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STUDY OF BETA HCG IN CERVICOVAGINAL SECRETIONS IN WOMEN WITH PRETERM LABOUR AND NORMAL PREGNANCY

Gynaecology and Obstetrics

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ABSTRACT

Background: The aim of this prospective study was to find out association of β-hCG level in cervico-vaginal secretion with preterm labour and a cut-off value for prediction of pre-term delivery.

Methods: 150 cases were enrolled between 24-36 weeks of gestation including 75 cases as control (group II) having no pre-term labour pain and 75 cases in the study group having preterm labour pain of which 50 had preterm delivery (group Ia) and 25 had term delivery(group Ib).

Results: Mean value + S.D. of β-hCG (mIU/ml) in cervico-vaginal secretion in study group Ia (26.46±19.10) were significantly higher than Ib (8.34±10.62) and control group (4.62±9.69) ($p<0.001$). The optimum β-hCG cut off for predicting the Ia cases was > 19.16 (mIU/ml) with sensitivity 64% and specificity 92%.

Conclusions: β-hCG level >19.16 mIU/ml in cervico-vaginal secretion can be used as predictor of preterm delivery in patients presenting with preterm labour.

KEYWORDS

β-hCG, cervicovaginal secretions, preterm labour, preterm delivery.

INTRODUCTION

Preterm birth is the delivery of a baby before 37 completed weeks of gestation [1]. Most of the neonatal mortality occurs when they are born before 34 gestation weeks [2]. To determine the high risk of premature delivery in a pregnant women, accurate biochemical markers are needed that would potentially allow improved surveillance and more timely intervention to improve the outcome [3-6]. Various biochemical markers have been studied and proposed as predictor of preterm delivery like salivary estriol, MSAFP, fetal fibronectin, alkaline phosphates, prolactin, insulin like growth factor 1 and 2, cervicovaginal β-hCG [7-9].

Human chorionic gonadotropin (hCG) is a glycoprotein and is one of the studied markers to predict preterm delivery. β-hCG was found in cervicovaginal secretions in high concentration until 20 weeks gestation, but it remained at a stable level after 20 weeks of gestation [10]. β-hCG presence in maternal serum and amniotic fluid is because of diffusion throughout pregnancy and the amount of β-hCG in the cervicovaginal secretions reflect the levels in the maternal serum and the amniotic fluid. The elevated β-hCG levels in the cervicovaginal secretions may be result of the inflammatory process that can precede the onset of labor[11].

The present study was aimed to find out (1) an association between human β-hCG levels in cervicovaginal secretions and preterm labour, (2) an appropriate cut-off value of human β-hCG levels in cervicovaginal secretions for prediction of preterm labour.

MATERIALS & METHODS

This Prospective, cohort study was done in Department of Obstetrics & Gynaecology in Hind Institute of Medical Sciences, Safedabad, Barabanki from December 2017 to November 2018. Women enrolled between 24 and 36 weeks of pregnancy with or without labour pains attending Antenatal OPD and those admitted as emergency. Estimation of Gestational age was done on the basis of the first day of menstruation (LMP). If last menstrual period (LMP) was unreliable then ultrasonography was done for estimation of gestational age. The reported age on the basis of ultrasonography was considered as the gestational age if the estimated difference between LMP and ultrasonography was more than ten days.

Inclusion Criteria

Included singleton pregnancy accurately dated by early second trimester ultrasonographic examination, cervical dilatation<3 cm, intact amniotic membranes (i.e. no obvious leakage of amniotic fluid and negative ferning and nitrazine paper reaction test result), absence of any maternal and fetal complications at admission and during pregnancy.

Exclusion Criteria

Included placenta praevia, vaginal bleeding, hypertensive disorders, fetal growth retardation, fetal distress, fetal congenital anomalies and multiple gestations.

In present study, a total of 150 subjects were included of which 75 were in study group and 75 in control group.

STUDYGROUP: - Patient who came with preterm labour pains, tocolytic given and then patient followed till delivery (n=75). The study group was further subdivided into two groups.

Study group Ia: - Patient who came with preterm labour pain, treated with tocolytic but had preterm delivery (n=50).

Study group Ib: - Patient who came with preterm labour pains, treated with tocolytic and delivered at full term (n=25).

II. CONTROL GROUP: - Patient with normal pregnancy with no preterm labour pain and followed till delivery (n=75). Patient's particulars and detail history taking and clinical examination were done and noted in a structured proforma.

Cervicovaginal β-hCG level: Cervicovaginal secretion samples were obtained before per vaginal examination and prior to tocolytic therapy administration. For obtaining samples of cervicovaginal secretions, a cotton tipped swab was placed first into the endocervical canal and then into the posterior fornix for 30 seconds and then removed and placed in a tube containing 1 ml of saline solution which was shaken for 1 minute followed by centrifugation for 5 minutes at the rate of 1500 rpm. Refrigeration of Supernatant was done at temperature of -20°C for up to 30 days. Accu-Bind (ELISA Microwells) Kit manufactured by Monobind Inc Lake Foresit CA-92630, USA and commercially available sensitive test cassettes was used for quantitative and qualitative estimation of β-hCG respectively.

Details of statistical tests

The data was analyzed using SPSS software, version 15.0. For comparison of demographic data and patient characteristics chi-square test was used. The data was found to be asymmetric and not normal, hence non-parametric evaluation was done using Mann-Whitney U test to compare the data. Pearson's correlation was used to find interrelationship of β-hCG level with age, gestational age and BMI. The confidence level of the study was kept at 95%, hence a p-value <0.05 indicated statistically significant association. Logistic regression model was used for predicting groups on the basis of β-hCG level, and the sensitivity, specificity and other validity parameters were calculated for the fitted models.

RESULTS

Out of a total of 150 subjects enrolled in the study, 75 (50.0%) were controls, while 75 (50.0%) were cases among which a total of 50 (33.3%) were in Study Group Ia and remaining 25 (16.7%) were in Study Group Ib. (Figure 1)

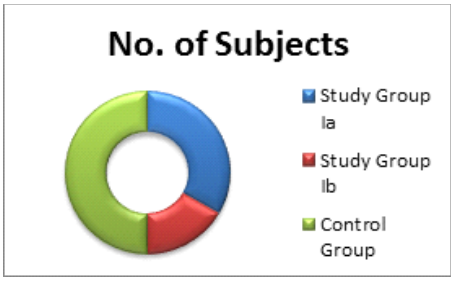


Figure 1: Distribution of subjects

The mean age ± SD in study group Ia, Ib and control group were 25.08±3.17, 25.6±3.57, 26.96±3.66 respectively. In Study Group Ia, Ib and control group most of the subjects were in lower and middle socioeconomic class. Most of the cases in study group Ia and Ib were in parity range 2-3 while in control group most were in parity range 0-1. Most of the cases in control group and both the study groups lie in body mass index (BMI) range of 18.5 -24.9 kg/m2. Statistically, there was no significant difference between study and control groups with respect to age (p=0.742), socioeconomic status (p=0.060), parity (p=0.401) and BMI (p=0.188). (Table 1)

TABLE - 1: DISTRIBUTION OF SUBJECTS ACCORDING TO AGE, SOCIOECONOMIC STATUS, PARITY AND BMI

Parameter	Study Groups		Control	Chi Square test
	Ia	Ib		
	No. (%)	No. (%)	No.(%)	
Age (Year)				
<=20	4 (8)	0 (0)	4 (5.33)	x^2=3.51 (df=6) p=0.742
21-25	24 (48)	12 (48)	30 (40)	
26-30	19 (38)	12 (48)	36 (48)	
>30	3 (6)	1 (4)	5 (6.67)	
Mean Age ±SD	25.08 ±3.17	25.6 ±3.57	26.29 ±3.66	
Socio-economic Status				
Lower	33 (66)	9 (36)	38 (50.7)	x^2=8.92 (df=4); p=0.060
Middle	16 (32)	15 (60)	37 (49.3)	
Upper	1 (2)	1 (4)	0 (0)	
Parity				
0-1	19 (38)	12 (48)	35 (46.7)	x^2=4.04 (df=4); p=0.401
2-3	28 (56)	13 (52)	33 (44)	
>3	3 (6)	0 (0)	7 (9.3)	
BMI (kg/m2)				
<18.5	0 (0)	2 (8)	1 (1.3)	x^2=6.15 (df=4) p=0.188
18.5-24.9	40 (80)	19 (76)	57 (76)	
25-29.9	10 (20)	4 (16)	17 (22.7)	
Mean BMI ±SD	23.28 ±1.96	22.35 ±2.62	23.72 ±2.33	

Table 2 shows that there is statistically significant rise in mean value of β-hCG in study group Ia (26.46±19.10 mlU/ml) as compared to study group Ib (8.34± 10.62 mIU/ml) (p<0.00001) and control group (4.62±9.69 mlU/ml) (p<0.00001) respectively. Overall highly significant difference was found between study and control group (p<0.00001)

TABLE - 2 β-HCG LEVELS IN DIFFERENT GROUPS AND MUTUAL COMPARISONS

Groups (No.)	β -hCG level Mean ±SD (mIU/ml)		
Study group Ia (50)	26.46 ± 19.10		
Study group Ib (25)	8.34 ± 10.62		
Study group overall (75)	20.42 ± 18.76		
Control Group (75)	4.62 ± 9.69		
Comparisons (Mann Whitney U Test)			
Ia vs. Ib	Ia vs. control	Ib vs. Control	Study vs. Control
U=195 z=4.827 p<0.00001	U=369.5 z=-7.584, p<0.00001	U=463.5 z=-3.769, p= 0.00016	U=833 z=7.438, p<0.00001

The only significant and positive correlation of β-hCG level was found with Gestation at which sample taken (r=0.2227, p=0.006159) [Table 3]. So for predicting cases with β-hCG level, the Gestation at which sample taken must be required to include in the model.

TABLE – 3: CORRELATION OF β-HCG LEVEL WITH AGE, GESTATION AGE AND BMI

Variable	β-hCG	
	Pearson Correlation	p-value
Age (Yrs)	-0.032	0.697469
Gestation at which sample taken (Wks)	0.2227	0.006159
BMI (kg/m2)	-0.1567	0.055497

On applying Logistic regression model, equation 1 and equation 2 is derived for prediction of Ia cases on the basis of β-hCG level and Gestation Age compared to β-hCG level only respectively [Table 4]

TABLE - 4: The Logistic Regression Model For Predicting Group Ia Cases On The Basis Of B-hcg Level And Gestation Age At Which The Sample Taken Compared To B-hcg Level Only

β-hCG level and Gestation Age				
Variable	B	S.E.	p-value	Exp(B)
β-hCG (mIU/ml)	0.108	0.019	<0.001	1.114
Gestation at which sample taken (wk)	0.173	0.076	0.023	1.189
Constant	-7.599	2.472	0.002	0.001
β-hCG level only				
Variable	B	S.E.	p-value	Exp(B)
β-hCG (mIU/ml)	0.112	0.019	<0.001	1.118
Gestation at which sample taken (wk)	-	-	-	-
Constant	-2.146	0.318	<0.001	0.117

Equation 1:-

$P = 0.108(\beta\text{-hCG}) + 0.173(\text{GA of sample}) - 7.599$

Ia case will be predicted if P>0.

Equation 2:- $P = 0.112(\beta\text{-hCG}) - 2.146$

Ia case will be predicted if P>0 or β-hCG > 19.16 (mIU/ml), the optimum cut off for predicting the cases.

From the above logistic regression model, the reliability parameters of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy (DA) were 64%, 92%, 80%, 83.6% and 82.7% respectively for β-hCG and 62%, 92%, 79.5%, 82.9% and 82% respectively for β-hCG and gestational age [Table 5].

TABLE - 5: The Reliability Parameters Of Logistic Regression Model For Predicting Group Ia Cases On The Basis Of B-hcg Level And Gestation Age At Which The Sample Taken Compared To B-hcg Level Only

β-hCG level and Gestation Age (Ia)			
Parameter	Estimated Value	95% Confidence Interval	
		Lower Limit	Upper Limit
Sensitivity	62.0	54.2	69.8
Specificity	92.0	87.7	96.3
PPV	79.5	73.0	85.9
NPV	82.9	76.9	88.9
DA	82.0	75.9	88.1
β-hCG level only (Ia)			
Parameter	Estimated Value	95% Confidence Interval	
		Lower Limit	Upper Limit
Sensitivity	64.0	56.3	71.7
Specificity	92.0	87.7	96.3
PPV	80.0	73.6	86.4
NPV	83.6	77.7	89.6
DA	82.7	76.6	88.7

DISCUSSION

In the present study, we evaluated and compared β-hCG value in cervicovaginal secretions among preterm labour and normal pregnancy and its cut-off value in prediction of preterm labour. By making an early diagnosis of asymptomatic patients that are at risk for preterm birth, preterm delivery can be prevented and fetal lung

maturation can be accelerated, thus duration of hospital stay and intervals of follow up visits will be decreased. Moreover, aggressive tocolytic therapy must be avoided [12].

Anai et al. were the first to measure β-hCG level in vaginal fluid and suggested that quantitative measurement of β-hCG level from vaginal fluid may serve as a useful marker of premature rupture of fetal membranes[13].

In present study, there was no statistically significant difference in the mean age between study and control group. Lower socioeconomic status predisposes to preterm delivery which was similar to the study by RL Weck [14]. There was no statistically significant difference between increased parity and preterm birth in our study which was similar to study done by Ranjbar M et. al [15] while another study done by Shaikh K et al from Pakistan showed that increased parity was as a risk factor for preterm birth, and it has been proposed that physiologic risk factors common in multiparous women (e.g., placenta praevia, placental abruption, postpartum hemorrhage) may partly explain the higher risk of preterm birth[16]. In present study, we found no association between body mass index and preterm delivery which was contradictory to study by Dayeon Shin and Won O. Song which showed that women having BMI<19kg/m2 were associated with 25.7% and 10.1% chances of preterm labour and preterm delivery respectively[17].

In present study, we found statistically significant rise in the level of cervico-vaginal β-hCG in the study group (20.42 ± 18.76 mIU/ml) as compared to the control group (4.62±9.69 mIU/ml). Among the study group, statistically significant difference was observed with Ia group (26.46 ± 19.10 mIU/ml) having higher level of cervicovaginal β-hCG than Ib group (8.34 ±10.62 mIU/ml) (p<0.00001). These findings were similar to study done by Mishra N et al which showed mean value of 23.46±8.86 SD mlU/ml and 7.81 ± 16.19 SD mlU/ml in the study group and control group respectively showing that mean β-hCG level in study group was significantly higher than control group (P <0.0001)[18].

In present study, the only significant and positive correlation of β-hCG level was found with gestation at which sample taken (r=0.2227, p=0.006159). Study group Ia (preterm labour and preterm delivery group) had significantly higher mean β-hCG levels as compared to study group Ib (preterm labour and term delivery group) (26.46±19.10 vs. 8.34 ±10.62 mIU/ml respectively, P<0.00001) and the optimal cut-off β-hCG for predicting the preterm delivery using β-hCG levels only was 19.16 mIU/ml with sensitivity 64%, specificity 92%, positive predictive value 80% and negative predictive value as 83.6%. Similar was the observation by Sak et. Al where preterm delivery group had significantly higher cervicovaginal β-hCG levels compared with normal controls (94.7±37.7 vs. 35.5±14.8 mIU/ml, respectively, P<0.001) and the optimal cut-off β-hCG level value of 75 mIU/ml gave the sensitivity of 76%, specificity 91.6%, positive predictive value 95.0% and negative predictive value as 79.9%[19].

Another similar study by Garshashbi et.al including 540 patients having preterm labour found 3.2 fold increase of cervico-vaginal β-hCG in preterm than in term delivery and a single cervicovaginal β-HCG >77.8mIU/ml, between 20 and 28 weeks gestation, identified patients with subsequent spontaneous preterm birth vs. term delivery with sensitivity of 87.5% (95% CI: 47.4–97.9) and a specificity of 97% (95% CI: 86.5–99.4) with positive and negative predictive values of 88.5% and 98%, respectively. Multiple logistic regression indicates that cervicovaginal β-HCG level >77.8mIU/ml was an independent predictor of spontaneous preterm birth (adjusted odds ratio 19.97, 95% CI: 10.65–37.45) [20]. Adhikari et.al in his study found that to predict delivery <34 weeks, cervicovaginal HCG >14 mIU/ml had sensitivity, specificity, PPV and NPV of 83.3%, 85.5%, 33.3% and 98.3% respectively [21]. Bahasadri et.al. in a cross-sectional study including 123 women reported that β-hCG was higher in the cases of preterm premature rupture of membranes (PPROM) and it may be used as a suitable, fast and reliable test for detecting rupture of membranes [22]. Similar study by Esim et. al (2003) including 141 patients observed significantly higher level of β-hCG in confirmed PROM group compared to suspected or unconfirmed PROM and control group [23]. Bagga et.al (2010) included cervical length and β-hCG and reported higher level of cervico-vaginal β-hCG in preterm delivery compared to term delivery[24].

CONCLUSION

This study showed that β-hCG values levels in cervico-vaginal secretions were higher in patients who came with preterm labour pain and had preterm delivery as compared to patient with preterm labour pain with term delivery and normal pregnancy with no preterm labour pain. Cut off value of β-hCG >19.16 mIU/ml in cervico-vaginal secretion can be used as predictor of preterm delivery in patients presenting with preterm labour.

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