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ORIGINAL ARTICLE

Beta-HCG Concentration in Vaginal Fluid: Used as a Diagnostic Biochemical Marker for Preterm Premature Rupture of Membrane in Suspected Cases and Its Correlation with Onset of Labour

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Abstract

Objectives To evaluate β-hCG concentration in vaginal fluid as a biochemical marker for PPROM in suspected cases and its correlation with onset of labour.

Materials and Methods This is a prospective case–control study carried out in tertiary care centre in 1 year. Total 150 pregnant women of gestational age 28–36 week + 6 days were included and were divided into two groups: control (Group 1) ($n = 50$) normal antenatal patients. Group 2 cases with history of leaking per vaginum subdivided into two groups—Group 2A—($n = 50$) with no detectable leakage of amniotic fluid present on per speculum examination and Group 2B—($n = 50$) with minimal leaking per vaginum present upon per speculum examination (frank leaking were excluded). β-hCG level was measured by chemiluminescent microparticle assay, and all women were followed till onset of labour.

Results Mean β-hCG level in vaginal fluid was measured as 6.10 ± 8.52 mIU/mL, 57.10 ± 30.86 mIU/mL and 111.35 ± 36.01 mIU/mL in Group 1, Group 2A and Group 2B, respectively. By taking 21.5 mIU/ml as cut-off, receiver operating characteristic curve shows sensitivity 100%, specificity 92.0%, positive predictive value 92.6%, negative predictive value 100% and diagnostic accuracy 96%. Regarding the correlation of β-hCG level with onset of labour if the β-hCG level is < 21.5 mIU/ml, 100% pregnancy continued beyond 4 weeks and 56% women delivered within 4 weeks when β-hCG level is > 75 mIU/ml.

Conclusion β-hCG in vaginal fluid is a reliable biochemical marker for diagnosing suspected cases of PPROM and is well correlated with onset of labour.

Keywords β-hCG · Vaginal fluid · PPROM

Introduction

Premature rupture of membranes (PROM) is defined as rupture of the amniotic membranes before the onset of labour, regardless of gestational age [1]. Its prevalence ranges from 8 to 19.53% of term pregnancies and 2–25% of all pregnancies and is responsible for preterm birth which is one of the most important cause of perinatal mortality and morbidity throughout the world [2]. Preterm premature rupture

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of membranes (PPROM) refers to rupture of the amniotic membranes before 37 weeks of pregnancy [3].

PPROM is largely a clinical diagnosis based on history of watery discharge from vagina and confirmed on sterile per speculum examination. The traditional method for the diagnosis of PPROM relies on clinician ability to document three clinical signs on sterile per speculum examination: visual pooling of clear fluid from vagina, an alkaline pH of the cervicovaginal discharge detected by nitrazine test or microscopic ferning of the cervicovaginal discharge on drying [1].

β-hCG is a glycoprotein, biosynthesized by the syncytiotrophoblast, and is present in varying concentration in maternal serum, urine, and amniotic fluid during pregnancy. It is also secreted by the cervical glands and is present at a certain level in vaginal fluid. It is found in high concentration until 20 weeks of gestation, but after 20 weeks, it remains at a very low stable level in second and third trimester of pregnancy [2]. The mean level of β-hCG in the vaginal fluid in a pregnancy with intact membranes varies throughout the pregnancy from 37.9 mIU/mL in the first trimester to 9.5 mIU/mL in the second trimester, and from 6.3 to 7.71 mIU/mL in the third trimester. On the other hand, the β-hCG levels in pregnancies with PROM in the literature ranges from 330.88 to 468.06 mIU/mL [4].

The present study has been done to determine whether β-hCG in vaginal fluid can be used as a biochemical marker for PPROM in suspected cases; its correlation with onset of labour; its role in modifying the management and finally its role in maternal and neonatal outcome.

Materials and Methods

The present study was conducted in the Department of Obstetrics and Gynaecology in a Queen Mary Hospital from July 2018 to June 2019 in collaboration with Department of Pathology in King George's Medical University Lucknow, India.

Inclusion Criteria

The study includes 150 healthy antenatal subjects with singleton pregnancy whose period of gestation was between 28 and 36 week + 6 days (confirmed by USG and LMP) and willing to participate in the study.

Exclusion Criteria includes confirmed rupture of foetal membranes, gestational age < 28 weeks or ≥ 37 weeks, polyhydramnios, multiple pregnancy, abruptio placentae, placenta previa, presence of gross blood in vagina, symptoms of intraamniotic infections, cervical dilation of > 4 cm, congenital anomalies and preeclampsia.

Study Design

The study was a prospective case–control study comprising 150 pregnant women. The detailed history of all subjects including menstrual history, obstetrics history, presenting complaints, general examination, per abdominal and per speculum examination was done. These 150 subjects were divided into two groups: Group 1 (Control, $n = 50$) normal antenatal patients. Group 2 (Cases, $n = 100$) with history of leaking per vaginum subdivided into two groups—Group 2A—($n = 50$) with no detectable leakage of amniotic fluid on per speculum examination and Group 2B—($n = 50$) with minimal leaking per vaginum present on per speculum examination (subjects having frank leaking were excluded).

Study Procedure

Patient was laid in lithotomy position in good illumination. Sterile vaginal examination using a sterile speculum was done. In patients of Group 2B (leaking present) vaginal fluid from posterior fornix was aspirated directly through sterile 5-ml syringe, while in patient of Group 1 and Group 2A (leaking absent), vaginal fluid was aspirated 3 min after injecting 5 cc of normal saline. The samples were collected in plain vial, stored at temperature of 4–8 °C and were transported to laboratory in Department of Pathology for estimation of β-hCG level in a vaginal fluid. The sample were centrifuged for 5 min with 2500 r.p.m, and β-hCG titre was determined by Chemiluminescent microparticle assay (CMIA). Total duration of the test was 15–20 min.

Statistical Analysis

Data were collected and analysed by using Chi-square tests. It was expressed as mean ± SD. The optimum cut-off for the marker was determined by area under the receiver operating curve (a ROC). Using these cut-off points, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated. Significance level was set at p value of < 0.05.

Results

Demographic characteristics of cases and control showed no statistical significant difference ($p > 0.005$) (Table 1).

The mean value of β-hCG in vaginal fluid in Group 2B was 111.35 ± 36.01 which was significantly higher in comparison with Group 2A (57.10 ± 30.86) and Group 1 (6.10 ± 8.52) ($p < 0.001$) (Fig. 1).

Table 1 Comparison of demographic characteristics of subjects in term of age, parity, religion, residence, booking status and gestational age at time of admission

	Control	Case		*p* value
	GROUP 1	Group 2A	Group 2B	
Mean age ± SD (years)	24.60 ± 3.36	24.78 ± 3.49	24.63 ± 3.27	0.996
Parity				
Gravida 1	30 (60%)	30 (60%)	25 (50%)	0.833
Gravida 2	14 (28%)	13 (26%)	17 (34%)	
Gravida 3 or more	6 (12%)	7 (14%)	8 (16%)	
Religion				
Hindu	37 (74%)	35 (70%)	38 (76%)	0.849
Muslim	13 (26%)	15 (30%)	12 (24%)	
Residence				
Rural	31 (62%)	26 (52%)	31 (62%)	0.591
Urban	19 (38%)	24 (48%)	19 (38%)	
Booking status				
Booked	8 (16%)	12 (24%)	13 (26%)	0.500
Unbooked	42 (84%)	38 (76%)	27 (74%)	
Gestational age at time of admission				
28–31 weeks + 6 days	20 (40%)	29 (58%)	30 (60%)	0.080
32–36 weeks + 6 days	30 (60%)	21 (42%)	20 (40%)	

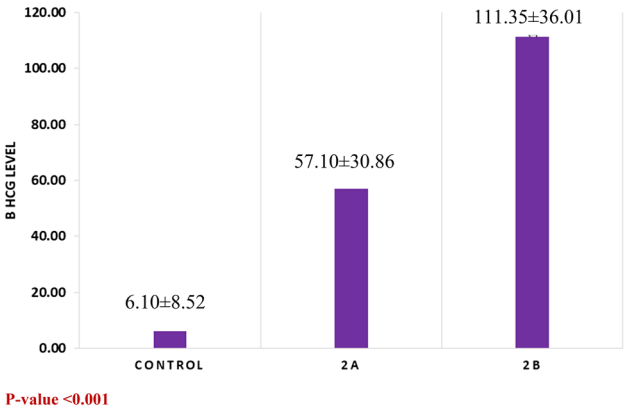

Fig. 1 Mean β-hCG levels (mIU/mL) obtained from vaginal fluid of pregnant women

Receiver operating characteristic (ROC) curve established the optimal cut-off of β-hCG in vaginal fluid as 21.5 mIU/ml. At this cut-off value, sensitivity was found to be 100%, specificity 92.0%, positive predictive value 92.6%, negative predictive value 100% and diagnostic accuracy 96% (Fig. 2).

Obstetrics characteristics among cases and control showed statistically significant difference in relation to gestational age at time of delivery, interval between complaints and delivery, type of delivery, birth weight and APGAR score. The mean birth weight and APGAR score in Group 2B was significantly lower in comparison with Group 2A and Group 1 (Table 2).

Our results showed that the value of β-hCG less than cut-off (21.5 mIU/ml) guarantees delivery after 4 weeks (NPV-100%), while the value more than 75 mIU/ml showed chances of delivery within 4 weeks in 56% women. So as the concentration of β-HCG increases duration of interval between complaints and delivery decreases (Table 3).

Discussion

β-hCG in vaginal fluid is a very good biochemical marker to determine suspected cases of PPROM and its correlation with onset of labour. Other biochemical markers used for detection of PPROM are: alpha-fetoprotein (AFP) [1, 5], foetal fibronectin (fFN) [6], insulin-like growth factor binding protein 1 (IGFBP-1) [7], prolactin [1], Creatinine [1, 8], urea [8] and placental alpha-macroglobulin 1 (PAMG-1) [7], but since the method using β-hCG is cost-effective, rapid, simple and easy to use, it is preferred over its other counterparts.

Similar study was conducted by Sak et al. [9] showed that mean neonatal birth weight and APGAR scores of neonates in the preterm group were significantly lower in comparison with the control group which is comparable with our study ($p < 0.001$) Al-Bayati et al. [10] concluded that value of β-hCG sampling in vaginal fluid was inversely proportional to duration of onset of labour. Tigga et al. [1] studied the duration from PROM to onset of labour and concluded that β-hCG is a better predictor of onset of labour in confirmed cases of PROM. Bahasadri et al. [3] and Tamer et al. [11] which showed that mean

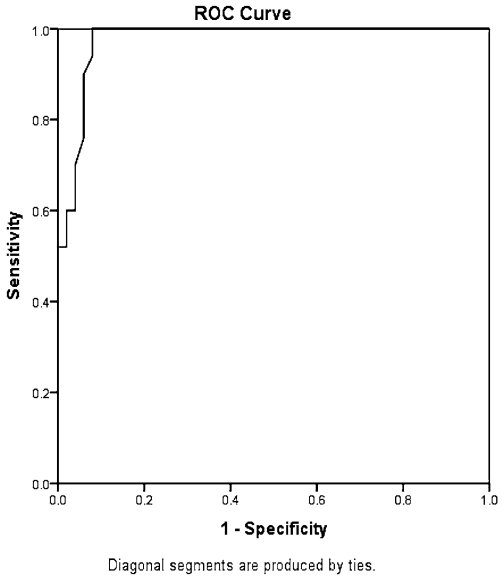

Fig. 2 Receiver–operator curve (ROC) analysis for the optimal cut-off point for vaginal washing fluid β-human chorionic gonadotrophin

Cutoff Value >=21.5
Sensitivity 100%
Specificity 92.0 %
PPV92.6%
NPV100 %
Diagnostic Acurracy 96.0%

Table 2 Comparison between obstetrics characteristic in between control group and study group

	Control	Group 2A	Group 2B	Chi sq	*p* value
GA at delivery					
28–31 weeks + 6 days	4 (8%)	9 (18.0%)	12 (24.0%)	52.40	< 0.001
32–36 weeks + 6 days	3 (6%)	12 (24.0%)	30 (60.0%)		
≥ 37 week	43 (86%)	29 (58.0%)	8 (16.0%)		
Interval between complaint and delivery					
<2 week	1 (2%)	8 (16%)	28 (56%)	71.05	< 0.001
2–3 weeks + 6 days	3 (6%)	11 (22%)	12 (24%)		
4–5 weeks + 6 days	8 (16%)	8 (16%)	9 (18%)		
≥ 6 week	38 (76%)	23 (46%)	1 (2%)		
Type of delivery					
Fullterm	44 (88%)	30 (60%)	7 (14%)	43.98	< 0.001
Preterm	6 (12%)	20 (40%)	43 (86%)		
Mean birth weight	2.52 ± 0.47	2.23 ± 0.55	1.94 ± 0.51	34.99	< 0.001
APGAR					
1 min	6.06 ± 1.68	4.73 ± 1.60	4.31 ± 1.65	14.81	< 0.001
5 min	7.54 ± 1.31	6.82 ± 1.31	6.49 ± 1.31		

β-hCG value in vaginal fluid was significantly higher in suspected cases of PPROM as compared to control. Abbas et al. [12] in addition to mean β-hCG values also pointed to the fact that mean gestational age of study group at time of delivery was lower in suspected cases of PPROM as compare to control. Similarly Elmahalawi et al. [13] concluded that the β-hCG level in cervicovaginal washing was higher in confirmed cases of PPROM as compare to normal antenatal patients (no history of leaking present).

Conclusion

β-hCG is a very sensitive marker to detect PPROM in suspected cases and can be used as an adjunctive test. It is cost-effective, simple and rapid test. Patient can be sent home, and it helps to reduce hospital stay and financial burden and avoid unnecessary interventions like

Table 3 Correlation of time interval between sampling and delivery and β-hCG values

β-hCG level versus duration	Control ($n=50$)				Case							
					Group 2A ($N=50$)				Group 2B ($N=50$)			
	< 2 weeks	2–4 weeks	4–6 weeks	> 6 weeks	< 2 weeks	2–4 weeks	4–6 weeks	> 6 weeks	< 2 weeks	2–4 weeks	4–6 weeks	> 6 weeks
< 25 mIU/mL												
No.	0	0	**8**	**38**	0	0	0	0	0	0	0	0
%	0.0	0.0	**16.0**	**76.0**	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
25–49 mIU/mL												
No.	1	3	0	0	0	1	5	**22**	0	1	0	0
%	2.0	6.0	0.0	0.0	0.0	2.0	10.0	**44.0**	0.0	2.0	0.0	0.0
50–74 mIU/mL												
No.	0	0	0	0	0	1	2	1	0	0	1	1
%	0.0	0.0	0.0	0.0	0.0	2.0	4.0	2.0	0.0	0.0	2.0	2.0
75–99 mIU/mL												
No.	0	0	0	0	**3**	**6**	1	0	**9**	**6**	7	0
%	0.0	0.0	0.0	0.0	**6.0**	**12.0**	2.0	0.0	**18.0**	**12.0**	14.0	0.0
100–124 mIU/mL												
No.	0	0	0	0	**5**	**3**	0	0	**9**	**2**	1	0
%	0.0	0.0	0.0	0.0	**10.0**	**6.0**	0.0	0.0	**18.0**	**4.0**	2.0	0.0
125–149 mIU/mL												
No.	0	0	0	0	0	0	0	0	**2**	**3**	0	0
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	**4.0**	**6.0**	0.0	0.0
≥ 150 mIU/mL												
No.		0	0	0	0	0	0	0	**8**	0	0	0
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	**16.0**	0.0	0.0	0.0

If β-hCG level < 21.5 mIU/mL—100% patient delivered after 4 week

If β-hCG level > 75 mIU/mL—56% patients delivered within 4 weeks

The bold values signify number of patients who were delivered within the specified level of beta-hcG

administration of antibiotics, corticosteroids, tocolysis therapy and induction of labour.

Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest in the study.

Research Involving Human Participants and/or Animals Yes and an informed consent were taken from the patients.

Ethical Statement A prior approval was obtained from the King George's Medical University (K.G.M.U.) of Lucknow, India ethics committee vide letter no-794/Ethics/18 to conduct this research.

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Dr. Soumya Jain is working in the Department of Obstetrics and Gynaecology KGMU, Lucknow, as a junior resident. She has completed her MBBS from Motilal Nehru Medical College Allahabad. She has presented various papers and posters in State level conference. She plans to strive and continue her work in the field of infertility.