

## ORIGINAL ARTICLE

# Diagnostic ACCURACY of SERUM $\beta$ -Hcg in Threatened Miscarriages Keeping Ultrasound as Gold Standard

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## ABSTRACT

**Introduction:** Miscarriage is very common, with nearly one in four women experiencing an early pregnancy loss in her lifetime, although the majority of these are miscarried before they are recognized. 80% of miscarriages occur before 12 weeks of gestation, with miscarriage rates decreasing sharply after the first trimester. Miscarriage is the most common complication of pregnancy. About 25-30% of all pregnancies have some bleeding during the pregnancy. Usually no significant pain exists, although mild cramps may occur. More severe cramps may lead to an inevitable abortion.

**Objective:** To determine the diagnostic accuracy of serum  $\beta$ -HCG in threatened miscarriages for early pregnancy loss keeping the ultrasonography as gold standard.

**Study Design:** Cross Sectional validation study.

**Material and Methods:** We conducted a cross-sectional validation study of 140 out/in patient with early pregnancy loss due to threatened miscarriages visiting to Pakistan Institute of Medical Sciences that is a tertiary care hospital from March 2022 to Feb 2023. Patients fulfilling the inclusion criteria were included in the study. Transabdominal/ Transvaginal ultrasound was performed to confirm the number and viability of pregnancy. At the same time measurement of serum  $\beta$ -HCG was done. The mean age of study patients was 30.12 $\pm$ 15.08 years ranging from 15-45 years.

**Results:** In our study 140 women presenting with threatened abortion were enrolled. 90]

, / [p= [-p,...m-0p0b bnhju89hj bht67uy76tfrcv (64.2%) women had age less than 30 years while 50 (35.0. 8%) women had age more than 30 years. Regarding pregnancy related outcome 42(30%) females had miscarriage while 98 (70%) females continued normal pregnancy. 32 women had true positive (p=0.0032) and 10 women had false positive, (p=0.0004). 88 women had true negative (p=0.0005) and 10 women had false negative (p=0.0004). The sensitivity of serum  $\beta$ -HCG is 76.2%, (p=0.0003) with specificity of 89.8% (p=0.0005). The negative predictive value of  $\beta$ -HCG 89.7% (p=0.00032) and its positive predictive value is 76.2% (p=0.0005).

**Conclusion:** In our study we found out that serum Beta-hCG has lower sensitivity and positive predictive value, while specificity, negative predictive value are towards higher. So this test has high validity as for as concerning the diagnosis of early pregnancy loss in Threatened miscarriage.

**Keywords:** Threatened miscarriages, serum $\beta$ -HCG, Pregnancy loss, ultrasonography.

## INTRODUCTION

Threatened miscarriage is defined by the National Library of Medicine (2012) as bleeding during the first 20 weeks of pregnancy with or without uterine contractions while the cervix is closed<sup>1</sup>. About 25-30% of all pregnancies have some bleeding during the pregnancy. Usually, no significant pain exists, although mild cramps may occur. More severe cramps may lead to an inevitable abortion<sup>2</sup>. Threatened abortion is the most common complication in pregnancy, occurring in 20% of all pregnancies. The condition may progress to miscarriage in approximately 50% of cases or may resolve. There is bleeding but the fetus is still alive. The incidence of fetal loss in threatened miscarriage after detection of embryonic/fetal heart activity is 3.4%<sup>3</sup>. Miscarriage is very common, with nearly one in four women experiencing an early pregnancy loss in her lifetime, although the majority of these are miscarried before they are recognized. 80% of miscarriages occur before 12 weeks' gestation, with miscarriage rates decreasing sharply after the first trimester<sup>4</sup>.

One study by Ahmed compares Biochemical and Ultrasonographic predictors of outcome in threatened abortion. This study showed sensitivity, specificity, PPV and NPV of  $\beta$  HCG were 88.6%, 81.1%, 45.6 and 96.8, respectively<sup>5</sup>. Ultrasonography showed sensitivity, specificity, PPV and NPV were 98.1%, 99.1%, 89.2 and 91.4, respectively and for CRL were 46.4%, 40.1%, 35.5 and 33.7, respectively<sup>6</sup>.  $\beta$  HCG and progesterone are good biochemical markers and FHR and CRL are good Ultrasonographic markers for the prediction of outcome in women with threatened abortion<sup>7</sup>.

The rationale of this study is to explore the diagnostic accuracy of  $\beta$ -HCG, so that it may be utilized in the diagnosis of threatened miscarriage that has a huge burden of mortality in Pakistan<sup>8</sup>. We did this study to assess the diagnostic value of serum  $\beta$ -HCG for prediction of pregnancy outcome in threatened miscarriages, if proven, then is the better option opted for detection of miscarriages.

**Objectives:** To determine the diagnostic accuracy of serum  $\beta$ -HCG in women with early pregnancy loss due to threatened miscarriages keeping the ultrasonography as gold standard.

### OPERATIONAL DEFINITION

**Threatened miscarriage:** It is defined by the National Library of Medicine (2012) as bleeding during the first 20 weeks of pregnancy with/without uterine contractions while the cervix is closed.

**$\beta$ -HCG:** Human chorionic gonadotropin is a hormone produced during pregnancy. It was detected by doing blood test and positive by the time of first missed period. Serum  $\beta$ -HCG level < 20ng/dl during first 20 weeks of pregnancy is suggestive of early pregnancy loss due to threatened miscarriages.

**Ultrasonography:** It will show presence of gestational sac with mean diameter > 20mm. If an embryo has CRL > 6mm with no cardiac activity. Ultrasonography will be done at presentation and was confirmed on 2<sup>nd</sup> week.

**Outcome:** The outcome of pregnancy was judged as miscarriages.

**Sensitivity:** The ability of  $\beta$ -HCG test to detect threatened miscarriage in pregnant females (Miscarriage positive, according to ultrasonography).

**Specificity:** The ability of  $\beta$ -HCG test to detect pregnant females with no threatened miscarriage

**Negative Predictive Value (NPV):** The proportions of pregnant females who are test negative and truly do not have threatened miscarriage.

**Positive Predictive Value (PPV):** The proportions of pregnant females who are test positive and truly have threatened miscarriage.

**True Positives:** Pregnant females who have positive  $\beta$ -HCG test and positive ultrasonography for threatened miscarriage.

**False Positives:** Pregnant females who have positive  $\beta$ -HCG test and negative ultrasonography for threatened miscarriage.

**True Negatives:** Pregnant females who have negative  $\beta$ -HCG test and negative ultrasonography for threatened miscarriage.

**False Negatives:** Pregnant females who have negative  $\beta$ -HCG test and positive ultrasonography for threatened miscarriage.

## MATERIALS AND METHODS

**Study Design:** Cross Sectional Study.

**Setting:** This study was conducted at in/out patient department of Gynaecology and Obstetrics department, Loralai Teaching Hospital, Loralai from March 2022 to Feb 2023

**Duration of Study:** The study was completed within six (6) months after the approval of the synopsis

**Sample Size:** Calculated by using WHO (world health organization) sample size calculator where

Sensitivity: 64.1%.

Specificity: 81.4%.

Confidence level: 95%.

Absolute precision: 10%.

Population proportion: 20%.

The sample size was 140 patients.

**Sampling Technique:** Non-Probability Consecutive Sampling.

**Inclusion criteria:** All the pregnant women presenting to antenatal booking clinic of MCH up to thirteen weeks of gestation with per vaginal bleeding were included in this study.

**Exclusion criteria:** Twin/Triplet Pregnancies (Detected by ultrasonography), Ectopic pregnancy (Detected by ultrasonography), Severe uterine anomalies (Detected by ultrasonography), Hypertension (If blood pressure is  $>130/85$ ), Diabetes Mellitus (By checking fasting blood sugars two times two days apart should be  $>126$ ), Chronic Liver Disease, by examining the patients and doing LFT, s, serum albumin and PT, aPTT, SLE or Antiphospholipid antibody syndrome. (By doing ANA level).

**Data Collection Procedure:** An application for study approval from the hospital ethical committee was submitted. All patients presenting with per vaginal bleeding in early pregnancy fulfilling the inclusion criteria were enrolled for study. All patients were explained about the purpose of study, risk benefit ratio and option to refuse participation in the study By taking informed written consent from the patients before collection of data. Accurate dating of pregnancy was done by the last menstrual period. In case of uncertainty about the dates, gestation was determined by ultrasound scan. Transabdominal/ Transvaginal ultrasound was performed to confirm the number and viability of pregnancy. At the same time patients are asked about the blood test for measurement of  $\beta$ -hCG and explaining the procedure of taking blood. Blood was withdrawn by all aseptic measures and stored in a serum bottle. Sample was clearly marked with patient's name, admission number and sent to pathology lab. The report was prepared by consultant pathologist.

Miscarriage was suspected if on ultrasound the gestational sac has a mean diameter greater than 20 mm, with no evidence of any embryo or yolk sac or if the embryo has crown rump length greater than 6 mm with no evidence of cardiac activity. The diagnosis of miscarriage was confirmed by repeated ultrasound examination at least one week later. Follow up pregnancies was continued till the miscarriage confirmed/or till final diagnosis. All information's were recorded on proforma.

**Data analysis:** The data was analysis by using Statistical Package for Social Sciences version 10 (SPSS 10). Categorical variables such as testing positive for  $\beta$ -HCG and ultrasonography were presented as frequencies. Continuous variables such as age of the women and duration of pregnancy were presented as mean  $\pm$  standard deviation. The sensitivity, specificity, PPV and NPV of serum  $\beta$ -HCG test was calculated by using 2x2 Table as shown below.

TEST RESULT	Ultrasonography positive	Ultrasonography negative
$\beta$ -HCG Positive	True Positive (TP)	False Positive (FP)
$\beta$ -HCG Negative	False Negative (FN)	True Negative (TN)

Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the  $\beta$ -HCG test will be using the following standard formulas.

Sensitivity =  $TP/TP+FN*100$

Specificity =  $TN/TN+FP*100$

Positive Predictive Value =  $TP/TP+FP*100$

Negative Predictive Value =  $TN/TN+ FN * 100$

## RESULTS

140 (one hundred and forty) women with threatened miscarriage were included in the study. The mean age of study patients was 30.12 $\pm$ 15.08 years ranging from 15-45 years. (Table 1)

90 (64.2%) women had age less than 30 years while 50 (35.8%) women had age more than 30 years.

Regarding pregnancy related outcome 42(30%) women had miscarriage while 98 (70%) women continued normal pregnancy. (Table 2)

In our study we found out that 32women had true positive ( $p=0.0032$ ) and 10women had false positive, ( $p=0.0004$ ). 88 women were true negative ( $p=0.0005$ ) and 10 women had false negative ( $p=0.0004$ ). (Table 3)

The sensitivity of serum  $\beta$ -HCG is 76.2%, ( $p=0.0003$ ) with specificity of 89.8% ( $p=0.0005$ ). The negative predictive value of serum  $\beta$ -hCG 89.7% ( $p=0.00032$ ) and its positive predictive value is 76.2% ( $p=0.0005$ ). (Table 4)

Table 1: Baseline characteristics of study patients (n = 140)

	Number	%age
Age (years)		
Mean + SD	30.12 + 15.08	
Range (min-max)	15 – 45	
Age categories (years)		
15 to 20	20	14.20%
21 to 30	70	50%
31 to 40	40	28.6%
41 to 45	10	7.1%

Table 2: Distribution of Patients according to pregnancy outcome n = 140

Category	Number of Patients	% Age of Patients
Miscarriage	42	30%
Normal Pregnancy	98	70%

Table 3: Diagnostic Accuracy of  $\beta$ -HCG calculated using 2x2 Table n= 140

Test Result	Ultrasonography Positive	Ultrasonography Negative
$\beta$ - HCG Positive	True Positive(TP) 32	False Positive(FP) 10
$\beta$ - HCG Negative	False Negative(FN) 10	True Negative(TN) 88

Table 4: Diagnostic Accuracy of Ultrasonographic test n= 140

Sensitivity	$TP/TP+FN*100$	76.2%
Specificity	$TN/TN+FP*100$	89.8%
Positive Predictive Value	$TP/TP+FP*100$	76.2%
Negative Predictive Value	$TN/TN+ FN * 100$	89.7%

## DISCUSSION

Threatened miscarriage, vaginal bleeding before 20 gestational weeks is the commonest complication in pregnancy, occurring in about a fifth of cases<sup>9</sup>. Miscarriage is 2.6 times as likely, and 17% of cases are expected to present complications later in pregnancy. Although general practitioners and gynaecologists often see this condition, management of threatened miscarriage is mostly empirical. Bed rest is routinely recommended, and about a third of women presenting with threatened miscarriage are prescribed drugs. However, two thirds of the general practitioners recommending this do not believe it affects outcome<sup>10</sup>.

Duan L and his colleagues conducted a retrospective study on 245 intrauterine pregnant women from January 2006 to October 2008<sup>11</sup>. 175 women with threatened miscarriages who consulted for vaginal bleeding received exogenous progesterone supplements. There were 108 patients with ongoing pregnancies until delivery and 67 patients with inevitable miscarriages. Control group included 70 pregnant women<sup>12</sup>. Serum concentrations of progesterone and  $\beta$ -HCG were measured by Microparticle enzyme immunoassay between the fourth and fifth gestational weeks<sup>13</sup>. The mean serum levels of progesterone and  $\beta$ -HCG in patients with inevitable miscarriages ( $13.76 \pm 5.52$  ng/ml,  $3,647.00 \pm 2,123.00$  mIU/ml, respectively) were significantly lower than these levels in normal intrauterine pregnancies ( $31.67 \pm 5.86$  ng/ml,  $13,437.00 \pm 6,256.00$  mIU/ml, respectively) and ongoing pregnancies ( $25.47 \pm 6.18$  ng/ml,  $8,492.00 \pm 2,389.00$  mIU/ml, respectively) ( $P < 0.001$ ). Serum progesterone combined with  $\beta$ -HCG measurements, with a diagnostic accuracy of 85.7% (sensitivity 88.1%, specificity 84.3%), had the best prognostic reliability and significant differences were found when this parameter was compared with the predictive value of a single progesterone (diagnostic accuracy 72.5%, sensitivity 76.1%, specificity 70.4%) or  $\beta$ -HCG (diagnostic accuracy 74.8%, sensitivity 64.1%, specificity 81.4%) determinations<sup>14</sup>. A combination of two biochemical parameters shows substantial improvement over a single-marker strategy<sup>15</sup>.

However, in our study, 140 (one hundred and forty) women with threatened miscarriage were included in the study. The mean age of study patients was  $30.12 \pm 15.08$  years ranging from 15-45 years. 90 (64.2%) women had age less than 30 years while 50 (35.8%) women had age more than 30 years. In our study most of the pregnant women had low education level 30 (21.4%) were illiterate, 23 (16.5%) women were those who got their education till primary while 36 (25.7%) has completed their secondary education. Only 51 (36.40%) study women had more than matriculation education status. Hence results of our study showed that miscarriages are more common in less educated people. Our study showed that most of the studies participants belong to poor socioeconomic status 100 (71.4%), only 40 (29.6%) women belong to high social background. Regarding pregnancy related outcome 42 (30%) females had miscarriage while 98 (70%) females continued normal pregnancy. 2 (4.7%) miscarriages occurred in Multiparous women and 40 (95.3%) miscarriages occurred in Nulliparous women. ( $p=0.0004$ ). 32 women had true positive ( $p=0.0032$ ) and 10 women had false positive, ( $p=0.0004$ ). 88 women had true negative ( $p=0.0005$ ) and 10 women had false negative ( $p=0.0004$ ). The sensitivity of  $\beta$ -HCG is 76.2%, ( $p=0.0003$ ) with specificity of 89.8% ( $p=0.0005$ ). The negative predictive value of  $\beta$ -HCG 89.7% ( $p=0.00032$ ) and its positive predictive value is 76.2% ( $p=0.0005$ ).

Beta-hCG is important to confirm the pregnancy and distinguish it from dysfunctional uterine bleeding or bleeding from another etiology. The hCG level is also important to help distinguish a complete abortion from a threatened abortion or ectopic pregnancy<sup>16</sup>. If the hCG level is above 1500-2000 mIU/mL, then transvaginal ultrasonography should detect a viable intrauterine pregnancy. A level over 3000 mIU/mL should enable one to visualize a viable intrauterine pregnancy by transabdominal ultrasonography<sup>17,18</sup>. If the values are so elevated, the cervical canal is closed, and the patient's history is consistent with passing

tissue (which a physician has confirmed), then an empty uterus on ultrasonography is consistent with a completed abortion. However, if the hCG level is elevated, no history of passing tissue is present, and the ultrasonography demonstrates an empty uterus, one must assume that an ectopic pregnancy is present until proven otherwise<sup>19,20</sup>. Low hCG levels (ie,  $< 200$  mIU/mL) may make the diagnosis more difficult. Observation and monitoring the hCG levels every few days may be an option if the patient is stable and not complaining of pain. If these low hCG levels plateau and fall, the patient will likely miscarry or have a tubal abortion on her own. However, if the values rise, then follow-up ultrasonography is necessary to determine whether an intrauterine pregnancy or an ectopic pregnancy is present and subsequent appropriate management is necessary. The hCG level should rise at least 53% every 2 days during the early first trimester.

## CONCLUSION

In our study we found out that serum Beta-hCG has lower sensitivity and positive predictive value, while specificity, negative predictive value are towards higher side. So this test has high validation as for as concerning the diagnosis of Threatened abortion.

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