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Evaluation of phosphorylated insulin like growth factor binding protein-1 and sonographically measured cervical length for prediction of preterm birth in threatened preterm labor: a clinical approach

Abstract

Background and Objectives: Measurement of cervical length using Transvaginal Sonography (TVS) is commonly used to identify those patients of threatened preterm labor who are likely to deliver. Biochemical markers in cervical secretions namely fetal fibronectin and Phosphorylated Insulin like Growth Factor Binding Protien-1 (phIGFBP-1) have also been used to improve predictability. This study evaluated bedside kit test for phIGFBP-1 and cervical length measurement by TVS, individually and in combination, for prediction of preterm birth in patients with threatened preterm labor.

Material and Method: A prospective observational study was conducted at a tertiary centre in India where women between 28+1 and 36+6 weeks period of gestation with threatened preterm labor were recruited and rapid bed-side test for phIGFBP-1 and TVS for measurement of cervical length were done. Patients were followed till delivery and data was collected and analysed.

Results: 468 patients completed the study. Statistical analysis of sensitivity, specificity, PPV and NPV showed that phIGFBP-1 was a better predictor of preterm birth compared to cervical length. There was very good correlation of phIGFBP-1 for prediction of delivery in the crucial period of next 7 days with a kappa of 0.833 (0.780-0.886). Cervical length and phIGFBP-1 were shown to be independent predictors on multivariate regression analysis.

Conclusion: A negative result for phIGFBP-1 in cervico-vaginal secretions can predict quite accurately that threatened preterm labor will not progress to preterm birth. Cervical length measurement though reasonably good predictor, it does not add to the accuracy. In patients tested positive for phIGFBP-1, cervical length, being a time tested conventional method may be measured in selected patients and incorporated in the management algorithm in order to use the tests to guide management plan vis a vis utilizing the resources optimally.

Keywords: phigfbp-1, tvs, cervical length, preterm birth, threatened preterm labor, predictive tests

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Abbreviations: FFN, fetal fibronectin; NPV, negative predictive value; TVS, transvaginal; ROC, receiver operating characteristic

Introduction

Preterm birth which accounts for 5-13% of total births,[1] is an enigma in obstetrics as despite decades of research the precise etiology is not clear. Consequently, it is difficult to identify pregnancies which are likely to end in preterm birth. Among those presenting with threatened preterm labor, more than half do not deliver prematurely even without any treatment.[2] Predicting the outcome in patients with threatened preterm labor is important as by treating those who are likely to deliver preterm, perinatal outcome can be improved. The prediction is easier in patients of threatened preterm labor where tests for fetal fibronectin (FFN) and Phosphorylated Insulin like Growth Factor Binding Protien-1(phIGFBP-1)[3,4] and sonologically measured cervical length[5,6] have been used with varying degrees of accuracy.

A study had been conducted earlier to compare bedside test for phIGFBP-1 and FFN in a cohort of patients with threatened preterm labor pains.[7] Secondary analysis of the same data is now being presented where FFN test has been excluded as its specificity and negative predictive value (NPV) were much lower than for phIGFBP-1 test. Sonologically measured cervical length by transvaginal route (TVS) has been added to phIGFBP-1 in an attempt to evaluate the two tests as predictors of preterm birth and whether their combined use adds to the predictive accuracy. Retrospective analysis of the previous data was done with the aim to create a model that can be put into practical use in the clinical setting and to analyze if this could reduce the number of patients being hospitalized for treatment of threatened preterm labor.

Material and methods

A prospective observational study was conducted in a cohort of

patients who presented with threatened preterm labor. The details of ethical clearance, patient selection and material used have already been published.[7] In addition, TVS for cervical length measurement was done using following method. Patient was laid in lithotomic position after emptying the bladder. The transvaginal probe was placed in anterior fornix without undue pressure. Cervix was focused in sagittal plane such that the image occupies 75% of the screen and length of the end cervical canal was measured from internal so to external so in a straight line. Three measurements were taken and the shortest of the three was taken as final cervical length.

The tests used for the statistical analysis have also been detailed earlier.[7] Additionally, for analysis in this study, receiver operating characteristic (ROC) curve was plotted and best cervical length cut off was calculated for prediction of overall preterm births i.e. births at less than 37 weeks gestational age and early preterm births i.e. birth at less than 34weeks gestational age. Univariate and multivariate analysis was performed for the two predictors. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

Results

Of 550 recruited patients, complete data of 468 patients was available for which analysis was done. Rest of the patients were excluded as they either lost to follow up or delivered elsewhere and final outcome data was not available.

No demographic characteristic was found to significantly affect gestational age at which delivery occurs. At the time of recruitment 5.77%(27) were between gestational age of 34 and 37weeks. Among all the patients of threatened preterm labor, 41.88%(196) delivered prior to 37weeks and 19.01%(89) delivered before 34 gestational weeks.

The total number of patients who were phIGFBP-1 positive was 35.68 %(167). Of these 95.21% delivered before 37weeks, constituting 81.12% of total preterm births and 50.29% delivered before 34 weeks, constituting 94.38% of total early preterm births. Mean gestational age at delivery among patients positive for phIGFBP-1 was 32.9 (±2.25) weeks as compared to 37.9 (±1.52) weeks among phIGFBP-1 negative patients ($p<0.001$).

For phIGFBP-1 test the sensitivity, specificity, PPV and NPV for predicting early preterm delivery were 94.38%, 78.10%, 50.30% and 98.34% respectively and the same parameters to predict delivery within next seven days of testing were 94%, 91.82%, 84.43% and 97.01% respectively (Table 1).

The NPV of phIGFBP-1 for predicting delivery in next 48 hours was found to be 98.34% with a negative likelihood ratio of 0.06. For prediction of delivery in next seven crucial days, phIGFBP-1 had best kappa of 0.833 (0.780-0.886), suggestive of very good correlation between test and gestational age at delivery.

For evaluating cervical length, ROC curve was plotted Figure 1 and the best cervical length cut off for prediction of early preterm birth was observed to be 22.5mm with sensitivity, specificity, PPV and NPV of 71.91%, 72.82%, 38.32% and 91.69%. As shown in Table 2, these statistical parameters are not significantly different from those for cervical length of 25mm, which is well documented in literature and considered to be standard for clinical use. The cut off for predicting overall preterm birth was found to be 27.5mm.

Table 1 For phIGFBP-1 test the sensitivity, specificity, PPV and NPV for predicting early preterm delivery were 94.38%, 78.10%, 50.30% and 98.34% respectively and the same parameters to predict delivery within next seven days of testing were 94%, 91.82%, 84.43% and 97.01% respectively

			Sensitivity	Specificity	Positive predictive value	Negative predictive value
Pogc[c] at Delivery	<37 weeks	phIGFBP-1[a]	81.11%	97.06%	95.21%	87.71%
		CxL[b]	71.94%	81.98%	74.21%	80.22%
		p value	0.18	0.008	0.001	0.17
	<34 weeks	phIGFBP-1[a]	94.38%	78.10%	50.30%	98.34%
		CxL[b]	79.77%	68.60%	37.37%	93.52%
		p value	0.005	0.22	0.11	0.31
Interval From Testing to Delivery	< 7 days	phIGFBP-1[a]	94.00%	91.82%	84.43%	97.01%
		CxL[b]	80.67%	78.30%	63.68%	89.57%
		p value	0.01	0.008	0.002	0.11

[a]phIGFBP-1, Phosphorylated Insulin like Growth Factor Binding Protein-1

BCxL-Cervical length (cut off < 25 mm)

[c]POG, Period of Gestation

Cervical length was less than 25mm in 40.6% of recruited patients. However, about a quarter of these delivered beyond 37gestational weeks. Of the remaining three fourths who delivered preterm, almost half delivered before 34weeks.

Table 1 compares the statistical parameters of phIGFBP-1 and cervical length as predictors of preterm birth, early preterm birth and delivery within next 7 days. It shows that phIGFBP-1 is the single best predictor.

Univariate logistic regression of cervical length of 25mm showed odds ratio of 8.62(95%CI 4.92-15.10) for predicting early preterm birth, which rose to 11.67(95%CI 7.52-18.10) for predicting overall preterm birth (Table 2). Corresponding odds ratios for phIGFBP-1 test were59.91 (95%CI 23.53-152.53) and 141.81(95%CI 64.42-312.19) respectively. All the values were statistically significant except for odds ratio of 8.62, seen for cervical length cut off of 25mm to predict early preterm birth, which was only moderately significant. Multivariate regression analysis of the dichotomized tests showed that both the tests were significant predictors which were independent of one another. Therefore these can be used both individually and in combination.

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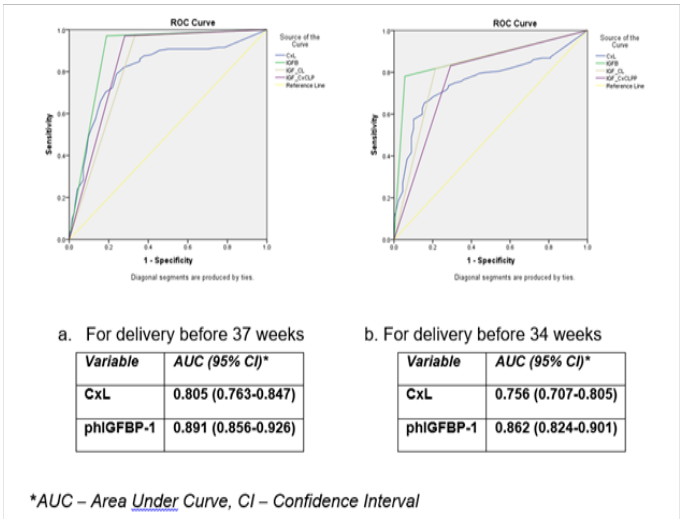
Table 2 Univariate analysis of cervical length and phIGFBP-1

	P-value	OR*	95% CI
Preterm birth (<37 Weeks)			
phIGFBP-1	0.0001	141.81	64.42-312.19
CL <2.5	0.0001	11.67	7.52-18.10
Early preterm birth (<34 Weeks)			
phIGFBP-1	0.0001	59.91	23.53-152.53
CL <2.5	0.0001	8.62	4.92-15.10

*OR-Odds Ratio



a. For delivery before 37 weeks

Variable	AUC (95% CI)*
CxL	0.805 (0.763-0.847)
phIGFBP-1	0.891 (0.856-0.926)

b. For delivery before 34 weeks

Variable	AUC (95% CI)*
CxL	0.756 (0.707-0.805)
phIGFBP-1	0.862 (0.824-0.901)

*AUC – Area Under Curve, CI – Confidence Interval

Figure 1 For evaluating cervical length, ROC curve was plotted.

As shown in Table 3, when both tests were used in combination the specificity and PPV for prediction of preterm birth prior to 37 weeks were significantly increased as compared to that of cervical length alone. However, no significant difference was observed for delivery before 34weeks. On combining cervical length with phIGFBP-1 the specificity for delivery before 34weeks improves but this improvement was not statistically significant when compared to that of phIGFBP-1 (81.99%; 78.1% respectively) alone. However, sensitivity of the combination drops significantly as compared to that of phIGFBP-1 alone.

Among patients who tested positive for phIGFBP-1, 86.23% had cervical length below 25mm. In contrast, when phIGFBP-1 was negative, 84.72% of the patients had cervical length above the cutoff of 25mm. 87.64% of births before 34weeks occurred in patients in whom both tests were positive. The two tests were in agreement with each other 85.26% of times and in rest of the 14.74% (69 out of 468), 23 tested positive for phIGFBP-1 with cervical length of more than 25mm, whereas 46 had cervical length less than 25mm but were tested negative for phIGFBP-1. Among these 69 patients, 10.14% (7 out of 69) delivered before 34weeks, all of whom belonged were phIGFBP-1 positive but had cervical length more than 25mm. This suggests that universal use of one test and selective, sequential use of another test would be the best strategy to predict the outcome of threatened preterm labor and avoiding unnecessary admissions and treatment.

Discussion

It was inferred after statistical analysis of the data (Table 2) (Table 3), that rapid bedside test for phIGFBP-1 in cervicovaginal secretions, is better than sonographically measured cervical length through transvaginal route for prediction of preterm birth among patients with threatened preterm labor. Given its high NPV, phIGFBP-1 test can be relied upon to accurately predict those cases who will not deliver when the test result is negative. Multiple regression analysis done in this study suggested that the two tests were independent, justifying their combined use.

Kekki et al.[4] were the first authors to demonstrate phIGFBP-1 as a predictor of preterm birth and determined its cut off value in cervicovaginal secretions among patients with threatened preterm labor. This was followed by many studies showing high sensitivity (70-80%) and negative predictive value (79-90%) of the test.[8–11]

Table 3 Comparison of phIGFBP-1 and cervical length, individually and in combination for prediction of preterm birth (<37 weeks) and early preterm birth (<34 weeks)

POGc at delivery		Sensitivity	Specificity	Positive predictive value	Negative predictive value
<37 week	phIGFBP-1[a]	81.11%	97.06%	95.21%	87.71%
	phIGFBP-1 + CxL	66.84%	97.06%	97.24%	80.24%
	p value	0.04	1	0.89	0.18
	CxL[b]	71.94%	81.98%	74.21%	80.22%
	phIGFBP-1 + CxL	66.84%	97.06%	97.24%	80.24%
	p value	0.56	0.0008	0.0002	1
<34 week	phIGFBP-1[a]	94.38%	78.10%	50.30%	98.34%
	phIGFBP-1 + CxL	78.65%	81.79%	50.36%	94.22%
	p value	0.003	0.58	0.96	0.56
	37.37%	79.77%	68.60%	37.37%	93.52%
	phIGFBP-1 + CxL	78.65%	81.79%	50.36%	94.22%
	p value	0.8	0.08	0.07	1

[a]phIGFBP-1, Phosphorylated Insulin like Growth Factor Binding Protein-1.
[b]CxL, Cervical length (cut off < 25 mm).
[c]POG, Period of Gestation.

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Meta-analysis by Sotiriadis et al.[12] concluded that short cervical length can be used to help scrutinize symptomatic patients for further treatment. They estimated negative predictive values of 94.8%, 96.3% and 95.8% at cervical length of 15mm, 20mm and 25mm respectively. These variable cut offs were calculated in different studies and can be attributed to heterogeneous population, variable gestational age at testing and also to inter-observer differences. After being studied in many large studies, 25mm has been defined as standard cut off value for high risk asymptomatic patients[13,14] and many studies calculated it to be the cut off in symptomatic patients as well.15 In this study, ROC curve was plotted and 22.5mm and 27.5mm were recorded as best cut off for predicting preterm birth before 34weeks and 37 weeks respectively. However the statistical parameters for 25mm and 22.5mm were not significantly different. Hence, to maintain uniformity with literature, cervical length cut off of 25mm was considered for statistical comparisons.

Only recently, few studies evaluated and compared phIGFBP-1 and cervical length in symptomatic patients. These were conducted with limited sample size. The first such study was conducted in patients who were asymptomatic but at high risk due to previous events by Bittar et al.[16] showing improved prediction by sequential combined use of cervical length in mid trimester and phIGFBP-1 detection in early third trimester, predicting 91.7% of early preterm births and 80% of total preterm births. They concluded that two tests are independent, as shown by multivariate analysis.

Paternoster et al.[17] assessed both parameters in 201 patients with threatened preterm labor and determined cervical length cut off to be 26mm with sensitivity, specificity, PPV and NPV of 86.4%, 71.9%, 34.5% and 96.8% respectively and having odds ratio of 16.18 (4.46-58.66). These parameters for phIGFBP-1 were 52.9%, 89.2%, 48.7% and 90.8% respectively with odds ratio of 9.29 (4.05-21.3). They also found the two tests to be independent of each other. The combination was shown to be better for predicting preterm birth than either test alone with a greater specificity (96.1%) and positive predictive value (64.3%) but the statistical comparison was not done. In this study similar statistical parameters for cervical length were observed with better parameters for phIGFBP-1.

Another study of 246 symptomatic patients done by Rahkonen et al.[18] concluded that for prediction of early preterm delivery, combination of phIGFBP-1 and cervical length (using 25mm cut off) had lower sensitivity but higher positive predictive value than either test alone. The high NPV of phIGFBP-1(97.6%) was found to be comparable to that of cervical length (97.4%) and hence concluded that the former is an alternative to the latter as it is cheaper and does not require great expertise in performing the test. But the study had preterm birth rate of only 4.1%, which is much lesser than usually observed.

In this study it was observed that on combining the two tests, sensitivity fell significantly as compared to phIGFBP-1 test alone. Table 3 Similarly NPV also was less but the difference was not statistically significant. The sensitivity and NPV of combination was similar to that of cervical length alone. In contrast to this, the combination had better specificity and PPV as compared to cervical length alone. However the difference was statistically significant only in predicting overall preterm birth and not for early preterm birth. Specificity and PPV remained statistically similar both for combination and for phIGFBP-1 testing alone. These results indicate the increased predictability on combining phIGFBP-1 with cervical length.

Brik et al.[19] studied the results of cervical swab phIGFBP-1 test and cervical length in 276 symptomatic women. Cut off for cervical length was observed to be 20.5mm. It was concluded that phIGFBP-1 test is a reasonable predictive test for preterm birth (sensitivity, specificity, PPV and NPV of 59%, 66%, 23.4% and 88.6% respectively) but did not improve the predictive value of cervical length considering admission to delivery interval.

Danti et al.[20] proposed that phIGFBP-1 testing is needed only among patients with cervical length between 20 and 30 mm when the specificity is low, though this study had only 60 patients. These variable results of combination of cervical length and phIGFBP-1 suggest that both the tests should only be done in selected patients in order to utilize resources efficiently.

It is well known that for a test to be used for screening it should have both high sensitivity and negative predictive value. Testing for phIGFBP-1 fulfilled these criteria, more so for delivery in the crucial period of next seven days after testing (sensitivity 94% and NPV 97.01%). The comparison of statistical parameters for both tests clearly showed that test for phIGFBP-1 is a better test. The odds ratio of phIGFBP-1 test was highly significant for predicting preterm births before 34 gestational weeks whereas, 25 mm cut off of cervical length was found to be only moderately significant for prediction of early preterm birth as suggested by odds ratio of 8.62(4.92-15.10).

Since these two tests are independent, their combination can be made use of to improve the predictive accuracy in selected patients though, which one should be done first may be questioned. The statistical parameters shown in table 3 imply that phIGFBP-1 should be done first as addition of cervical length does not confer further benefit. The additional advantage of bedside test for phIGFBP-1 is that it is also an objective, easy to perform test which does not need expertise and expensive equipment. Hence it can also be done at smaller centers by paramedics. In contrast, TVS for cervical length needs expertise and availability of an expensive machine. Hence we suggest phIGFBP-1 to be done first and TVS for cervical length to be performed in only those who test positive of phIGFBP-1.

As phIGFBP-1 has greater negative predictive value, patients with negative test can be discharged. In this study 64.31% (301) admissions of patients with threatened preterm labor pains could have been avoided. Among these patients only 1.66%(5) had early preterm birth none of which could have been predicted by cervical length alone. Specificity of the combination is more than that of phIGFBP-1 alone(81.99% vs 78.1%). Those with both the tests positive should be admitted and started on treatment as is suggested by the fact that 87.64% of those who delivered before 34 weeks fall in this group.

If the patients with positive phIGFBP-1 test result but cervical length more than 25mm had been admitted, observed and treated only if pain persisted, treatment in many could have been safely avoided. There were 23 patients falling in this group who tested positive for phIGFBP-1 but had cervical length above the cutoff of 25mm. Among these, 17 patients delivered after 34 gestational weeks in whom treatment could have been avoided safely, whereas six patients had early preterm birth. All these cases require admission and observation but treatment needs to be started only in certain cases of continuing symptoms/signs. The data has been translated into the following

algorithm Figure 2 which we suggest has practical utility without compromising maternal or perinatal safe try.

Figure 2 Suggested algorithms for management of patients with threatened preterm labor. The strength of the study was the size of the cohort studied. However, there were few limitations as well. Despite being a subjective test where inter observer variation could be present, TVS for measuring cervical length was not done by the same person. Also there were around 15% of patients who were lost to follow up. The study presents a very basic assessment of decreased cost and not a scientifically calculated cost-benefit ratio analysis. Another drawback of the approach which has been suggested here is the number of the patients which would be missed. By this approach 1.06% of total patients would deliver before 34 weeks, where treatment has not been instituted. The proposed algorithm needs to be validated by larger studies, where patients who were not given any intervention could be followed up telephonically or by paramedics conducting home visits.

To conclude, bedside phIGFBP-1 test appears to be a better test to rule out the risk of preterm birth in patients with threatened preterm labor in comparison to evaluation of cervical length. Cervical length measured by TVS has been the time tested predictor and can be done in selected patients. By following this approach we can limit the number of hospitalizations. Additionally, of those who are admitted, treatment could be avoided in many patients. This would result in saving on resources by avoiding unnecessary treatment and minimizing fetomaternal exposure to drugs. Additionally, transfer of patients to higher center can be avoided if risk of preterm birth is ruled out at smaller centers by an inexpensive and objective test with a high degree of accuracy.

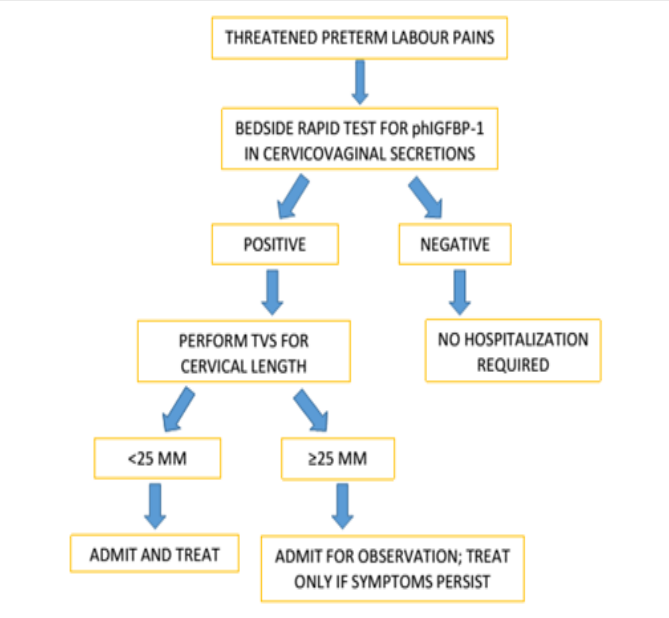

Figure 2 Suggested algorithms for management of patients with threatened preterm labor.

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Conflict of interest

Author declares that there is no conflict of interest.

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