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An analysis of cervicovaginal β -HCG and prolactin levels as a predictive biomarker of preterm birth in symptomatic women

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Abstract

Background: Preterm birth is a major cause of neonatal and infant illness and mortality in developing countries. It is associated with severe suffering for both the mother and neonate as well as long-term disabilities; hence interventions to prevent preterm birth are critical. Therefore, accurate markers for determining whether a pregnant woman is at high risk for preterm delivery could lead to better surveillance and more timely intervention to improve outcomes.

Aims: To determine and compare predictive value of cervicovaginal β -Human Chorionic Gonadotropin (β -hCG) and Prolactin levels for preterm delivery in symptomatic women.

Materials & Methods: All the consenting eligible pregnant women between 28 to 36 weeks gestation who were hospitalized with symptoms of preterm labour were recruited for the study. One cervicovaginal fluid sample per woman was collected and quantitative estimation of β -hCG and Prolactin with Enzyme Linked Immunosorbent Assay (ELISA) kits was done. They were followed up till their delivery and divided into two groups depending on the outcome i.e., whether they had a term delivery or preterm delivery.

Results: A total of 40 women were involved in the analysis of which 28 (70%) progressed to have a preterm delivery and the rest 12 (30%) continued till term. The association between delivery outcome and mean cervicovaginal β -hCG and Prolactin levels was found to be statistically significant with p-value < 0.001. The optimal cut-off value for cervicovaginal β -hCG in predicting preterm delivery was reported to be greater than 15.54 mIU/ml, with specificity, sensitivity, negative predictive value and positive predictive value of 100%, 60.7%, 52.2%, and 100% respectively. Whereas, the specificity, sensitivity, negative predictive value and positive predictive value of cervicovaginal prolactin at a cut-off of greater than 6.24 ng/ml in predicting preterm delivery were found to be 83.3%, 89.29%, 76.9%, and 92.6% respectively. The area under the receiver operating characteristic (ROC) curve for cervicovaginal β -hCG and Prolactin levels was 0.820 and 0.920 respectively.

Conclusion: Cervicovaginal Prolactin level was found to be a better predictor of preterm delivery in symptomatic women when compared to cervicovaginal β -hCG level.

Keywords: β - Human chorionic gonadotropin (β -HCG), prolactin, preterm delivery, predictor

Introduction

Preterm birth, as described by WHO, is "Any birth before 37 completed weeks of gestation or fewer than 259 days of gestation since the first day of the last menstrual period [1]." Approximately 15 million premature babies are born yearly with around 1 million deaths being attributed to the complications arising from prematurity [2]. Preterm birth is responsible for approximately 75% of neonatal deaths, with the majority of them occurring in babies born before 34 weeks of gestation [3-4]. Predisposing factors include maternal, fetal, and placental factors, as well as mechanical factors like cervical incompetence and uterine overdistention, bacterial infection, inflammation, and hormonal changes [5].

Preterm labour has traditionally been diagnosed using clinical indicators such as symptoms, history of preterm birth, and clinical examination [6]. Although several biochemical markers such as phosphorylated insulin-like growth factor binding protein-1, Plasma urocortin, fetal Fibronectin, and hCG, are currently being investigated, no single biomarker with the sensitivity and reliability to detect spontaneous preterm birth has emerged to date [7-9]. A single biomarker or even a combination, if found, can help expedite timely intervention, improve the outcome and reduce the associated perinatal morbidity and mortality.

During pregnancy, prolactin, a protein, is secreted by amnion, decidua, cytotrophoblast, and

syncytiotrophoblast whose content in amniotic fluid peaks during 2nd trimester and then plateaus thereafter [10-12]. β -hCG is a glycoprotein secreted by syncytiotrophoblast during pregnancy, with fluctuating concentrations in maternal serum, amniotic fluid, and urine. It is found in high concentrations until 20 weeks of pregnancy but then falls to a steady low level in the second and third trimesters [13].

The rationale behind the presence of both these markers i.e., β -hCG and prolactin in the cervicovaginal fluid have been hypothesized to be due to subclinical membrane rupture or injury or decidual-membrane separation during the process of labour which could serve as effective predictors of preterm birth [14].

Various studies have shown the presence of β -hCG and prolactin in cervicovaginal fluid and have established the importance of these biomarkers in preterm labour. However, there is a dearth in studies comparing the diagnostic value of these markers in predicting preterm birth. Hence, this study has been planned to further the knowledge about potential biomarkers that could possibly help in predicting preterm births.

Materials and Methods

This was a prospective study which was conducted on women with singleton pregnancies with gestational age between 28 weeks to 36 weeks admitted to the labour room with labour pains associated with uterine contractions of 4 or more in 20 minutes, cervical dilatation < 3 cms, effacement of < 80%, with intact membranes with absence of any other maternal or fetal complications such as pregnancy induced hypertension, diabetes in pregnancy, antepartum hemorrhage (abruptio placenta, placenta previa), chorioamnionitis, fetal growth disorders & fetal congenital anomalies.

The gestational age was calculated according to the first day of last menstrual period (LMP) and confirmed by the early second trimester ultrasound. If the difference between them was more than ten days, then the gestational age as reported by the ultrasound scan was considered. Also, when the women was unsure of her LMP, the gestational age as determined by the ultrasound was considered.

The approval for the study was obtained from the Institutional ethics committee. Informed written consent was taken from the study participants and only those participants who had given consent were included in the study.

A detailed history was taken from the consenting women following which cervicovaginal fluid samples were obtained prior to per vaginal examination. For obtaining samples, a sterile cotton-tipped swab was first placed in endocervical canal and later in the posterior fornix for 20-30 seconds each which was then put in a sterile tube comprising of 1 ml of saline solution. This solution was shaken for 1 minute, then centrifuged at a speed of 2000 rpm for 20 minutes. The supernatant was quantitatively assayed for prolactin and β -hCG using Enzyme Linked Immunosorbent Assay (ELISA) kits manufactured by Shanghai Coon Son Biotech Co., Ltd, China.

Irrespective of tocolysis, they were followed up until their delivery and divided into two groups depending on the outcome i.e., Group I: women who arrived in preterm labour and gave birth prematurely & Group II: Women who arrived in preterm labour and went on to have a term delivery. All the relevant parameters were collected and documented in a structured study proforma.

Data was entered into Microsoft excel data sheet and analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chi-

square test or Fischer's exact test (for 2 x 2 tables only) was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test was used as a test of significance to identify the mean difference between two quantitative variables. Receiver operating characteristic curves (ROCs) were constructed for both β -hCG and Prolactin in predicting preterm delivery and optimal cut-off points was chosen for the calculation of sensitivity, specificity, positive and negative predictive values.

Results

The final analysis consisted of 40 subjects with ages varying from 18 - 33 years. The mean cervicovaginal β -hCG level was highest (24.6 mIU/ml) among the 30 to 33 years age group. No significant statistical difference was seen between cervicovaginal β -hCG levels between groups of different ages with $p > 0.05$ (Figure 1 and Table 1). The mean cervicovaginal Prolactin level was highest (11.09 ng/ml) among the 30 to 33 years age group followed by the 18 to 21 years age group (11.033ng/ml). The association between cervicovaginal Prolactin level and age was significant statistically with $p < 0.05$ (Fig 2 and Table 2). Out of 40 subjects, 20 (50%) subjects were Primigravida and the rest 20 (50%) subjects were Multigravida. The result shows no significant statistical difference between parity and cervicovaginal β -hCG and Prolactin levels with $p > 0.05$ for both (Figure 3 and Table 3). Among 40 subjects, 3 (7.5%) subjects belonged to very preterm, 13 (32.5%) subjects belonged to moderate preterm, and the maximum subjects i.e., 24 (60%) belonged to late preterm. Mean cervicovaginal β -hCG level was highest i.e., 34.39 ± 1.5 mIU/ml among subjects with very preterm gestation followed by subjects with moderate preterm gestation (17.76 ± 7.7 mIU/ml) and late preterm gestation (13.07 ± 7.6 mIU/ml). The association between gestational age at sample collection and cervicovaginal β -hCG level was observed to be significant with $p < 0.001$ statistically (Figure 4 and Table 4).

Mean cervicovaginal Prolactin level was found to be highest i.e., 12.61 ± 0.79 ng/ml among subjects with very preterm gestation followed by subjects with late preterm gestation (9.9 ± 4.2 ng/ml) and moderate preterm gestation (8.68 ± 4.7 ng/ml). There was no significant difference found between gestational age at sample collection & mean cervicovaginal prolactin level with p of 0.342 value statistically (Figure 5 and Table 5). Out of 40 subjects, majority of them i.e., 28 (70%) progressed to have a preterm delivery while 12 (30%) of them continued till term and had a term delivery. Mean cervicovaginal β -hCG level was found to be more among subjects with preterm delivery (19.20 mIU/ml) as compared to term delivery (9.43 mIU/ml). There was a significant difference observed between delivery outcome & mean cervicovaginal β -hCG level with p -value < 0.001 statistically (Fig 6 and Table 6). Mean cervicovaginal Prolactin level was found to be more among subjects with preterm delivery (10.88 ng/ml) as compared to term delivery (4.95 ng/ml). There was a significant difference observed between delivery outcome & mean cervicovaginal Prolactin level with p -value < 0.001 statistically (Figure 7 and Table 7).

The area under the cervicovaginal β -hCG curve was 0.820 whereas, for cervicovaginal Prolactin, it was 0.920. Therefore, cervicovaginal Prolactin is slightly better than cervicovaginal β -hCG in predicting preterm delivery. The specificity and PPV (100%, 100%) of cervicovaginal β -hCG in predicting preterm delivery was comparatively higher than that of cervicovaginal Prolactin (83.3%, 92.6%) whereas, the sensitivity and NPV of cervicovaginal prolactin (89.29%, 76.9%) was comparatively

higher than that of cervicovaginal β -hCG (60.7%, 52.2%) (Figure 8 and Table 8).

Discussion

The present study sought to compare and correlate cervicovaginal β -hCG and Prolactin levels as a predictor of preterm birth in symptomatic women. In present analysis, out of 40 subjects, majority (47.5%) belonged to group of age 22-25 years followed by 27.5% belonging to 18 - 21 years group with a mean of 23.7 ± 3.53 years. Radwan AM *et al.* [15], performed a study on 120 women of which 80 of them presented with symptoms of preterm labour whose mean age was reported to be 25.57 ± 4.03 years. Similarly, the mean age was found to be in that of the comparable range in research conducted by Gupta R *et al.* [16], Garshasbi *et al.* [17], and Gurbuz *et al.* [18] where the mean ages were identified to be 25.19 ± 4.1 years, 24.7 ± 6.3 years and 25.8 ± 4.7 years respectively.

In the present study, there was equal distribution between primigravida (50%) and multigravida (50%). However, contrasting results were obtained in a study by Gupta R *et al.* [16], where the majority (67.1%) belonged to the multigravida group, and in a study by Sanchez Ramos *et al.* [19], where 66.3% belonged to the multigravida group. In the present study, 70% progressed to have a preterm delivery while 30% continued till term. A similar outcome was observed in research done by Gurbuz *et al.* [18] where 78.4% of the women had preterm delivery. In a research done by Radwan AM *et al.* [15], 50% of them progressed to preterm delivery. In the present research, the association between gestational age at sample collection and cervicovaginal β -hCG level was statistically significant. Similarly, a significant difference was observed between delivery outcome and β -hCG where cervicovaginal β -hCG levels were found to be significantly more among subjects with preterm delivery. This was in concordance with the results obtained by Gupta R *et al.* [16], where the preterm group was considerably greater β -hCG levels (39.38 ± 19.66 mIU/ml) compared to the term group (21.86 ± 11.18 mIU/ml). Similar findings were found by Mishra *et al.* [20], Radwan AM *et al.* [15], Garshasbi *et al.* [17], Guvenal *et al.* [21], Ranjbar *et al.* [22] among many others.

The current study showed no significant relationship between the parity and mean cervicovaginal β -hCG level, although the levels in primigravida (13.66 ± 7.52 mIU/ml) were low as compared to multigravida (18.89 ± 9.6 mIU/ml). Radwan AM *et al.* [15] reported an insignificant and negative correlation between parity and mean β -hCG level. Through the receiver operating characteristic curve, the present study obtained optimum cut-off of β -hCG level in predicting preterm delivery as > 15.54 mIU/ml, with specificity, sensitivity, NPV, and PPV of 100%, 60.7%, 52.2%, and 100% resp. The current study's findings were compared to those of other research conducted by Bernstein *et al.* [23], who showed that a cervicovaginal β -hCG cut-off level of > 50 mIU/ml before 34 weeks of pregnancy has specificity, sensitivity, negative and positive predictive values of 87%, 50, 93, and 33%, resp. Table 9 compares the results of several investigations to evaluate the optimum cut-off for cervicovaginal hCG with respect to specificity, sensitivity, NPV, and PPV.

In present study, the highest level of prolactin was seen in women in the 30 - 33 years age group and the association between cervicovaginal prolactin and age was statistically significant. On the contrary, no statistical significance was observed in maternal age and prolactin levels in a research by

Mazor *et al.* [24]. In current study, mean cervicovaginal Prolactin level was observed to be highest among subjects with very preterm gestation. The present study showed a statistically significant variation between mean cervicovaginal Prolactin level and delivery outcome. Mean cervicovaginal Prolactin levels were found to be significantly more among subjects with preterm delivery (10.88 ± 3.52 ng/ml) as opposed to term delivery (4.95 ± 2.49 ng/ml). Similar results were obtained in a study by Mehrotra S *et al.* [25] (11.81 ± 9.3 ng/mL in women having preterm delivery vs 4.61 ± 6.2 ng/mL in women having term delivery). According to O'Brien *et al.*, [26] cervicovaginal Prolactin level was more in preterm labouring women compared to asymptomatic controls ($p < 0.0001$; 50% vs. 5%). Similarly, the prolactin levels in the preterm group were found to be considerably higher than those in the term delivery group by Guvenal *et al.* [21]. Comparison of various studies for optimal cut-off of cervicovaginal Prolactin with Specificity, Sensitivity, NPV, and PPV is illustrated in Table 10.

Through the receiver operating characteristic curve, the present study obtained the optimal cut-off of cervicovaginal Prolactin level in predicting preterm delivery as > 6.24 mg/ml, with specificity, sensitivity, NPV, and PPV of 83.3%, 89.29%, 76.9%, and 92.6% respectively. In patients who were symptomatic and delivered before 37 weeks of gestation, O'Brien *et al.*, [26] provided cut-off values > 2 mg/mL with specificity of 79%, sensitivity of 88%, NPV of 65%, and PPV of 80%. In the research by Guvenal *et al.* [21], prolactin readings > 1.8 ng/mL were considered positive. According to these numbers, the cervicovaginal prolactin had sensitivity, specificity, PPV, and NPV of 50%, 96%, 67%, and 93%, respectively, for predicting preterm birth. The area under the curve in current research for cervicovaginal β -hCG level was 0.820 while that for cervicovaginal Prolactin level was 0.920. This indicates that cervicovaginal Prolactin is slightly better than cervicovaginal β -hCG in predicting preterm delivery. A similar conclusion was drawn by Guvenal *et al.* [21].

Table 1: Association between age and cervicovaginal β -hCG level (N=40)

	Age group (In years)	n	Mean	Standard Deviation	P-value
Cervicovaginal β -hCG level	18 - 21	11	15.94	7.10	0.267
	22 - 25	19	15.32	9.88	
	26 - 29	6	14.33	6.28	
	30 - 33	4	24.60	10.41	

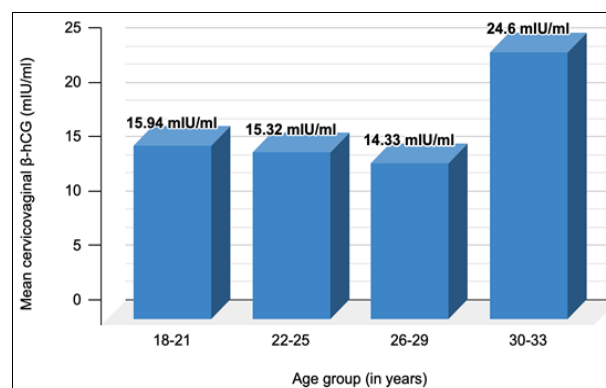
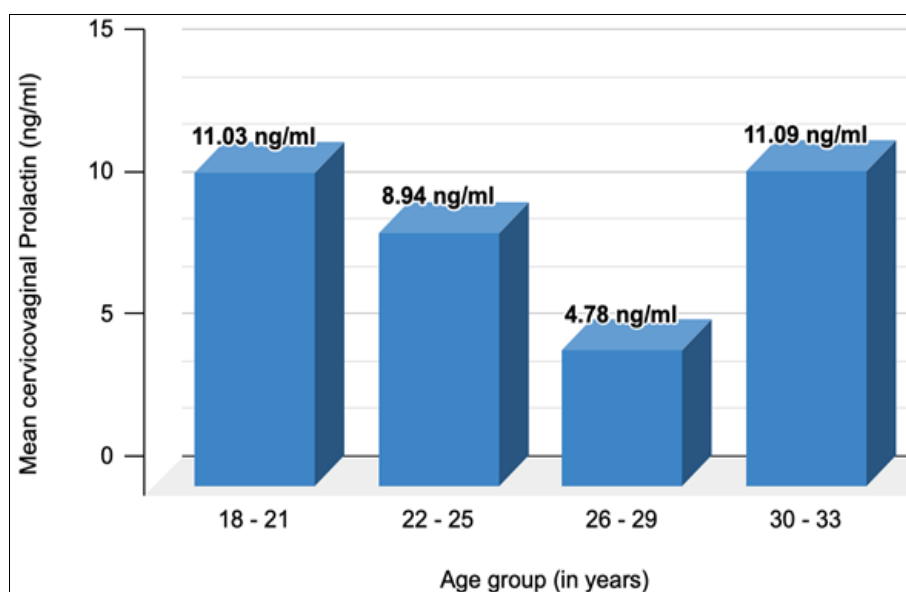


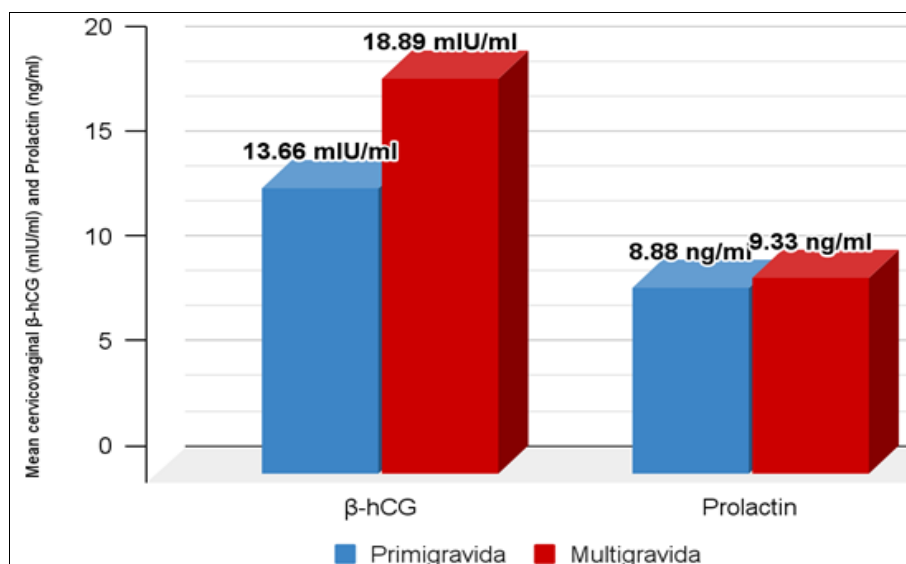
Fig 1: Bar chart showing comparison of age and mean cervicovaginal β -hCG level (N=40)

Table 2: Association between age and cervicovaginal Prolactin level (N=40)

	Age group	n	Mean	Standard Deviation	Standard Error	P-value
Cervicovaginal Prolactin level	18 - 21	11	11.03	3.61	1.08	0.018
	22 - 25	19	8.94	3.94	0.90	
	26 - 29	6	4.78	2.59	1.05	
	30 - 33	4	11.09	5.36	2.68	

**Fig 2:** Bar chart showing comparison of age and mean cervicovaginal Prolactin level (N=40)**Table 3:** Association between parity and cervicovaginal β -hCG and prolactin levels (N=40)

	Parity	n	Mean	Standard Deviation	P-value
β -hCG (mIU/ml)	Primigravida	20	13.66	7.52	0.063
	Multigravida	20	18.89	9.60	
Prolactin (ng/ml)	Primigravida	20	8.88	4.11	0.741
	Multigravida	20	9.33	4.45	

**Fig 3:** Bar chart showing comparison of parity and mean cervicovaginal β -hCG and Prolactin levels (N=40)**Table 4:** Comparison of mean cervicovaginal β -hCG level according to gestational age at sample collection (N=40)

Gestational age	Mean cervicovaginal β -hCG level (mIU/ml)	Standard Deviation	P - value
Very Preterm (28-31 completed weeks)	34.39	1.51	< 0.001
Moderate Preterm (32-33 completed weeks)	17.76	7.74	
Late Preterm (34-36 completed weeks)	13.07	7.65	

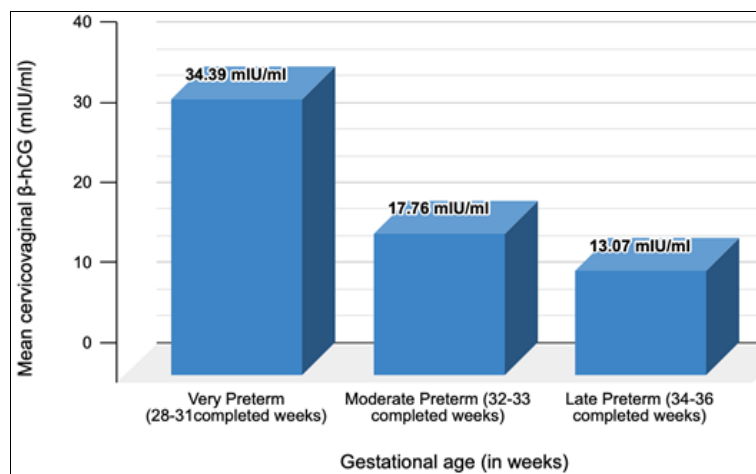


Fig 4: Bar chart showing comparison of mean cervicovaginal β-hCG level and gestational age at sample collection (N=40)

Table 5: Comparison of mean cervicovaginal Prolactin level according to gestational age at sample collection (N=40)

Gestational age	Mean cervicovaginal Prolactin level (ng/ml)	Standard Deviation	P - value 0.342
Very Preterm (28 - 31 completed weeks)	12.61	0.79	
Moderate Preterm (32 - 33 completed weeks)	8.68	4.73	
Late Preterm (34 - 36 completed weeks)	9.9	4.2	

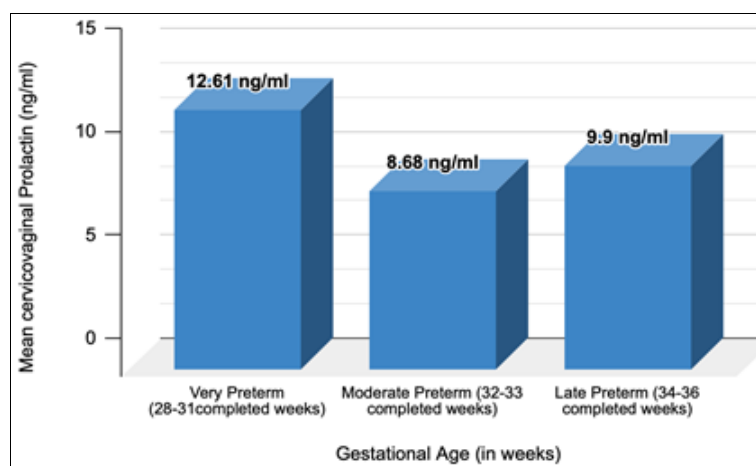


Fig 5: Bar chart showing comparison of mean cervicovaginal Prolactin level and gestational age at sample collection (N=40)

Table 6: Comparison of mean cervicovaginal β-hCG level according to delivery outcome (N=40)

	Term		Preterm		P-value
	Mean	Standard Deviation	Mean	Standard Deviation	
β-hCG (mIU/ml)	9.43	2.67	19.20	9.07	< 0.001

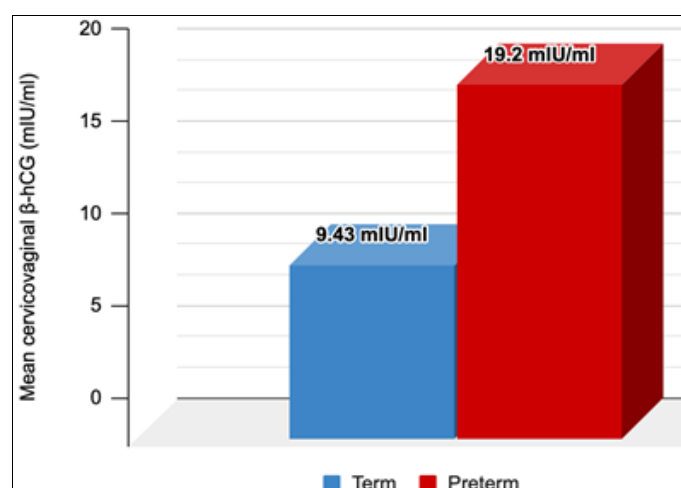
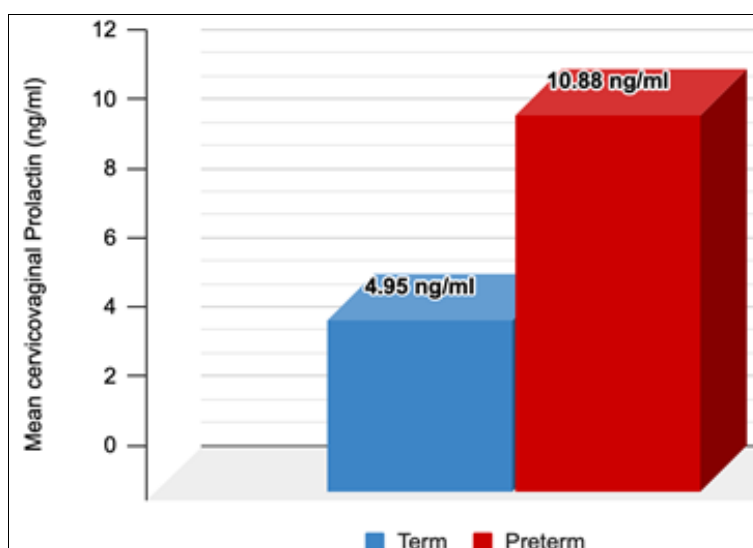


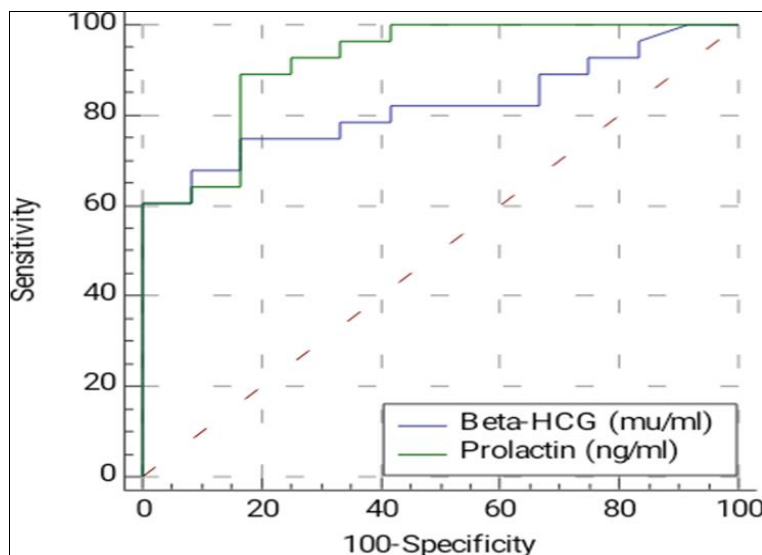
Fig 6: Bar chart showing comparison of mean cervicovaginal β-hCG level according to delivery outcome (N=40)

Table 7: Comparison of mean cervicovaginal Prolactin level according to delivery outcome (N=40)

	Term		Preterm		P-value
	Mean	Standard Deviation	Mean	Standard Deviation	
Prolactin (ng/ml)	4.95	2.49	10.88	3.52	< 0.001

**Fig 7:** Bar chart showing comparison of mean cervicovaginal Prolactin level according to delivery outcome (N=40)**Table 8:** Comparison of Sensitivity, Specificity, PPV, NPV of cervicovaginal β -hCG and Prolactin in predicting preterm delivery

	β -hCG	Prolactin
Sensitivity	60.7%	89.29%
Specificity	100.00%	83.3%
PPV	100.0%	92.6%
NPV	52.2%	76.9%

**Fig 8:** Comparison of Receiver Operating Characteristic (ROC) curves for cervicovaginal β -hCG and Prolactin level in predicting preterm delivery**Table 9:** Comparison of various studies for optimal cut-off of cervicovaginal β -hCG with Sensitivity, Specificity, PPV, NPV

Study	Study Population	β -hCG Cut- off level (mIU/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV %
Present study	40	15.54	60.7	100	100	52.2
Bernstein <i>et al.</i> [23]	77	50	50	87	33	93
Guvenal <i>et al.</i> [21]	60	27.1	87.5	65.4	28	97
Gupta R <i>et al.</i> [16]	134	36.45	71.9	81.8	74.5	79.7
Sanchez Ramos <i>et al.</i> [19]	86	19	55.6	71.2	46.9	77.8
Radwan <i>et al.</i> [15]	80	11	92.5	67.5	74	90
Garshasbi <i>et al.</i> [17]		540				
	20-24 weeks	77.8	66.7	86.5	33	94
	24-28 weeks	90.9	80	92.2	63	74

Adhikari K <i>et al.</i> [27]	75					
	Delivery <37 weeks	4.75	70	61.81	40	85
	Delivery <34 weeks	22.12	83.3	85.50	33.3	98.3
Ibrahim IM <i>et al.</i> [28]	390	34.5	100	98.79	93.75	100
Bagga R <i>et al.</i> [29]	100	45	85.7	80	69.76	91.2

Table 10: Comparison of various studies for optimal cut-off of cervicovaginal Prolactin with Sensitivity, Specificity, Positive predictive value, Negative predictive value

Study	Study Population	Prolactin Cut-off level (ng/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Present study	40	6.24	89.29	83.3	92.6	76.9
O' Brien <i>et al.</i> [26]	40	2	88	79	80	65
Guvanal <i>et al.</i> [21]	60	1.8	50	96	67	93
Mehrotra <i>et al.</i> [25]	75	7	80	80	88.64	64.52

Conclusion

It can be concluded that cervicovaginal prolactin and β -hCG levels can be used as potential biomarkers for the prediction of preterm birth in symptomatic women and that between the two, cervicovaginal Prolactin is marginally a better predictor. More importantly, the study also reports a high negative predictive value of cervicovaginal Prolactin as compared to other studies as well as with cervicovaginal β -hCG, because of which, its usage could lead to a reduction in unnecessary patient hospitalization and manipulative procedures or operations to some extent. The limitations of this study are that it is a single centre based study with a small sample size. Hence, larger studies at multiple centers are required to gain a better understanding of the definitive role of these biomarkers in the prediction in high-risk population.

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Author's Contribution

Not available

Conflict of Interest

Not available

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