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COMPARISON OF TWO RAPID QUALITATIVE ASSAYS (BETA-HUMAN CHORIONIC GONADOTROPIN AND PHOSPHORYLATED INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-1) FOR PREDICTION OF PRETERM BIRTH IN SYMPTOMATIC WOMEN

Gynaecology

Rajeshwari Kumari* Senior Resident, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi, India *Corresponding Author

Kiran Guleria Director Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi, India

Amita Suneja Director Professor & Head, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi, India

Neha Gami Assistant Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi, India

Priyanka Meena Senior Resident, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi, India

ABSTRACT

Introduction: Preterm birth (PTB) it has a major and significant direct and indirect effect on the economy of the nation. The use of various biophysical & biochemical markers have been used for prediction of PTB.

Aim: To compare the two rapid qualitative (QL) assays in cervicovaginal secretions as predictors of preterm birth in symptomatic women.

Methods: 120 women with symptoms and signs of preterm labor (PTL) were recruited and cervicovaginal secretions were collected for qualitative assessment of -hCG and pIGFBP-1 at admission and subsequently managed as per hospital protocol till delivery.

Results: -hCG assay was highly specific for predicting preterm birth (PTB) before 37 weeks (sensitivity of 72%, specificity 94.7%, PPV 74.6%, NPV 94%) and more sensitive for predicting PTB before 34 weeks of gestation (sensitivity 89.55%, specificity 35.6%, PPV 88.95%, NPV 37%). The sensitivity, specificity, NPV and PPV for predicting PTB within 48 hours were 86.4%, 81.6%, 91.2% and 73.1%; within 7 days were 83%, 88.1%, 86.8% and 84.6%; and within 14 days were 71.6%, 92.5%, 72.1% and 92.3% respectively.

Conclusion: Both -hCG and pIGFBP-1 assays were equally accurate (high NPV) in predicting PTB before 37 weeks in symptomatic women. The pIGFBP-1 was better in predicting PTB before 34 weeks, within 48 hours, 7 days & 14 days. βhCG assay may be preferred in low resource countries because of low cost, universal availability and equivalent predictive abilities for PTB in symptomatic women.

KEYWORDS

Preterm labour, -β-hCG, pIGFBP-1, Cervicovaginal secretions

INTRODUCTION

PTB is the leading cause of perinatal and neonatal morbidity (50%) and mortality (75%) worldwide and the rates appear to be rising[1,2]. It is also a dominant risk factor for long term impairments like neurological and developmental delay, vision and hearing disorders, thus affecting the quality of the adult population of nation. The rates of PTB is highest (85%) in low and middle income countries and according to WHO (2012) India is biggest contributor to the world's prematurity burden, with almost 3.6 million premature births accounting for 23.6% of around 15 million global preterm births. In India National Institute of Biomedical Genomic started a programme for preterm births in 2013 with a financial outlay of around 48.85 crore[3]. Thus, it has a major and significant direct and indirect effect on the economy of the nation. The use of various biophysical & biochemical markers like Home uterine activity monitoring (HUAM), uterine artery velocitometry by color flow Doppler, electromyography of uterine activity, transvaginal cervical ultrasonography, fetal fibronectin, interleukin 8, 6, 1, granulocyte elastase, -hCG and albumin and vitamin-D binding protein in cervicovaginal secretions, maternal salivary estriol estimation, salivary progesterone and increased plasma levels of CRH have been proposed to improve clinical prediction of preterm birth, but their clinical use is limited by delayed reporting, non- availability of commercial kits and inconsistent predictive accuracies[4]. 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 preterm birth whereas in others, an appropriate intervention or referral to a higher center can be done to improve neonatal outcome. Recent literature has suggested that the presence of beta subunit of human chorionic gonadotropin in cervicovaginal secretions (UPT kit) predicts preterm delivery[5]. Also phosphorylated insulin like growth factor binding protein -1(pIGFBP-1 kit) has been introduced as a commercial qualitative bedside test kit to diagnose PTL[6-8]. It detects pIGFBP-1 (>10µg/l) shed into cervicovaginal secretions, from tissue damage of chorio-decidual interface as a result of fetal membrane detachment, in early stage of labor.

This prospective study was planned to compare the efficacy of these two bedside kits (Actim Partus kit and velocit kit) in predicting PTL.

PATIENTS AND METHODS

After approval by ethical committee of our institution, 132 consecutive women with features suggestive of PTL attending the obstetric emergency of Guru Teg Bahadur Hospital, Delhi, India, over a period of 6 months were examined and finally 120 women who fulfilled the following criteria were recruited into the study for data analysis: (1) 24 to 36^{+6} weeks of gestation,(2) regular uterine contractions (at least 6 in 1 hour), (3) with or without one or more of the symptoms suggestive of PTL- abdominal pain, backache, pelvic pressure and increased vaginal discharge and (4) Intact membranes. Women with confirmed rupture of foetal membranes, presence of gross blood in the vagina, cervical dilation of more than 3 cm, known or suspected placenta previa / abruption, Cervical cerclage, trauma precipitating the patient's symptoms, congenital anomalies of uterus/foetus, prior tocolysis, signs and symptoms of chorio-amnionitis, fetal growth restriction, preeclampsia/gestational hypertension, multiple pregnancies and chronic medical disorders were excluded from the study. At recruitment, informed written consent was taken from each subject and detailed clinical profile and history was obtained. For Collection of cervicovaginal secretions two cotton tipped swabs were placed; one in endocervical canal for testing pIGFBP for 15 seconds and the second in posterior fornix for testing hCG for 1 minute. A commercially available immuno-chromatography based rapid strip test (Actim Partus Test; Medix Biochemica, Kauniainen, Finland) was used to detect pIGFBP. The swab was placed in a plastic test tube available in the kit and rinsed in buffer solution for approximately 15 seconds. The swab was then removed and dipstick was placed into the tube. Results were read after 5 minutes and interpreted as **Positive:** If two distinct blue lines appeared in the result window, **Negative:** If only one blue line appeared and **Invalid:** If no line appeared. The kit used for performing qualitative βhCG test was the commonly available UPT kit (Velocit Kit – Dr. Reddy's Laboratories, Code No. 19063). The threshold for detection is 25mIU/ml. After one minute, the other swab

from posterior fornix was removed and transferred to a plastic tube containing 1 ml of normal saline solution and tube was shaken prior to Swab's disposal. Swab containing macroscopic evidence of blood was discarded. Three drops of solution was added into the sample well and the result was read after 3 minutes and interpreted as **Positive:** If two distinct purple lines appeared in the result window, one at C (control) and one at T (test) **Negative:** If only one purple line appeared in the result window at C, **Weakly positive:** If one distinct purple line at 'C' and faint purple line at 'T' and was consider as negative in the present study and **Invalid**: If no line appeared in the result window after the migration of the sample. The managing obstetricians were blinded to the results of both tests and clinical care was administered according to hospital protocol. All women were followed up until delivery. In case patient was discharged from hospital after first admission, she was followed by means of telephonic contact, during OPD visits, subsequent admission in the hospital and delivery records.

After delivery each subject was allocated to one of the following two groups for the purpose of analysis. Women delivering before 37 weeks of gestation were allocated to **group I (preterm group)** which was further subdivided into *group1a: early preterm* (<34 weeks) and *group1b: late preterm* (34-36^{+6} weeks). The women delivering at or after 37 weeks were allocated to **group II (term group).** The subjects in two groups were compared for their demographic profile, general characteristics and the accuracy of both test kits for prediction of deliveries within 48 hours, within 7 days, early (<34 weeks) and late (≥34 weeks) preterm birth, need for tocolysis and neonatal outcomes. Demographic profile and general characteristics were compared using unpaired student t-test (quantitatively) and using Chi square test (qualitatively). Mc- Nemar was used to compare sensitivity, specificity, PPV and NPV.

RESULTS

3544 women with s/s of PTL were screened from the emergency obstetric wards over a period of one year. Out of these 132 fulfilled the recruitment criteria. Of these, four were excluded due to medical and obstetrical complications (preeclampsia-1, intrahepatic cholestasis of pregnancy-1, APH-2), two were lost to follow up, one had vaginal infection, two required preterm caesarean section due to foetal distress, one underwent cervical cerclage procedure and two declined to participate after recruitment. 120 subjects completed the study. Out of these, 64 women delivered preterm (group 1) and 56 delivered at term (group II). In preterm group 19 were early preterm and 45 were late preterm. Incidence of PTB in present study was **53.33%** (64/120). Age, SES, gravidity, parity and number of previous abortions did not turn out to be significant risk factors for PTB. History of UTI in present pregnancy and history of previous PTB were significant risk factors for PTB **(p=0.001**). The clinical symptoms and obstetrical parameters did not differ in two groups except effacement of cervix and fetal station; both of which significantly advanced in group 1 at initial recruitment.

Majority of women 50/64 (78.1%) in group 1 tested positive for pIGFBP and in group II only 2/56 had a positive test, the difference was highly significant (**p=0.001**). This test was found to be highly specific (96.4%) and moderately sensitive (78.1%) with a PPV of 96.2% and NPV of 79.4% **(Table 1).**

Table 1: Qualitative hCG and qualitative pIGFBP response in group I and group II

Qualitative βhCG	Group I (n=64)	Group II (n=56)	p-value
Positive(n=49)	46(71.87)(TP)	3(5.35)(FP)	0.001
Negative (n=71)	18(28.12)(FN)	53(94.64)(TN)	
Qualitative pIGFBP			
Positive (n=52)	50(78.12)(TP)	2(3)(FP)	0.001
Negative (n=68)	14(21.87(FN)	54(96.42)(TN)	

In group Ia all women had positive test and in group Ib (68.88%) women had a positive test, the difference not being significant (p=0.006) inferring thereby that pIGFBP-1 performed equally well in prediction of both early and late PTB (Table 2). Similarly in group I majority of women 46/64 had positive hCG, test and in group II only 3/56 tested positive. The difference between these two groups was highly significant **(p=0.001) (Table 2).** In group Ia) majority 17/19 (89.47%) had positive test and in group Ib 29/45 (64.44%) had a positive test **(Table 2)**. Thus inferred that hCG assay performed equally well(highly sensitive and high NPV) in predicting early and late preterm deliveries.

Table 2: Qualitative hCG and pIGFBP response in group Ia and group Ib

Qualitative βhCG	Group Ia (n=19) n (%)	Group Ib (n=45) n (%)	p-value
Positive (n=46)	17(89.47)	29(64.44)	0.42
Negative (n=18)	2(10.52)	16(35.55)	
Qualitative pIGFBP-1			
Positive (n=50)	19(100)	31(68.88)	0.06
Negative (n=14	0(0)	14(31.11)	

The sensitivity, specificity, PPV and NPV of hCG for predicting PTD before 37 weeks were72%, 94.7%, 94%, and 74.6% respectively which was comparable to sensitivity, specificity, PPV, and NPV of pIGFBP-1 : i.e. 78.1%, 96.4%, 96.2% and 79.4% respectively.

In present study 7/8(86%) had positive hCG response and all the eight women (100%) who delivered at less than 32 weeks of gestation had a positive qualitative pIGFBP-1 response. 11/12 (92%) had positive hCG response and all 12(100%) women had positive qualitative pIGFBP-1 response, who delivered between 32-34 weeks. Qualitative hCG assay predicted 28/44 (64%) and predicted qualitative pIGFBP-1 assay 30/44 (68%) women between 34-36+6 weeks. Therefore, we observed that qualitative pIGFBP-1 assay to be marginally better than in predicting PTB before 34 weeks of gestation. The predictive ability of both the assays was equivalent between 34-36^{+6} weeks of gestation. These assays were further compared to asses which of the two are better in predicting birth at various intervals after admission. 44/120 (36.7%) women delivered within 48 hours after admission, βhCG predicted 36(30%) and pIGFBP-1 predicted 38 (31.7%) of these cases correctly. The sensitivity, specificity, PPV and NPV of qualitative βhCG was81.8%, 82.8%, 73.5% and 88.7% and of pIGFBP-1 is 77.4%, 88.1%, 83.7% and 83.1% respectively. Both βhCG and pIGFBP-1 assays, were found to have a high NPV for delivery within 48 hours, which is crucial for completion of corticosteroid therapy. There is a gradual decline in sensitivity and NPV of both these assays for predicting PTB after 48 hours to upto 7 days and 14 days, although specificity and PPV gradually increases **(Table 3**). If the test is negative at admission, this will help us in counselling and reassuring the patient and leave us enough time to complete the course of corticosteroid therapy. On the other hand, if test is positive at admission, we should exhaust all our treatment options (corticosteroid, tocolysis, surfactant and referral to advanced neonatal centres).

Table 3: Comparison of diagnostic accuracy of Qualitative hCG and pIGFBP-1 response in predicting admission to delivery interval

	Assay	Delivery within 48 hours	Delivery within 7 days	Delivery within 14 days
Sensitivity	pIGFBP-1	86.4	83	71.6
	βhCG	81.2	77.4	67.2
	p-value	0.625	0.375	0.375
Specificity	pIGFBP-1	81.6	88.1	92.5
	βhCG	82.9	88.1	92.5
	p-value	1.000	1.000	1.00
PPV	pIGFBP-1	73.1	84.6	92.3
	βhCG	73.5	83.7	91.9
	p-value	1.00	1.00	1.00
NPV	pIGFBP-1	91.2	86.8	72.1
	βhCG	88.8	83.1	69
	p-value	0.375	0.356	0.375

p value <0.05 is significant.

Thus present study shows that both these assays are almost equally accurate in predicting preterm delivery within 48 hours, 7 days and 14 days after admission. However, the cost of pIGFBP-1 kit is 10 times the cost of hCG kit, which makes hCG assay a choice in low resource setting.

DISCUSSION

Despite advances in technology and state of the art care, preterm birth with its associated perinatal morbidity and mortality represents one of the major unsolved problems in obstetrics. Recognizing the need for an inexpensive, quick and reliable predictor, in the present study, we

evaluated the predictive abilities of βhCG and pIGFBP-1 test kits in forecasting PTB. Both the tests have shown a high and almost equal predictive accuracy for prediction of preterm birth. In the current study, 41% tested positive for βhCG assay. This test has a reasonably good sensitivity (72%), a high specificity (94.7%) and high PPV (94%) and NPV of 74.6%, to predict deliveries before 37 weeks of gestation. Before 34 weeks of gestation, this test has a high sensitivity (89.5%) and NPV (88.9), but the specificity (94.7%) and PPV (37%) are low. Rengaraj G and co-workers in a previous study from our institution, observed the sensitivity, specificity, PPV and NPV of 78%, 95%, 90% and 88%, respectively, for βhCG kit in predicting PTB; which is quite similar to present study, thus reinforcing the use of qualitative βhCG assay as a simple, bedside and quick test with high specificity and PPV, to predict PTB[5]. Few other studies in literature have also found qualitative assessment of βhCG in cervicovaginal secretions as a predictor of PTB.

Several studies carried out on women with premature regular contractions have shown variable range of predictive values of cervicovaginal pIGFBP-1 for detection of spontaneous preterm delivery before 37 weeks (sensitivity: 2-100%, specificity: 65-96%, PPV: 11-96 % and NPV: 86-100%)[6-8]. We found a high PPV and specificity of this assay in our population as compared to other studies, whereas sensitivity and NPV are quite comparable with other studies. In systematic review of symptomatic women, the sensitivity, specificity, NPV and PPV of pIGFBP-1 to predict delivery within 48 hours after testing were 86.4%, 81.6%, 73.1% and 91.2% respectively, which was almost similar to the values obtained for pIGFBP-1 in the present study. In predicting PTB before 34 weeks pIGFBP-1 had high NPV of 100%. The PPV of pIGFBP-1 before 14 days was as high as 92.3% which is much higher than reported in other studies. This could be possibly due to lower cut off point set for pIGFBP concentration at 6.4µg/l in other studies, thus reducing the sensitivity, specificity and predictive rates.

On comparing, the predictive accuracies of qualitative pIGFBP assay for prediction of PTB at various intervals after admission with other studies, it was found that in present study, the sensitivity and NPV for predicting delivery within 48 hours was less but specificity and PPV was more than in study by Ting et al. The predictive accuracies for delivery within 14 days in our population was better than study by Ting and Brik et al. This assay continued to fare better in our study population (high PPV and high specificity) for predicting delivery beyond 48 hours up to 14 days. So the inference drawn from all these studies including ours, it appears that pIGFBP-1 assay consistently shows high NPV (86-100%) across all population. Therefore a negative result indicates a low likelihood of delivery, but a positive test may not be interpreted as an indication of labor or a reason for admission on its own. The present study clearly reveals that both assays (βhCG assay and pIGFBP) are highly sensitive and specific predictors of PTB possessing high NPV and showed no significant statistical difference in their performance in our study population. Both assays are rapid, bedside, simple and easy to perform without much discomfort to patients. The additional advantage of βhCG is its 10 times lower cost and universal availability of kit which makes it a preferred choice in low resource poor countries. To the best of our knowledge, no such comparative studies of βhCG and pIGFBP are available in published literature.

CONCLUSION

The present follow-up study concluded that both qualitative βhCG and pIGFBP-1 assays were simple, rapid bedside, easy to perform and equally accurate in predicting PTB. Both these assays have high NPV specially for predicting delivery within 48 hours. Thus, women having negative test results at admission can be safely observed and reassured. Since, qualitative βhCG is extremely cost effective and universally available, it is a better choice in resource poor low income countries to predict PTB in symptomatic women.

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