on Day 4 serum  $\beta$ -hCG was a good predictor of successful medical management. Out of the 28 patients managed medically, 21 (75%) had resolution of ectopic pregnancy, remaining 7, who did not show a subsequent decline on the fourth day, required either repeat dosage or surgical intervention. The study also revealed a positive correlation between initial  $\beta$ -hCG values and site of ectopic gestation. More than 80% (16/19) of patients with cornual ectopic had initial values greater than 10,000 mIU/ml.

**Conclusions:** Serum  $\beta$ -hCG is a complementary and a useful tool in diagnosis & management of ectopic pregnancy.

**Keywords:** Serum  $\beta$ -hCG, Ectopic pregnancy

### INTRODUCTION

The incidence of ectopic pregnancies accounts for 2% of all the pregnancies.<sup>1</sup> Ectopic pregnancy is a significant cause for maternal morbidity and mortality in the first trimester of pregnancy. The increased awareness among the patients and availability of simple diagnostic modalities like estimation of serum  $\beta$ -hCG and a high resolution transvaginal sonography has made the management of ectopic pregnancy easier. Improved understanding of the disease process, its early diagnosis with certainty by sensitive  $\beta$ -hCG estimation has opened up various treatment options like expectant and medical management with usage of folic acid antagonist, methotrexate. Surgery is indicated only in cases with

suspected tubal rupture when other options are contraindicated. However a high index of suspicion is required to diagnose and timely intervene in cases of ectopic pregnancy, as sometimes the clinical findings, ultrasound picture and serum  $\beta$ -hCG values may not correlate.

The aim of the present study was to correlate serum  $\beta$ -hCG with respect to presentation & management of ectopic pregnancy.

### METHODS

We performed an observational analysis of 176 women with ectopic pregnancies, who were managed at the

Department of obstetrics and gynaecology in a tertiary care hospital, after obtaining institutional ethical committee approval. All women with the diagnosis of ectopic pregnancy had initial estimation of serum  $\beta$ -hCG and a transvaginal sonography.

The ultrasound appearance of ectopic, the sac size, presence of fetal pole and cardiac activity, ring of fire appearance, evidence of hemoperitoneum and rupture was documented and analyzed subsequently in comparison with clinical features and  $\beta$ -hCG.

We strictly adhered to the departmental protocol for the management of ectopic pregnancies.

Twenty eight patients were managed medically with 50 mg/m<sup>2</sup> methotrexate on the first day. The serum  $\beta$ -hCG values were repeated on day 4 of injection. If  $\beta$ -hCG decreased by then, it was considered a satisfactory response, if not an additional dose was administered, provided the patient continued to be hemodynamically stable.

Expectant management (patients did not receive any interventions in this groups) was carried out in fourteen patients with the initial  $\beta$ -hCG value of <1000 mIU/ml. We went for emergency laparotomy whenever patient had evidence of intraperitoneal bleed irrespective of serum  $\beta$ -hCG values.

We divided the patients into four groups based on their initial serum  $\beta$ -hCG value as group 1 (<1000 mIU/ml), group 2 (1001-3000 mIU/ml), group 3 (3001-5000 mIU/ml) and group 4 (>5000 mIU/ml).

The findings on ultrasound, mode of management, success of medical management, site of ectopic gestation was compared and analyzed among these groups. The percentage change in serum  $\beta$ -hCG value on day 4 of methotrexate therapy as an indicator of successful medical management was also analyzed.

## RESULTS

One hundred and seventy six patients with ectopic pregnancy were studied. The mean age was 28 years, with 65% of patients being multiparae. The demographic profile of patients is depicted in Table 1.

Among the risk factors for ectopic pregnancy we found that 16% (n=29) patients had previous history of ectopic pregnancy. Nineteen (11%) patients had ectopic pregnancy due to failure of contraception (postpartum sterilization 6, concurrent sterilization (during cesarean delivery) 5, laparoscopic sterilization 3, and cu-T *in situ* 5). Five patients with history of salpingostomy and two patients following tubal recanalization also had ectopic pregnancies.

**Table 1: Contributory factors for ectopic pregnancy.**

Risk factors	n (%)
<b>Previous ectopic pregnancy</b>	29 (16.4)
<b>Failed contraception</b>	19 (10.7)
PPS	6 (3.4)
Concurrent	5 (2.8)
LS	3 (1.7)
Cu T <i>in situ</i>	5 (2.8)
<b>Tubal surgery</b>	9 (5)
Recanalization	2 (1)
Salpingectomy	6 (3.4)
Salpingostomy	1 (0.5)
<b>PID</b>	6 (3.4)
<b>Infertility</b>	13 (7.4)
<b>Tuberculosis</b>	3 (1.7)

The patients were divided in to 4 groups based on their serum  $\beta$ -hCG value. Group 1 and 2 constituted 51 (29%) each. There were 19 (11%) in group 3 and 55 (32%) patients in group 4. The categorization of groups is depicted in Table 2.

**Table 2: Grouping based on serum  $\beta$ -hCG values (n=176).**

Serum $\beta$ -hCG (mIU/ml)	n (%)
Group 1 (<1000)	51 (29)
Group 2 (1001-3000)	51 (29)
Group 3 (3001-5000)	19 (11)
Group 4 (>5000)	55 (32)

The mode of management is shown in Table 3. Total of 176 patients, 42 (24%) were managed conservatively (expectant management 14, medical management 28). It was interesting to know that all women in expectantly management group (n=28) had successful outcome. Among 28 women who received medical management with methotrexate 21 patients had successful outcome, whereas the rest (n=7) had ruptured ectopic requiring emergency surgical intervention.

**Table 3: Types of management.**

Mode of management	Number n (%)
<b>Conservative management</b>	42 (24)
Expectant	14 (8)
Medical	28* (16)
<b>Surgical management</b>	134 (76)
Laparoscopy	88 (50)
Laparotomy	53* (30)

\*7 failed medical cases managed by laparotomy

The ultrasound findings showed a poor correlation with serum  $\beta$ -hCG value. In group 1 with serum  $\beta$ -hCG (<1000 mIU/ml), sixteen patients presented with

hemoperitoneum and fourteen of them already had ruptured ectopic on arrival, requiring surgical intervention. The lowest level at which rupture occurred in the present study was  $\beta$ -hCG level of 429 mIU/ml. Three patients in the same group had presence of fetal cardiac activity with serum  $\beta$ -hCG levels less than 1000

mIU/mL, hence had to be managed surgically. In the present study, we found that the serum  $\beta$ -hCG levels alone did not correlate with ultrasound findings. The correlation of serum  $\beta$ -hCG with ultrasound findings is depicted in Table 4.

**Table 4: Correlation serum  $\beta$ -hCG with ultrasound findings (n=176).**

Findings on ultrasound	Group 1 (<1000 mIU/mL)	Group 2 (1001-3000 mIU/mL)	Group 3 (3001-5000 mIU/mL)	Group 4 (>5000 mIU/mL)
Rupture	14	20	9	31
Ring of fire appearance	13	31	9	25
Hemoperitoneum	16	20	11	32
Cardiac activity	3	9	1	17

Methotrexate treatment in patients with ectopic pregnancy was successful in 21 cases (75%), but the same failed in 7 cases (25%). Of 28 patients managed

medically 18 patients received single dose methotrexate and remaining 10 patients received multiple dosages, maximum of 3 doses. The influence of serum  $\beta$ -hCG on medical management is depicted in Table 5 below.

**Table 5: Influence of serum  $\beta$ -hCG on medical management (n=28).**

Medical management	Group 1 (<1000 mIU/mL)	Group 2 (1001-3000 mIU/mL)	Group 3 (3001-5000 mIU/mL)	Group 4 (>5000 mIU/mL)
Successful	6	9	2	4
Failure	0	3	1	3

Mean  $\pm$  SD of Serum  $\beta$ -hCG (mIU/mL) in success group: 3495  $\pm$  2919, failure group: 5086  $\pm$  3271

The fall in  $\beta$ -hCG value was studied on patients on medical management (n=28). In 12 out of 21 patients who demonstrated a mean decrease of 47.5% decrease in  $\beta$ -hCG values, no further treatment was required and the ectopic resolved spontaneously. The remaining (n=9) required second dose of methotrexate, as they had elevations in  $\beta$ -hCG levels on day 4 of treatment and they too had improvement on day 7.

Eight patients out 28 patients in medical management group were taken up for emergency surgery as they had rupture of ectopic sac. When we studied the  $\beta$ -hCG regression in them, we found that they had steep rise in the serum  $\beta$ -hCG by a mean of 68% between days 1 to 4.

In the present study, the prevalence of ampullary, cornual, isthmic and fimbrial ectopic pregnancies were 76 (43.2%), 19 (10.8%), 18 (10.2%), 28 (15.9%) respectively (Table 6).

The commonest site of implantation of ectopic sac was observed to be at ampullary region of the tube. However in 35 (19.9%) the site of ectopic could not be commented upon as they belong to non-surgical group of management. The patients with ampullary and fimbrial ectopic pregnancy had a varied distribution of serum  $\beta$ -hCG values. On the other hand the patients with isthmic pregnancy seemed to have a lower  $\beta$ -hCG value with 12(66.7%) of patients having  $\beta$ -hCG of <1000 mIU/ml, whereas all except one patient with cornual ectopic pregnancy had high  $\beta$ -hCG of >5000 mIU/ml at the time of presentation. This observation was statistically significant (P value 0.001).

Of 176 ectopic studied 28 (15.9%) had very high initial serum  $\beta$ -hCG value of >10000 mIU/ml, 84.2% (16/19) of patients with such high  $\beta$ -hCG value were found to have cornual ectopic (Table 7). Higher the  $\beta$ -hCG value higher is the cornual ectopic.

**Table 6: Correlation between serum  $\beta$ -hCG and site of ectopic (n=141).**

Site of ectopic pregnancy	Group 1 (<1000 mIU/mL)	Group 2 (1001-3000 mIU/mL)	Group 3 (3001-5000 mIU/mL)	Group 4 (>5000 mIU/mL)	Total
Ampullary	18 (23.7%)	22 (28.9%)	13 (17.1%)	23 (30.3%)	76
Fimbrial	2 (7.1%)	16 (57.1%)	3 (10.7%)	7 (25 %)	28
Cornual	0	0	1 (5.3%)	18 (94.7%)	19
Isthmic	12 (66.7%)	3 (16.7%)	0	3 (16/7%)	18

P value 0.001

**Table 7: Influence of very high serum  $\beta$ -hCG on site of ectopic (n=141).**

Site of ectopic pregnancy	<10000 mIU/mL n=113	$\geq$ 10,000 mIU/mL n=28	Total
Ampullary	73 (96%)	3 (3.9%)	76
Fimbrial	22 (78.6%)	6 (21.4%)	28
Cornual	3 (3%)	16 (84.2%)	19
Isthmic	15 (83.3%)	3 (16.7%)	18

P value 0.001

## DISCUSSION

Ectopic pregnancy is one of the most common obstetric emergencies encountered. The incidence of ectopic pregnancy seems to be increasing due to factors like increased pelvic inflammatory disease, more prevalence of sexually transmitted diseases, smoking, delayed age at marriage and conception, increased ART techniques. Improved knowledge and awareness about ectopic pregnancy among patients and Doctors in periphery can aid in reducing mortality associated with ectopic pregnancies. A simple test like serum  $\beta$ -hCG is a valuable and complementary tool in making diagnosis of ectopic pregnancy.

In present study, the importance of serum  $\beta$ -hCG in the management of ectopic pregnancy was analyzed.

The early diagnosis is essential to minimise chance of ectopic rupture and also improve the success of medical management. This also avoids salpingectomy in a nulliparous woman and increases the possibility of tubal preservation. The present study clearly shows that serum  $\beta$ -hCG value doesn't always correlate with ultrasound findings, a very low value of serum  $\beta$ -hCG can still have presence of cardiac activity and can present with rupture, requiring surgical intervention.

In present study the overall success rate of medical management was 75%, which is essentially in accordance to the other published data.<sup>1,2</sup> The failure of medical therapy was defined as requirement of surgical therapy

after methotrexate was begun. The initial  $\beta$ -hCG value of <1000 mIU/ml did not have any failure, in the failure group the mean level of  $\beta$ -hCG was 5086 mIU/ml as compared to success group which was 3495 mIU/ml. The findings of this study were in accordance with a recent meta-analysis which suggested that the initial  $\beta$ -hCG level is the most important predictor of methotrexate success in ectopic pregnancy.<sup>3</sup> A recent study on medical management including 238 patients also showed that the initial  $\beta$ -hCG value as the most important predictor of the outcome of treatment.<sup>4</sup> Another study showed the initial  $\beta$ -hCG concentration is the most important determinant of conservative treatment failure.<sup>5</sup> The meta-analysis recently published seems to suggest that only serum  $\beta$ -hCG concentrations may be a predictor of successful or unsuccessful medical management of ectopic pregnancy after methotrexate treatment.<sup>6</sup>

In present study, the treatment success was found to be related to the decline in the  $\beta$ -hCG values between day 0 and 4. The day 4  $\beta$ -hCG when showed a declining trend had successful outcome, those patients who had risen in the value of  $\beta$ -hCG on day 4 either required subsequent dosage of methotrexate or had failed medical management requiring surgical intervention.

The findings of this study mainly confirm the results of several published studies, who found that an early decline in the serum  $\beta$ -hCG was associated with a higher rate of successful treatment.<sup>2,7</sup> A study by Celik et al.<sup>8</sup> evaluated the use of percentage decline of serum  $\beta$ -hCG between days 1 to 4 following administration of methotrexate as an indicator of treatment success. They found that 20% decline was associated with a very high chance of subsequent treatment success, with positive predictive value as high as 97%.<sup>8</sup> However in the present study the mean decline of serum  $\beta$ -hCG more than or equal to 30% was found to have successful outcome. Our study mostly confirms the results of previous studies who reported treatment success of 88-100% in those women with early decline in serum  $\beta$ -hCG between days 0 to 4, however our study had success of 75% this difference in the result may be due to small sample size analyzed.<sup>8,9</sup> It is important to monitor serial  $\beta$ -hCG values subsequent to methotrexate administration until complete resolution of the ectopic.

**Table 8: Previous study J. Bouyer et al. (2002).**

Site of ectopic pregnancy	Cornual	Isthmic	Ampullary	Fimbrial	Total	P value
<b>Number (n)</b>	41	201	1175	186	1679	
Diagnosis before 6 weeks	12 (32.4)	75 (40.5)	520 (39.7)	75 (43.1)	620 (40.7)	0.03
Tubal rupture	13 (36.1)	46 (23.7)	178 (15.7)	22 (12.2)	259 (16)	0.001
Profuse hemoperitoneum	12 (31.6)	67 (33.7)	318 (27.4)	66 (36.1)	494 (29.9)	0.03
hCG concentration (mIU/ml)						
Mean $\pm$ SD	10605 $\pm$ 21060	5058 $\pm$ 9734	3722 $\pm$ 8169	3210 $\pm$ 5684	4023 $\pm$ 8733	0.01
<b>Present study: Sandya et al. (2015)</b>						
<b>Number (n)</b>	19	18	76	28	141	
Diagnosis before 6 weeks	12 (40.0)	10 (52.6)	23 (38.3)	11 (34.3)	56 (39)	0.71
Tubal rupture	9 (47.4)	9 (50)	44 (57.9)	12 (42.9)	74 (52.5)	0.53
Hemoperitoneum	9 (47.4)	9 (50)	48 (63.2)	13 (46.4)	99 (56)	0.32
hCG concentration (mIU/ml)						
Mean $\pm$ SD	23312 $\pm$ 9911	3471 $\pm$ 5860	3814 $\pm$ 2892	5306 $\pm$ 1028	6694 $\pm$ 8408	0.0001

In the present study we found that very high initial serum  $\beta$ -hCG value of  $>10000$  mIU/ml predicts the site of ectopic pregnancy. There was a positive correlation between the cornual pregnancy and very high value of serum  $\beta$ -hCG, which was seen in 16 out of 19 cornual ectopics accounting to 84%, the other 3 patients with cornual ectopic had mean  $\beta$ -hCG value of 6067 mIU/ml. Two patients with lower  $\beta$ -hCG on arrival were initially managed medically but had had rupture with hemoperitoneum requiring surgical intervention. Hence all the patients with cornual ectopic finally required surgical mode of management. Thus serum  $\beta$ -hCG alone helps in predicting the site of ectopic and aids in decision making.

Table 8 shows comparison of various variables such as diagnosis before 8 weeks of gestation, incidence of rupture, hemoperitoneum, hCG concentration in the present study compared with previous study.

The results of the present study were compared to study by Bouyner et al.<sup>10</sup> Nearly 40% of ectopic pregnancies were diagnosed as early as 6 weeks. High index of suspicion and use of ultrasound has led to early diagnosis of ectopic pregnancies. Irrespective of the site of ectopic pregnancy the evidence of tubal rupture and hemoperitoneum was more or less equal in the present study, whereas study by Bouyner showed the rupture and hemoperitoneum was more in corneal and fimbrial ectopic pregnancy respectively. This observation was found to be statistically significant. The initial serum  $\beta$ -hCG values were significantly higher in cornual ectopic ( $>10000$  mIU/ml) which was comparable in both the studies.

## CONCLUSION

In conclusion we have found that, clinical presentation, ultrasound findings along with serum  $\beta$ -hCG & not serum  $\beta$ -hCG alone is a good predictor of management of

ectopic pregnancy. The initial serum  $\beta$ -hCG value is a useful tool in deciding the mode of management. Subsequent decline in levels of serum  $\beta$ -hCG on day 4 following medical management is associated with a higher rate of success. The early decline in the serum  $\beta$ -hCG appears to be a reliable indicator of eventually a successful medical therapy and also contributes in detection of resistant disease early which can be managed promptly. Rise in serum  $\beta$ -hCG on day 4 may be an indicator of either failure of medical management or imminent rupture requiring surgical treatment. Higher the initial serum  $\beta$ -hCG higher the incidence of cornual pregnancy. Hence serum  $\beta$ -hCG is a complementary and a useful tool in diagnosis & management of ectopic pregnancy.

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