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CLINICAL ARTICLE

Prediction of preterm labor by a rapid bedside test detecting phosphorylated insulin-like growth factor-binding protein 1 in cervical secretions

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ABSTRACT

Objective: To evaluate the utility of measuring phosphorylated insulin-like growth factor-binding protein 1 (phIGFBP-1) in cervical secretions to predict preterm birth among women with premature uterine contractions. *Methods:* A prospective study was conducted between September 27, 2013, and February 28, 2014, at a tertiary center in India. Participants with symptoms of preterm labor at 24–36 weeks underwent testing for phIGFBP-1 in cervical secretions. Cervical length was measured by ultrasonography. *Results:* Cervical swab samples tested positive for phIGFBP-1 among 34 (57%) of the 60 participants. Mean cervical length was 2.15 ± 0.63 cm among the 46 (77%) women who delivered preterm and 2.54 ± 0.47 cm among the 14 (23%) women who delivered at term. Of the 46 preterm deliveries, 29 (63%) women tested positive for phIGFBP-1 and 17 (37%) tested negative. Mean length of pregnancy at delivery was 32.11 ± 4.09 weeks and 35.77 ± 1.68 weeks among women who tested positive and negative for phIGFBP-1, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of phIGFBP-1 to predict preterm birth were 86.96%, 35.29%, 64.52%, and 66.67%, respectively. *Conclusion:* A rapid bedside test measuring phIGFBP-1 identified women at high risk of preterm delivery.

1. Introduction

Preterm delivery (i.e. before 37 weeks) is the most frequent cause of perinatal mortality worldwide, accounting for approximately two-thirds of all such deaths, and therefore representing a major challenge in obstetrics [1]. The overall frequency of preterm labor is reported to be 5%–15%, but estimates vary among different countries [2]. For example, the frequency is 8%–10% in India, 5%–7% in Europe, and 11%–15% in the USA [2]. Preterm labor is multifactorial in origin and it is difficult to predict onset. Most preterm births that occur in India reflect spontaneous onset of premature labor pains, whereas preterm deliveries in the USA have often been induced owing to maternal or fetal indications [3]. Premature births also raise financial costs to both parents and the hospital by approximately eight times when compared with the costs of delivering a term neonate weighing greater than 2500 g [4].

Approximately 20%–25% of women presenting with suspected preterm labor worldwide go on to deliver before 37 weeks; however, all women with symptomatic uterine contractions are given tocolytics and clinically managed in the same way [5]. The ability to distinguish patients who will experience premature delivery from those who will deliver at term is vital to ensure that therapy is directed only to individuals who actually need it. Such an approach would avoid unnecessary hospital admission, as well as the consequential adverse effects of tocolytics among women unlikely to deliver before term [5]. Furthermore, identification of high-risk patients would enable timely referral and transportation to a tertiary center with nursery and/or neonatal intensive care unit (NICU) facilities and thereby improve perinatal outcomes, particularly among neonates delivered before 34 weeks (when morbidity is still high).

Previous studies have aimed to identify women at high risk of preterm labor [6,7]. Many methods have been used to categorize such individuals, including a risk scoring system based on obstetric history, nutritional status, and demographic profile; administration of an ambulatory uterine contraction test; and detection of short cervical length by ultrasonography [6]. Potential biochemical markers include salivary estriol, prolactin in vaginal discharge, interleukin-6 in the amniotic fluid, and fetal fibronectin in cervical secretions [7]. However, none of these markers exhibit high sensitivity, positive predictive value (PPV), or negative predictive value (NPV); the markers also have low diagnostic accuracy for preterm labor (30%–50%) [8,9]. Consequently, attempts have been made to find a novel biochemical marker with high diagnostic accuracy.

The phosphorylated form of insulin-like growth factor-binding protein 1 (phIGFBP-1) has been shown to predict preterm labor among

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women in Finland with high sensitivity and PPV [10]. This molecule is secreted by both decidual and liver cells, and is present in the amniotic fluid at higher concentrations than are observed in the maternal serum. During the onset of delivery, fetal membranes detach from the decidua parietalis and a small amount of phIGFBP-1 is released into cervical secretions, where it can be detected using an antibody based assay [11,12]. Thus, testing cervical secretions for the presence of phIGFBP-1 might be helpful in detecting the onset of labor.

The aim of the present study was to assess the utility of phIGFBP-1 for prediction of preterm birth in an Indian population.

2. Materials and methods

A prospective study was conducted in the Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India, between September 27, 2013, and February 28, 2014. The All India Institute of Medical Sciences is a tertiary care and research center where only high-risk pregnancies are delivered. Eligible participants were women at 24–36 weeks of pregnancy who presented with abdominal pain and regular uterine contractions (>4 within a 20-minute period). Pregnancy length was calculated from the first day of the last menstrual period and had been confirmed by ultrasonography, which was performed at 18–20 weeks. Women with multiple pregnancy, vaginal bleeding, preterm rupture of membranes, pre-eclampsia, fetal growth restriction, and congenital malformations were excluded from the present study. The protocol was approved by the ethics committee of the All India Institute of Medical Sciences. All participants provided informed written consent.

A one-step rapid dipstick test (Actim Partus; Medix Biochemica, Kauniainen, Finland) was performed at admission to detect phIGFBP-1 in cervical secretions. The cervical specimen was taken using a sterile cotton-tipped swab during speculum examination. Only per speculum was used to assess the cervix; digital vaginal examination was not conducted among any study participants. The lower end of the swab was placed at the external cervical orifice and kept there for 10–15 seconds to absorb the secretions. The swab was placed in a test tube with extraction solution (a buffered solution containing bovine serum albumin, protease inhibitors, and preservatives) for 15–20 seconds and then discarded. The test strip was placed in the extraction solution and the result interpreted after 5 minutes while holding the dipstick in a horizontal position after removing it from the extraction solution. The test result was classed as positive, negative, or invalid when two, one, or no blue lines appeared on the dipstick. A positive result indicated that the concentration of phIGFBP-1 in the sample exceeded the cutoff (10 μg/L). The second line was used to confirm test performance.

Cervical length was measured after performing the dipstick test. Transvaginal ultrasonography was conducted using an HDI 5000 Sono ultrasonographic machine (Phillips, Boston, MA, USA) with a 7.5-MHz transvaginal transducer. The transducer was inserted in the vagina to obtain a sagittal view of the cervix. An adequate image for the measurement of cervical length was defined as the visualization of the internal os, external os, and endocervical canal. The image was then frozen and the cervical length measured as the shortest linear distance between the external os and the internal os along a closed endocervical canal.

Tocolytic therapy with a calcium-channel blocker was administered to all patients according to the clinical protocol of the All India Institute of Medical Sciences (10–30 mg oral nifedipine daily). Treatment was continued until 12–24 hours after uterine contractions had stopped. All participants were advised to undertake bed rest; fetal well-being was assessed by a non-stress test and biophysical profile. Prenatal corticosteroids (four 6-mg injections of dexamethasone 12 hours apart) were administered to the mother for enhancement of fetal pulmonary maturity. Route and timing of delivery were decided on a case-by-case basis, and cesarean delivery was performed only for obstetric indications.

The primary outcome was delivery before 37 weeks. Secondary outcomes were delivery within 48 hours and 7 days of performing the dipstick test, as well as perinatal outcomes. The number of women delivering before 37 weeks who had a positive phIGFBP-1 test result and a short cervical length was also assessed. The predictive value of phIGFBP-1 and cervical length was also compared.

The data were analyzed using SPSS version 16 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were expressed as the mean ± standard deviation. The Student t test after log transformation was applied for non-parametric variables. Categorical variables were compared using the χ^2 or Fisher exact tests as appropriate. $P < 0.05$ was considered statistically significant. The positive and negative likelihood ratios were calculated within the 95% confidence interval.

3. Results

Among 1344 deliveries recorded at the All India Institute of Medical Sciences during the study period, 105 (7.8%) were spontaneous preterm deliveries. A total of 95 women presenting with preterm symptomatic uterine contractions at 24–36 weeks of pregnancy were screened for the present study. Of these women, 11 had no documented objective uterine contractions and the predefined criteria for threatened preterm labor were not fulfilled; eight had preterm premature rupture of membranes; five had twin pregnancy; and two had placental abruption. In addition, six women did not give their consent and three were lost to follow-up. Consequently, 60 women were included in the final analysis. The demographic profile of the participants is shown in Table 1.

The rapid phIGFBP-1 test gave positive results among 34 (57%) of the 60 women included in the analysis. Negative tests results were recorded among 26 (43%) women. None of the test results was classified as invalid. Spontaneous preterm delivery occurred among 46 (77%) of the women. Preterm delivery occurred among 29 (85%) women who tested positive for phIGFBP-1 and 17 (65%) among those who tested negative for this biochemical marker.

The proportion of women who delivered within 48 hours of the phIGFBP-1 test was higher among those who tested positive than among those who tested negative delivered ($P = 0.04$) (Table 2). The delivery rate within 7 days of the test was higher in the positive test group than in the negative test group ($P = 0.57$) (Table 2).

In a subgroup analysis, mean cervical length at admission was similar among women who went on to have a preterm delivery and among those who delivered at term (Table 3). Although more than one-quarter of neonates who were delivered preterm and none who were delivered at term were admitted to the NICU, the difference between groups was not significant (Table 3).

The sensitivity, specificity, PPV, and NPV of the phIGFBP-1 test versus short cervical length (<2.5 cm) are presented in Table 4. When the two tests were used in combination, the sensitivity was 100.0% and the PPV was 70.6%. All the patients who tested positive for phIGFBP-1 and exhibited short cervical length (n = 18 [30%]) delivered preterm.

4. Discussion

The present study evaluated the diagnostic utility of a rapid bedside dipstick test for cervical phIGFBP-1 in predicting preterm delivery

Table 1
Demographic profile of the participants (n = 60).

Variable	Value[a]
Age, y	29.92 ± 5.14
Body mass index[b]	23.61 ± 2.45
Parity	0.9 ± 0.3
History of preterm delivery	18 (30)
Length of pregnancy at admission, wk	32.84 ± 3.24

[a] Values given as mean ± SD or number (percentage).
[b] Calculated as weight in kilograms divided by the square of height in meters.

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