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Human Chorionic Gonadotropin Assay in Cervicovaginal Secretions as a Predictor of Preterm Delivary

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Abstract

Preterm birth (PTB) is defined as birth before 37 weeks' gestation, accounts for 6–10% of all births and is a major contributor to neonatal and infant morbidity and mortality The aim of the current study is to assess the diagnostic accuracy of Beta-subunit of human chorionic gonadotropin (β-HCG) in cervico-vaginal secretion, as a biochemical predictor of preterm labor. A cross sectional study was conducted on(100) women between 24^{th} -36^{th} week of singleton pregnancy. The gestational age was determined by the first day of last menstrual period and confirmed by ultrasound, cervi-covaginal secretion samples was obtained through speculum examination from all the patient, the swab disposed of the sample was quantitatively tested for the level of beta-HCG, the level of beta HCG was measured by the radioimmunoassay method using a commercial kit, and the result was reported in milli-international units per milliliter, the results revealed that there was significant difference between both groups regarding S/D ratio of beta HCG (66.97- 21.45) as range S/D for preterm group was higher than full term group the qualitative test was found to have sensitivity, specificity, PPV, NPV and diagnostic accuracy to predict PTB of 68.33%, 96.06%, 75.93%, 94.35% and 91.79%,respectively, It was found to be more sensitive in the high-risk patients, but more specific in the low risk control group.

Keywords: Preterm birth, Predictor, HCG, Cervico-vaginal secretion.

1. Introduction

Preterm birth (PTB) is defined as birth before 37 weeks' gestation, accounts for 6–10% of all births and is a major contributor to neonatal and infant morbidity and mortality. Spontaneous preterm birth (SPB) accounts for about three quarters of these births and births before 30 weeks of gestation account for most neonatal deaths [1, 2].

Clinicians tend to divide preterm birth (PTB) into three subgroups: Extremely PTB (24 weeks to 27 weeks ±6 days), Very PTB (<31 weeks± 6 days), PTB (<36 weeks ±6 days)

Spontaneous preterm birth accounts for around 70% of all preterm birth and is either due to preterm labor or preterm premature rupture of membranes **[**3]. The remaining preterm births are medically induced because of fetal or maternal concerns and include abruption placentae, placenta praevia, fetal growth restriction, preeclampsia and other hypertensive diseases, and some miscellaneous cases [4].

Threatened preterm labor occurs in approximately 2% of pregnancies. However, 80% of these pregnancies will be proceed to term [5].

The diagnosis of threatened preterm labor is difficult by definition, regular contractions, with cervical effacement or dilatation, are required for diagnosing established labor [6,7]. Braxton– Hicks contractions, which occur after 24 weeks gestation, may be painful and can be misdiagnosed as preterm labor. This will lead to incorrect treatment in up to 80% of cases [8].

Preterm birth is one of the major clinical problems in obstetrics and neonatology as it is associated with perinatal mortality, serious neonatal morbidity and in some cases childhood disability. It is reported that 60-80% of all neonatal mortality and morbidity is due to preterm birth [9].

There are several factors associated with preterm birth: multiple gestation, previous preterm birth, maternal/fetal complications, low socio-economic status, drug use and assisted reproduction all increase the risk of preterm birth. The mechanisms responsible for these well-established associations are incompletely understood. In recent years, elucidation of at least some of the mechanisms of preterm birth has appeared promising as a result of the growing recognition that intrauterine infection or inflammation is common in cases of preterm birth [10].

Although various tocolytics medications prolong pregnancy minimal, once preterm labor has begun, their use is associated with potentially harmful maternal and infant side effects [11].

Hence, there is a need for a rapid, inexpensive, simple bedside test with high sensitivity and specificity for accurate prediction of preterm labor, so that unnecessary tocolysis can be avoided in women who are unlikely to have birth, whereas an appropriate intervention or referral to a higher center can be done in women likely to have preterm delivery [12].

The hypothesis that another molecule which is also manufactured by the placenta and found in cervical secretion could serve as a marker for prediction of preterm labor. This molecule is human chorionic gonadotrophin [13].

HCG consists of two subunits linked by disulfide bonds, the β subunite is consisting of 92 amino acids, it identical to & subunit of lutinizing hormone (LH), Follicular stimulating hormone (FSH) and thyroid stimulating hormone (TSH).

The β subunit is unique to HCG, containing a larger carbohydrate moiety and 145 amino acids, including a unique carboxyl terminal tail piece of 24 amino acids groups [14].

Appearance of human chorionic gonadotrophin (HCG) in both maternal serum and amniotic fluid is probably the result of directed HCG diffusion from the placenta Beta HCG had been described in cervicovaginal secretion of pregnant women [13].

β-HCG in cervicovaginal secretion mirrors the levels in the maternal serum and fluids rising until the beginning of the second trimester and then falling by 18 weeks gestation to plateau level for the reminder of pregnancy [15].

Recent literature has suggested that the presence of the beta sub unit of human chorionic gonadotrophin (β-HCG). In cervicovaginal secretion can predict preterm deliver [16].

2. Materials and methods

A study will be conducted with (100) women between 24th -36th week of singleton pregnancy.

The gestational age was be determined by the first day of last menstrual period and confirmed by ultrasound. The study was approved by the local ethics committee, and written consent be obtained after detailed information was given to every patient selected for the study.

Inclusion criteria include: Normal pregnant females with gestational age ranging between 24-36 weeks.

Exclusion criteria include: Vaginal bleeding. Premature rupture of membrane. Trauma & hypertension. Placenta previa. Abruption placenta. Fetal anomalies & cervical dilatation >4cm or more. Fetal distress and fetal growth restriction.

Every patient will be subjected to: Careful and detailed history taking. General examination. Abdominal examination. Investigation:

Ultrasound to confirm gestational age and to exclude congenital anomalies.

Before digital examination of the cervix, cervi-covaginal secretion samples was obtained through speculum examination from all the patient, as suggested by Bernstien et al.

Acotton tipped swab was placed first into endocervical canal and then into the posterior fornix each for 30 second in order to obtain the sample for assay beta HCG.

The swab was placed in a tube containing 1ml of saline solution and shaken for 1 min before the swab disposed of the sample was quantitatively tested for the level of beta-HCG, the level of beta HCG was measured by the radioimmunoassay method using a commercial kit, and the result was reported in milli-international units per milliliter.

3. Results

Total number of full term group was 88 (80%). The incidence of small for gestational age (SGA) newborn (when compared to the total number of each study group) was higher among preterm than term deliveries: (58.3%) versus (11.4%) while the incidence of appropriate gestational age (when compared to the total number of each study group) is higher among term deliveries: (88.6%) versus (41.7%).

Table (1) Comparison between both preterm and full-term group regarding clinic demographic data on admission: Comparison between both preterm and full-term groups regarding age and gestational age:

		Pre-term	Full term	T. test	P. value
Age	Range	20 – 38	18 – 38	2.526	0.115
	Mean ± SD	27.33 ± 6.26	25.09 ± 4.33		
Gestational age	Range	26 – 34	24 – 35	0.012	0.912
	Mean ± SD	29.83 ± 2.98	29.74 ± 2.76		

- Age: not significant - Gestational age: not significant

This table shows that there was no significant difference between both groups regarding mean age (in years), gestational age at time of examination.

Table (2) Comparison between both preterm and full-term group regarding to parity, previous preterm and mode of delivery:

			Pre-term	Full term	X^2	P-value
Parity	**PG**	**N**	**2**	**16**	**0.016**	**0.898**
		%	16.7%	18.2%		
	Multi	N	10	72		
		%	83.3%	81.8%		
Previous pre-term	+ve	N	6	32	0.854	0.355
		%	60.0%	44.4%		
	-ve	N	4	40		
		%	40.0%	55.6%		
Mode of delivery	Normal	N	7	38	1.052	0.305
		%	70.0%	52.8%		
	CS	N	3	34		
		%	30.0%	47.2%		

- Mode of delivery: not significant

This table shows that there was no significant difference between both groups regarding parity, previous pre-term and mode of delivery.

Table (3) Comparison between both preterm and full-term group regarding S/D ratio of β HCG.

β HCG	**Pre-term**		**Full term**
Range	34.90 – 95.50		15.5 – 85.5
Mean ± SD	66.97± 21.23		21.45 ± 10.46
T. test		48.183	
P. value		0.001*	

This table show that there was significant difference between both groups regarding S/D ratio (66.97- 21.45) as range S/D for preterm group was higher than full term group.

Table (4) Comparison between both preterm and full term group regarding to birth weight:

Birth weight	**Pre-term**		**Full term**
Range	1.2 – 2.3		1.5 – 3.8
Mean ± SD	1.83 ± 0.39		2.95 ± 0.36
T. test		21.668	
P. value		0.001*	

-Birth weight: significant.

The table show that theres a significant difference in birth weight between both group with P. Value Equale 0.001.

Table (5) This table shows that the incidence of SGA newborns was higher among preterm than Term deliveries:

Birth weight			**Pre-term**	**Full term**	**Total**
SGA		N	7	10	17
		%	58.3%	11.4%	17.0%
AGA		N	5	78	83
		%	41.7%	88.6%	83.0%
Total		N	12	88	100
		%	100.0%	100.0%	100.0%
Chi-square	X^2			16.512	
	P-value			0.001*	

This table shows that the incidence of SGA newborn was higher among preterm than full term :(58.3%) versus (11.4%) while the incidence of AGA is higher among term deliveries than preterm deliveries: (88.6 %) versus (41.7%).

Table (6) The sensitivity, specifity, positive predictive value and negative predictive value of β HCG S/D ratio (using cut off point) in predicting preterm labour:

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
β HCG	100	92	88	100	95

The mean cervico-vaginal β -HCG titer for the patients in PTB group was 52.25Miu/Ml while that of TB group was 15.22 Miu/Ml, the difference was statistically significant with p value<0.001.the mean cervico vaginal β HCG titer for the patient in PTB group was even higher Using the reciver operator characteristic curve the best cut of value of cervico-vaginal β HCG to predict PTB was calculated to be 34.5Mim/MI.

Preterm deliveries are those that occur at less than 37 weeks' gestational age, are account for 75% of perinatal mortality and more than half the long-term morbidity. Although most preterm babies survive, they are at increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications

Human chorionic gonadotropin (hCG) in cervical secretions was found in high concentration until 20 weeks' gestation; but after 20 weeks of gestation, it remained at a stable level, where the median levels of β-HCG were between 5.6 and 7.1 mIU/ml**.**

4. Discussion

The sources of the elevated levels of HCG in cervicovaginal secretions may be maternal serum or the amniotic fluid. Due to the moderately large size of the HCG molecule, it is unlikely that HCG leaks across the fetal membranes. It is possible that as a result of the inflammatory process that can precede the onset of labor, there is an escape of HCG from the maternal serum into thecervical secretions [17].

The idea of using cervicovaginal β-HCG detection to predict the possible occurance of spontaneous PTB is based upon the hypothesis that a subclinical inflammatory process is a final common pathway that results in spontaneous PTB, causing release of the components of maternal serum including β-HCG into the cervicovaginal secretions [15].

Also the disruption of the chorion and the decidua, that usually occur when the onset of labor is pending, will lead to the presence of β-HCG in the cervicovaginal secretions**.**

The diagnostic value of vaginal fluid β-HCG level was first described in 1997 by [13] who used it to diagnose premature rupture of membranes.One year later, [15], were the first to describe measuring β-HCG in the cervicovaginal secretion to predict PTB in high risk women.

This was followed by other 8 studies that investigated the same issue [12, 17].

Apart from the study conducted by [16].

In this study we recruited normal pregnant women with matched ages, gestational age, parity and past obstetric history [15], being the first authors to work in this issue,they had defined a control group to determine the pattern of cervicovaginal β-HCG in the normal pregnant.

The definition of high risk group based on the presence of clinical picture of threatened PTB was adopted previously by some authors [12], while the others defined their high-risk group based on the presence of risk factors for PTB [15].

We used the definition based upon their presentation, because it was found to be more predictive for the development of PTB afterwards [12].

None of the patients were receiving tocolysis, antibiotics nor dexamethasone prior to or at the time of cervicovaginal fluid sampling. Tocolysis may prolong pregnancy in those patients who are supposed to have PTB even with high cervicovaginal β-HCG levels.

It was problematic to have definitive conclusion concerning the issue of tocolysis and cervicovaginal fluid β-HCG levels this is also applicable to the administration of steroids and antibiotics because both can lead to decreased the inflammatory process and hence the cervicovaginal fluid β-HCG levels.

Apart from the study of [15], who repeated sampling every 2 weeks till delivery, the policy of single sampling of cervicovaginal β-HCG was adopted by this study and all previous studies [12].

The qualitative test was found to have sensitivity, specificity, PPV, NPV and diagnostic accuracy to predict PTB of 68.33%, 96.06%, 75.93%, 94.35% and 91.79%,respectively, It was found to be more sensitive in the high-risk patients, but more specific in the low risk control group.

This can be explained by the higher cervicovaginal β-HCG levels in the high-risk group than the low risk group patients who had PTB (60.53 ±18.94 versus 43.97 ±4.64 respectively), that led to improved test sensitivity in the expense of its specificity.

V.Cararach [17], found that positive qualitative test was associated with sensitivity of 64.3%, specificity of 70.7%, PPV of 51.4% and NPV of 80.4% for predicting PTB, while [12], estimated that sensitivity, specificity, PPV and NPV of positive test were equivalent to 78%, 95%, 90% and 88% respectively.

In this study, the performance of the quantitative test at its best cut-off value i.e.34.5 m IU/m, was found to be better than the qualitative test, this finding is different from that was previously described by [12] and. V.Cararach [17], who preferred the qualitative over the quantitative test. In comparison to the best cut-off value for the quantitative test in this study that was 34.5 m IU/m, similar values were previously described by some studies**.**

Other authors described much lower cut-off values Gayather Rengaraj [12], that reached down to 9.5 m IU/m, on the other hand [16], in their large study found the best cut-off value to be 77.8 m IU/m.

This difference in the cut-off values can be attributed to the difference in the design of these studies.

5. Conclusion

In conclusion, the qualitative test was found to have sensitivity, specificity, PPV, NPV and diagnostic accuracy to predict PTB of 68.33%, 96.06%, 75.93%, 94.35% and 91.79%,respectively, It was found to be more sensitive in the high-risk patients, but more specific in the low risk control group.

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