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Original Research Article

A Prospective Cohort Study of Cervical Phosphorylated Insulin-Like Growth Factor Binding Protein-1 Test to Predict Preterm Labor

Shubhangi Jain[1], Shraddha Chouhan[2], Anupama Dave[3], Akanksha Thora[4]

[1,2,3&4]Dept. of OBG, MGM Medical College & M.Y. Hospital, Indore, M.P.

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Corresponding author: Akanksha Thora
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Abstract

Background: Preterm delivery (PTD) is a multifactorial phenomenon with significant medical, health, economic, and human impacts. Despite identifying numerous risk factors, preterm birth is still difficult to predict.

Aims & Objectives: The purpose of this study is to determine whether phIGFBP-1, a phosphorylated form of insulin-like growth factor binding protein-1, can be used to predict Preterm labour.

Materials and Methods: A prospective cohort study was conducted, which included all pregnant women coming to the Emergency Room associated with MGM medical college, M.Y.H. and M.T.H Hospital, Indore, India with symptoms and signs suggestive of preterm labour who gave consent to be tested for the presence of phosphorylated IGFBP-1 in the cervical secretions; from June 2021 to June 2022.

Observation & Results: It was found that the NPV of the test was consistently higher than the PPV of the test at 48 hours, seven days as well as two weeks (95.8 % NPV and 60.7 % PPV at 48hours, 93.8 % NPV and 64.3 % PPV at seven days and 89.6 % NPV & 67.90 % PPV at two weeks).

Discussion: In the present study, we found out that the detection of phosphorylated insulin-like growth factor binding protein -1 in cervical secretions reliably predicts imminent risk of preterm delivery in pregnant women in the next 48 hours, seven days and two weeks after doing the test. Further studies need to be done to compare the role of the cervical phIGFBP-1 test with a combination of the test and other ways to predict the risk of preterm labour, like cervical fibronectin assay and cervical length measurement.

Introduction

Preterm delivery (PTD) is a multifactorial phenomenon with significant medical, health, economic, and human impacts. The prevalence of PTD varies by population and ranges from 5.0 to 15.0 per cent globally. PTDs occur more than half the time accidentally [1,2]. It is unclear what molecular processes result in PTD. The global rate of PTD has risen over the past few decades despite efforts to address the issue and advancements in medicine. One-half of all childhood neurological disabilities and approximately 75% of neonatal deaths are caused by preterm birth. Despite identifying numerous risk factors, preterm birth is still difficult to predict [3,4]. Over the past few decades, much research has been done to find new ways to predict PTD earlier and more accurately

[5,6,7]. Most predictive markers are significant when delivery is about to occur [6]. However, we require markers to screen the general pregnant population for antenatal care to identify women at high risk of subsequent PTD and concentrate preventive care on them. With varying degrees of accuracy, tests for fetal fibronectin (FFN), phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) and sonographically measured cervical length have been used in patients who are at risk of preterm labour [8,9,10,11].

Occult or clinical infection from the vagina is thought to cause inflammation in the choriodecidual space by stimulating cells to produce pro-inflammatory cytokines (IL-1, IL-8, TNF-). Prostaglandins (PGs), endo - and exotoxins, and proteases are all produced more readily due to these cytokines, and they can all lead to tissue disruption in the choriodecidual space. Chorionic and decidual products may leak into the cervix and vagina due to tissue disruption [12,13,14]. One of these products is phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1), a significant protein of the decidua that may leak into the lower genital tract due to tissue disruption brought on by inflammation [15]. It has been suggested that the presence of phIGFBP-1 in the cervicovaginal fluid is a reliable sign of an upcoming preterm birth. The purpose of this study is to determine whether phIGFBP-1, a phosphorylated form of insulin-like growth factor binding protein-1, can be used to predict Preterm labour.

Material and Methods

A prospective cohort study was conducted, which included all pregnant women coming to the Emergency Room associated with MGM medical college, M.Y.H. and M.T.H hospital, Indore, India with symptoms and signs suggestive of preterm labour who gave consent to be tested for the presence of phosphorylated IGFBP-1 in the cervical secretions; from June 2021 to June 2022.

Inclusion Criteria:

Women presenting with gestational age between 28+0 weeks and 36+6 weeks with signs & symptoms of threatened & early preterm labour with:

1. Cervical dilatation less than 3 cm and cervical effacement less than 80% or cervical length more than 1.5 cm.
2. Intact membranes.

Exclusion Criteria:

1. 1.Gestational age <28+0 weeks or >36+6 weeks.
2. Women present with gestational age between 28+0 weeks and 36+6 weeks with signs & symptoms of spontaneous threatened & early spontaneous preterm labour with Moderate or gross vaginal bleeding.
3. All those who did not give consent.

After explaining the procedure to the patient and getting the consent, the patient is placed in the dorsal position. A sterile speculum is introduced into the vagina, and the cervical os is visualized. A sterile Dacron swab was applied over the cervical os and was left for approximately 10-15 seconds to absorb cervical secretion. The specimen was extracted from the swab by swirling the swab vigorously in the tube containing the extraction solution for 5- 10 seconds. The aluminium foil pouch containing the dipstick was opened, and the yellow testing dip area of the stick was placed into a tube containing the sample and was held until the liquid entered the result area. The dipstick was removed from the solution and placed in a horizontal position. The result was observed in 5 minutes. When two blue lines were visible: Positive. When only one blue line (control line) was visible: Negative. The absence of a distinct control line meant an invalid result.

Data were entered into a Microsoft Excel spreadsheet and analysed using open-

source software. Continuous data will be expressed in terms of mean and SD. Categorical data were expressed in the form of proportions and percentages. Appropriate significance tests like t-test and chi-square were applied wherever necessary, and p-value <0.05 were considered statistically significant.

Observations & Results

- In the present study, we found that 60 (79%) study participants were 20-25 years of age.
- 64 (84.2%) study participants had BMI in the normal range.
- 53 (69.7%) study participants were multi-gravida.
- 33 (43.4 %) study participants had a history of abortion.
- 49 (64.5 %) study participants were multiparous women.
- In our study, 41 (53.9%) women had a history of previous spontaneous preterm birth.
- 30 (39.5%) women had a history of second trimester-induced or spontaneous miscarriage.
- 14 (18.4 %) women had a history of chronic infections like UTI, PID, vaginal infections.
- 9 (12%) women had twin pregnancies.

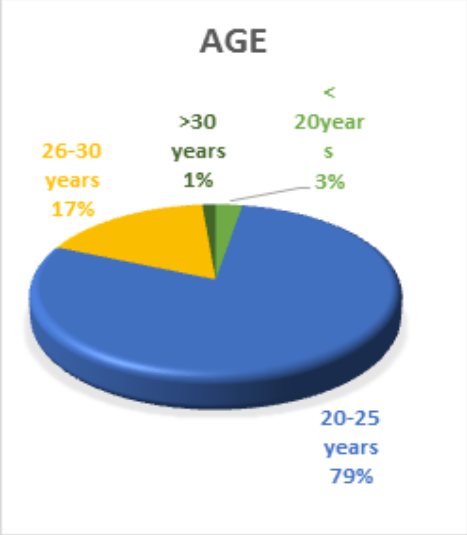

Figure 1: Distribution of study participants according to Age

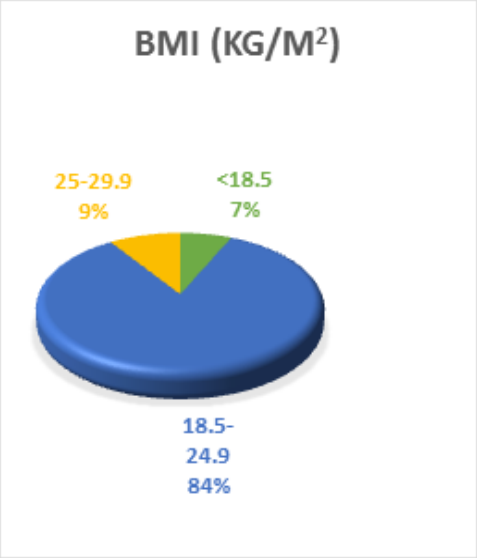

Figure 2: Distribution of study participants according to BMI

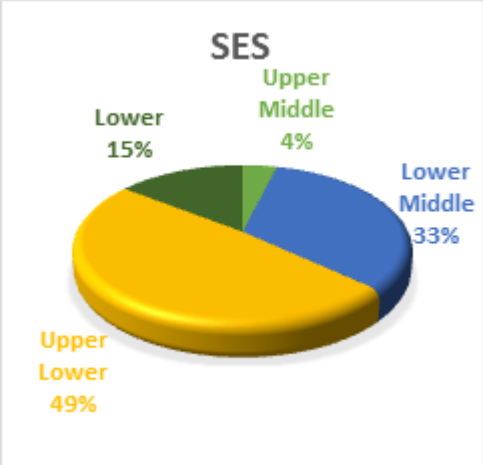

Figure 3: Distribution of study participants according to SES

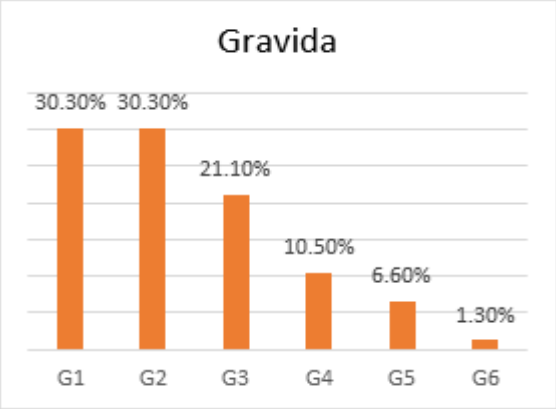

Figure 4: Distribution of study participants according to Gravidity

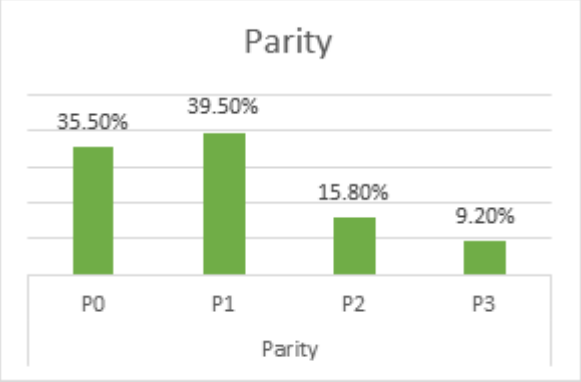

Figure 5: Distribution of study participants according to Parity

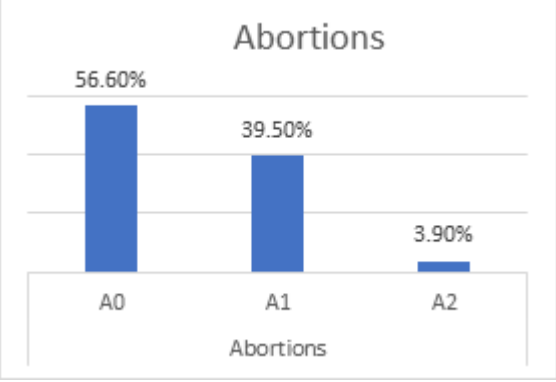

Figure 6: Distribution of study participants according to the number of Abortions

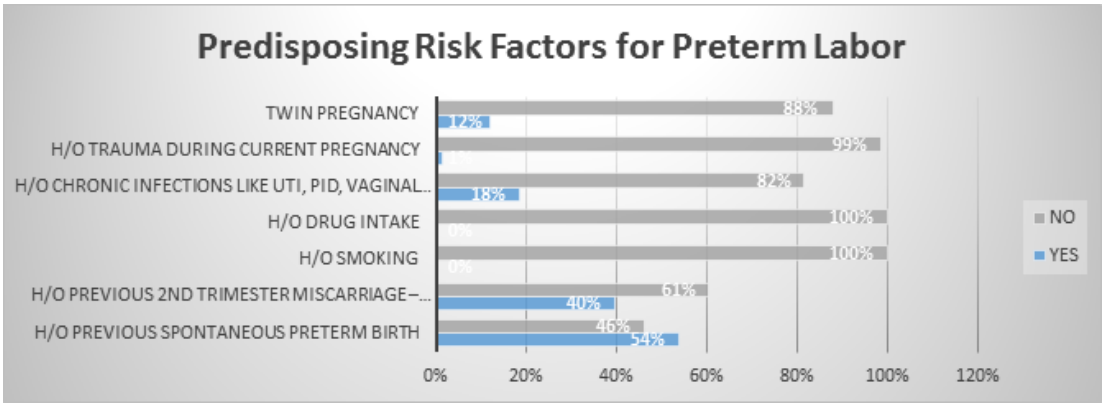

Figure7: Distribution of study participants according to predisposing risk factors for preterm labour

Table 1: Result of Cervical phosphorylated IGFBP-1 test of patients who went into labour within the next 48hours

IGFBP-1Test Results	Whether the study participant's Patient went into labour within the next 48 hours			
		Yes	No	Total
Positive	Count	17	11	28
	% within IGFBP-1test	60.70%	39.30%	100.00%
Negative	Count	2	46	48
	% within IGFBP-1test	4.20%	95.80%	100.00%
Total	Count	19	57	76
	% within IGFBP-1test	25.00%	75.00%	100.00%

Pearson Chi-Square = 30.15 p-value <<0.05 (significant)

Statistic	Value
Sensitivity	89.47%
Specificity	80.70%
Positive Predictive Value	60.71%
Negative Predictive Value	95.83%
Accuracy	82.89%

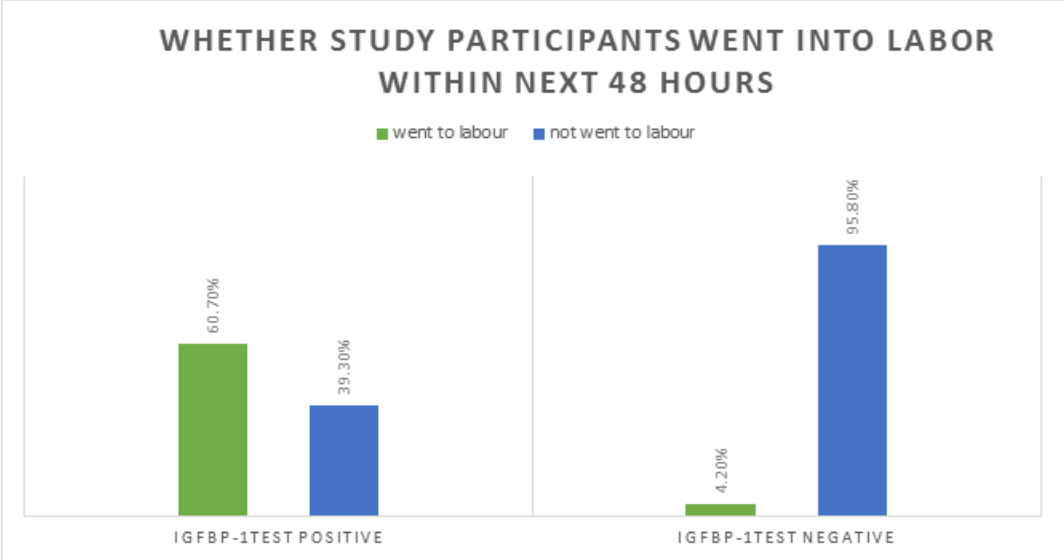

Figure 8: Result of Cervical phosphorylated IGFBP-1 test of patients who went into labour within the next 48hours

Table 1 & Fig. 8 show that 60.71% of the patients who tested POSITIVE for IGFBP-1 went into labour within the next 48 hours, and 95.83% who tested NEGATIVE did not go into labour within the next 48 hours. The sensitivity and specificity of the IGFBP-1 test for predicting preterm labour within the next 48 hours were 89.47% and 80.70%; receptively, that means the IGFBP-1 test is a good predictor for preterm prediction *within the next 48 hours*

Table 2: Result of Cervical phosphorylated IGFBP-1 test of patients who went into labour within the next seven days

	Whether study participants went into labour within the next seven days			
IGFBP-1test		Yes	No	Total
Positive	Count	18	10	28
	% within IGFBP-1test	64.30%	35.70%	100.00%
Negative	Count	3	45	48
	% within IGFBP-1test	6.30%	93.80%	100.00%
Total	Count	21	55	76
	% within IGFBP-1test	27.60%	72.40%	100.00%

Pearson Chi-Square=29.787 p-value << 0.05 (significant)

Statistic	**Value**
Sensitivity	85.71%
Specificity	81.82%
Positive Predictive Value	64.29%
Negative Predictive Value	93.75%
Accuracy	82.89%

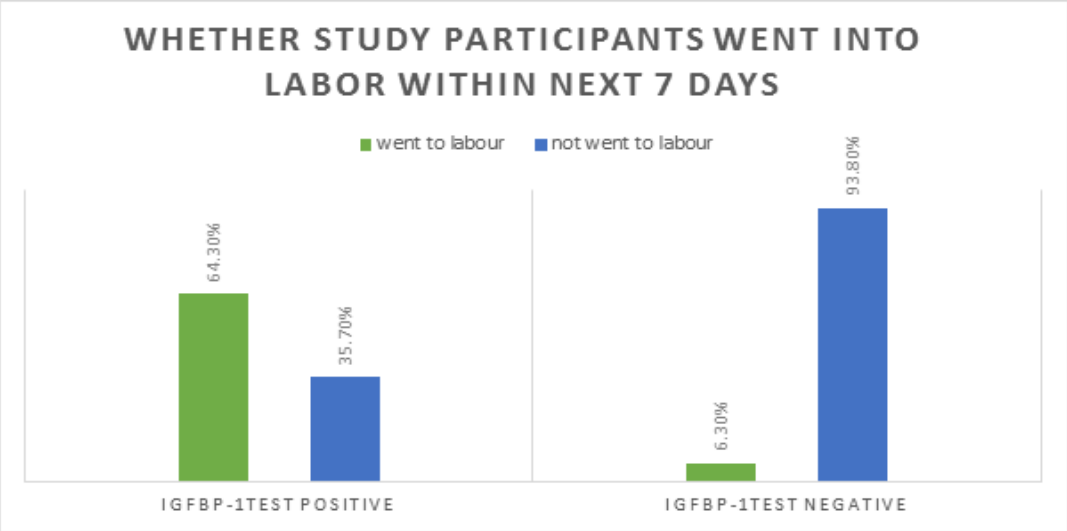

Figure 9: Result of Cervical phosphorylated IGFBP-1 test of patients who went into labour within the next seven days

Table 2 & Fig. 9 show that 60.30% of the patients who tested POSITIVE for IGFBP-1 went into labour within the next seven days, and 93.80% who tested NEGATIVE did not within the next 7days. The sensitivity and specificity of the IGFBP-1 test for predicting preterm labour within the next seven days were 85.71% and 81.82%, receptively, which means the IGFBP-1 test is a good predictor for preterm prediction within the next 7 days.

Table 3: Result of Cervical phosphorylated IGFBP-1test of study participants who went into labour within the next 2 weeks

	Whether Study participants went into labour within the next 2 weeks			
IGFBP-1test		**Yes**	**No**	**Total**
Positive	Count	19	9	28
	% within IGFBP-1test	67.90%	32.10%	100.00%
Negative	Count	5	43	48
	% within IGFBP-1test	10.40%	89.60%	100.00%
Total	Count	24	52	76
	% within IGFBP-1test	31.60%	68.40%	100.00%

Pearson Chi-Square 27.004 p-value << 0.05 (significant)

Statistic	**Value**
Sensitivity	79.17%
Specificity	82.69%
Positive Predictive Value	67.86%
Negative Predictive Value	89.58%
Accuracy	81.58%

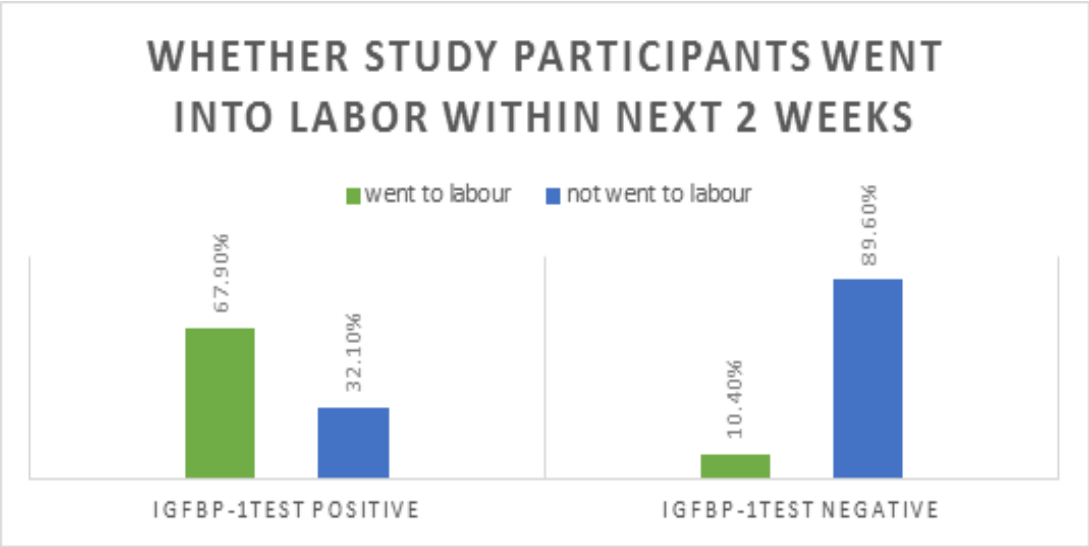

Figure 10: Result of Cervical phosphorylated IGFBP-1test of study participants who went into labour within the next 2 weeks

Table 3 & Fig. 10 shows that 67.90% of the patients who tested POSITIVE for IGFBP-1 went into labour within the next 2 weeks, and 89.6% who tested NEGATIVE did not within the next 2 weeks. The sensitivity and specificity of the phIGFBP-1 test for predicting preterm labour within the next 2 weeks were 79.17% and 82.69%, respectively, which means the phIGFBP-1 test is a good predictor for preterm prediction within the next 2 weeks.

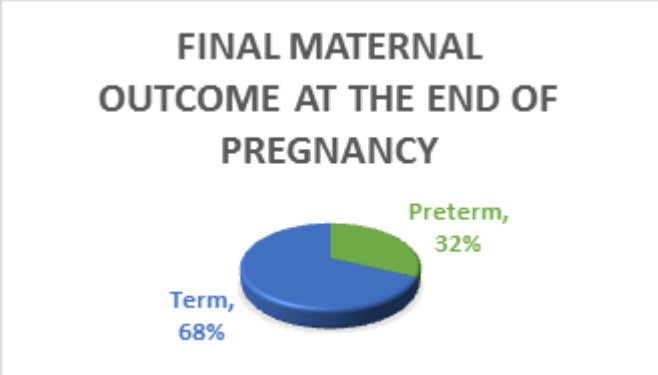

Figure 11: Distribution of study participants based on Final Maternal outcome at the End of Pregnancy

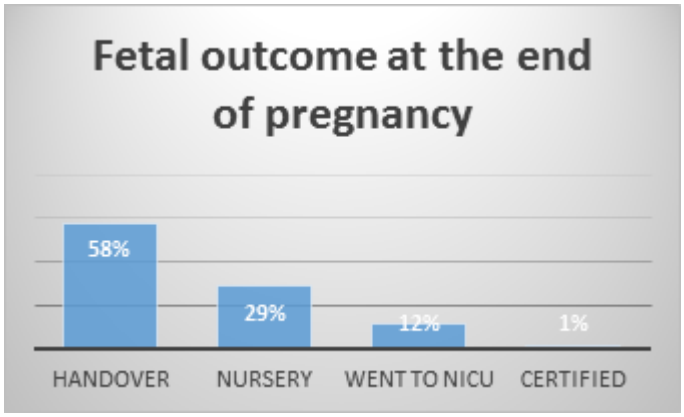

Figure 12: Distribution of study participants based on Fetal outcome at the end of pregnancy

Discussion

In the present study, we found out that the detection of phosphorylated insulin-like growth factor binding protein -1 in cervical secretions reliably predicts imminent risk of preterm delivery in pregnant women in the next 48 hours, seven days and two weeks after doing the test.

According to evidence found in the present study, a positive test (2 BLUE LINES) result indicates that phIGBP-1 concentrations in the cervical fluid extract are>/= 10 microgram/L indicating that tissue damage is present in the pregnant women presenting with signs & symptoms suggestive of Preterm Labor and hence, is likely to deliver within next 1-2 weeks. Whereas a negative test result (SINGLE BLUE LINE – only control line) means that phIGBP-1 concentration is less than ten microgram/L in the cervical secretions extracted from the women, which indicates that no significant changes have occurred in the choriodecidual layer; despite the pregnant women presenting with signs and symptoms of preterm labour; hence its highly likely that she will not deliver within 1-2 weeks.

In our study, it was found that the NPV of the test was consistently higher than the PPV of the test at 48 hours, seven days as well as two weeks (95.8 % NPV and 60.7 % PPV at 48hours, 93.8 % NPV and 64.3 % PPV at seven days and 89.6 % NPV & 67.90 % PPV at two weeks). These findings suggest that the cervical pIGFBP-1 test is more beneficial in ruling out the imminent risk of preterm delivery in a pregnant woman presenting with signs and symptoms of preterm labour. Having this information at hand allows us to differentiate patients who have harmless contractions from those with a real risk of preterm delivery; so that we can direct our medical attention and resources towards

those who need it more urgently and avoid unnecessary expenditure of time and money on the part of the patients as well as institutions.

Identifying high-risk pregnancies sooner allows us to do more intensive antenatal surveillance in pregnant women who need it and intervene timely to prevent or delay preterm delivery as much as possible and refer the patient to a higher centre with adequate neonatal care facilities for premature babies, thus reducing the neonatal morbidity and mortality associated to prematurity.

Moreover, Identifying Low-risk patients allows us to ease the anxiety of the expecting mother confidently and send her home since she does not need immediate hospitalization and intervention. Unnecessary use of medications & their side effects and unnecessary referrals to higher centres can be avoided, thus making this test highly beneficial in a developing country like India with limited resources at a large chunk of the health facilities, saving valuable resources of the state. Based on this study; it is safe to conclude that the Cervical phosphorylated IGFBP-1 test is a reliable and handy tool to rule out the imminent risk of preterm labour in pregnant women presenting with signs and symptoms suggestive of preterm labour; within 1-2 weeks of doing the test.

In investigations by Kwek et al., [16] bedside tests for IGFBP-1 were carried out on 47 women who were suspected of having preterm labour between 23 and 33 weeks. 18 women tested positive (38.3%), and 29 women tested negative (61.7%). Additionally, 91.7% of the individuals in the IGFBP-1 negative group experienced a delay of more than 7 days from the start of signs and symptoms of preterm labour. Only 44.4% of the women in the pIGFBP-1 positive group had a delay in contractions and delivery. According to the findings of this study, a bedside test for pIGFBP-1 can accurately predict preterm births that occur before 36 weeks of gestation with a sensitivity of 87.37% and a specificity of 82.6%. The test has a 77.8% positive predictive value and a 79.2% negative predictive value.

In research by Elizur et al. [17], the average gestational age at delivery in patients who tested positive for phIGFBP-1 alongside tests was 36.2+/- 2.4 weeks (p-value 0.001). According to the findings, a bedside test for PIGFBP-1 can accurately predict preterm births before 36 weeks of gestation with a sensitivity of 87.37% and a specificity of 82.6%. The test has a 77.8% positive predictive value and a 79.2% negative predictive value.

Using 36 pregnant women between the ages of 20 and 36 weeks who had frequent contractions, Lembet et al [18]. conducted prospective research. 18 individuals had a positive pIGFBP-1 beside the test, while 18 had a negative test. Only one of the 18 patients who had a positive test delivered at term, while the other 17 delivered prematurely (before 37 weeks). Two of the 18 women with negative tests gave birth prematurely (p 0.05). The pIGFBP-1 test for preterm delivery had sensitivity, specificity, and positive and negative predictive values of 89.5%, 94.1%, 94.4%, and 88.9%, respectively.

108 participants were enrolled in the study by Ting et al. [19] Patients who tested negative for pIGFBP-1 had a median gestational age at delivery of 37.4 weeks (within standard deviation [SD]). In contrast, those who tested positive for pIGFBP-1 had a median gestational age at delivery of 32.9 weeks (within standard deviation [SD]). A p-value of 0.001 was used. [20]

Limitations

As the study was done in a tertiary care government-run hospital setting, limited availability of funding resources and test expensiveness resulted in a small sample size.

The study included patients between gestational ages of 28 +0 weeks and 36 + 6 weeks. Hence this study does not comment on patients presenting with symptoms and signs of preterm labour before 28 weeks of gestation.

Recommendations

Based on the observations made, the following are the recommendations of the present study:

The cervical phIGFBP-1 test is a simple, one-step dipstick test that gives reliable and quick results (in 5 minutes) with easy-to-do sampling. This makes it easy to do for any clinician, nurse, or laboratory technician in urban or rural settings with minimal training. Test results are not affected by urine, intercourse, semen, vaginal medications, lubricants, bathing products, or infections and hence, can be reliably used without any interference from confounding factors present in most pregnant women. Therefore, this test can be used bedside and in clinics and aid in crucial decisions regarding managing patients symptomatic of preterm labour.

High Negative Predictive value of the test at 48hours, seven days and two weeks after doing the test (95.83 %,93.8 %, 89.6 %, respectively) allows us to safely interpret that a negative test result rules out the imminent risk of preterm delivery in next 1-2 weeks. Therefore, it allows us to send such low-risk patients home confidently and save valuable resources in a developing country with resource restrictions like India. Cervical phIGFBP-1 test should be used routinely at all hospitals and clinics, especially in government-run settings, for better allocation of our limited resources by selecting patients who need prophylactic administration of corticosteroid therapy for fetal lung maturation and to prepare patients for transport “in utero” to centres with units for premature newborn care.

Further studies need to be done to compare the role of the cervical pgIGFBP-1 test with a combination of the test and other ways to predict the risk of preterm labour, like cervical fibronectin assay and cervical length measurement.

Cost- Effectiveness Analyses need to be done to determine best practices in clinical settings in India.

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