

## Comparison of Bedside Test Kits for Prediction of Preterm Delivery: Phosphorylated Insulin-like Growth Factor Binding Protein-1 (pIGFBP-1) Test and Fetal Fibronectin Test

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### Abstract

**Objective:** The objective of the study was to compare the effectiveness of bedside test kits for pIGFBP-1 and fetal fibronectin test in predicting preterm delivery. **Materials and Methods:** Patients presenting with symptoms of preterm labour between 24 and 34 weeks of gestation were recruited. Both pIGFBP-1 and fetal fibronectin bedside tests were performed. Managing obstetricians and patients were blinded to the pIGFBP-1 and fetal fibronectin results. Tocolysis and steroid therapy were administered to all the recruited patients. Outcome data were collected after delivery. **Results:** One hundred and eight patients were recruited into the study. Fourteen patients had to be excluded from the final analysis due to incomplete data and failure to meet inclusion criteria. Ninety-four patients had complete data for analysis. Among those with negative pIGFBP-1 and fetal fibronectin results, the median [ $\pm$ standard deviation (SD)] gestational age at delivery was 37.4 weeks ( $\pm$ 2.8 weeks) and 37.4 weeks ( $\pm$ 2.1 weeks), respectively. Among those with positive pIGFBP-1 and fetal fibronectin results, the median ( $\pm$ SD) gestational age at delivery was 32.9 weeks ( $\pm$ 4.0 weeks) and 34.2 weeks ( $\pm$ 4.2 weeks), respectively ( $P < 0.001$  for both pIGFBP-1 and fetal fibronectin). A positive result with either test was associated with a significantly reduced admission-to-delivery interval. The median admission-to-delivery interval was 2.8 weeks shorter in the group with positive pIGFBP-1 results compared to those with a negative pIGFBP-1 result (2.3 weeks compared with 5.1 weeks) ( $P < 0.001$ ). This is 1.8 weeks shorter in the group with positive fibronectin results, compared to those with a negative result (3.3 weeks compared with 5.1 weeks) ( $P = 0.002$ ). Both pIGFBP-1 and fetal fibronectin tests have high negative predictive value (NPV) in predicting risk of delivery within 48 hours, 7, or 14 days (1.00; 0.92; 0.92 and 0.97; 0.89; 0.89, respectively). **Conclusions:** Both pIGFBP-1 and fetal fibronectin tests are effective adjuvant bedside test kits for the prediction of preterm delivery in patients presenting with signs or symptoms of preterm labour. pIGFBP-1 has the higher NPV of 1.00 in predicting risk of delivery within 48 hours.

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**Keywords:** Early delivery, Labour ward, Objective test

### Introduction

The incidence of premature labour in most European countries and in the United States has remained largely unchanged during the past decade at 8% to 9%.<sup>1</sup> Preterm delivery is a leading cause of neonatal morbidity and mortality. It accounts for 60% of all perinatal deaths.<sup>2</sup>

Only about 20% of women presenting with suspected preterm labour would actually deliver preterm.<sup>3</sup> In order to

institute specific therapy more appropriately, it is important to have adjuvant tests to help predict who is most likely to deliver preterm.

The detection of pIGFBP-1 in the cervical secretions of women presenting with preterm labour has been shown to be associated with an increased risk of preterm delivery.<sup>4,6</sup> A bedside test-kit for pIGFBP-1 has been developed and is commercially available under the trade name Actim Partus

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(Medix Biochemica, Finland). It is an immuno-enzymatic test relying on the monoclonal antibody 6303 as the detecting antibody. This antibody is specific for the phosphorylated form of IGFBP-1, which is the form found in high concentrations in the chorio-decidual interface. The product is marketed by Medix Biochemica (Finland) under the trade name Actim. The test kit is packaged with a sterile Dacron swab, which is gently applied to the cervix to absorb cervical secretions. The swab is removed and washed in the reaction buffer, then discarded. The test strip is then left in the reaction buffer and the immuno-enzymatic test allowed to take place. A single line visible in the reaction window at the end of 5 minutes is indicative of a negative test, while the presence of a second line is interpreted as a positive test.<sup>7</sup>

Fetal fibronectin is an extracellular matrix protein found at the interface between the chorion and decidua parietalis. It is normally undetectable from the cervix and vagina after 20 weeks of gestation.<sup>8</sup> The detection of fetal fibronectin concentrations of more than 50 ng/mL in the cervical or vaginal secretions after this gestational age has been associated with an increased risk of spontaneous preterm delivery.<sup>9-12</sup> Assay of fetal fibronectin in cervico-vaginal secretions has proven to be a valuable asset in the prediction of spontaneous preterm delivery since the test was first described by Lockwood and colleagues in 1991.<sup>8</sup> The bedside test kit (Actim Partus, Medix Biochemica, Finland) is packaged with a sterile Dacron swab, a test strip and a tube of reaction buffer as with the pIGFBP-1 test kit.

The aim of the study was to compare the clinical effectiveness of pIGFBP-1 and fetal fibronectin in the prediction of preterm delivery.

## Materials and Methods

We performed this study in our hospital from January 2003 through January 2005. All pregnant women were eligible for participation if they presented with symptoms that suggested preterm labour between 24 weeks and 34 weeks, a singleton gestation and intact membranes.

Gestational age was calculated based on the last menstrual period and confirmed by first or early second trimester ultrasonography. When a discrepancy of more than 10 days occurred, gestational age was set only by first trimester ultrasonographic examination. Women whose pregnancies were complicated by multiple gestation, preterm rupture of membranes, cervical cerclage, cervical dilatation of 3 cm or greater, placenta previa, chorioamnionitis, intrauterine growth restriction of fetus, preeclampsia, suspected fetal asphyxia, or a major fetal anomaly were excluded from recruitment into the study. The hospital ethics committee approved the study. All patients gave their informed consent before entering into the study.

Data collection included demographic variables (age, parity, gravidity, previous preterm delivery), cervical sampling for pIGFBP-1 and digital examination (cervical dilatation and effacement).

Before digital cervical examination, a speculum examination was performed. Two dry Dacron swabs were placed at posterior fornix, adjacent to the cervix for 10 seconds. The swabs were then removed, washed in the respective test reagent and analysed using the bedside fibronectin and pIGFBP-1 bedside test kits. Results were qualitatively reported as either positive or negative.

The managing obstetrician was blinded to the results of both tests, and administered clinical care according to hospital clinical guidelines for the management of preterm labour. This consisted of admission to the delivery suite and tocolysis with oral nifedipine as a first-line treatment agent and intravenous salbutamol as a second-line. Antenatal corticosteroid therapy was administered in the form of dexamethasone for fetal pulmonary maturation.<sup>13</sup>

Following delivery, data collection on gestational age at delivery, admission-to-delivery interval, mode of delivery, indication of delivery and baby status was completed. Microsoft SPSS 9.0 version was used for data analysis. Levene's test for equality of variances and *t*-test for equality of means were carried out.

## Results

One hundred and eight patients were recruited into the study. Fourteen patients had to be excluded from the final analysis due to incomplete data. Seven of these patients delivered in another hospital and thus delivery data was not available, 2 were found to be less than 24 weeks on admission, 1 had preterm prelabour ruptured of membranes, 2 had only either of the tests done, 1 was delivered prematurely because of severe pre-eclampsia and 1 had cervical dilatation >3 cm at admission.

Ninety-four patients had complete data for analysis. Table 1 shows the demographics and clinical characteristics of the study population. No statistically significant differences were observed concerning maternal and gestational age at admission, parity and gravidity. The difference in the mean cervical dilatation was statistically significant, with  $P < 0.05$ .

Among those with negative pIGFBP-1 and fetal fibronectin results (Table 2), the median [ $\pm$ standard deviation (SD)] gestational age at delivery was 37.4 weeks ( $\pm 1.8$  weeks) and 37.4 weeks ( $\pm 2.1$  weeks), respectively. Among those with positive pIGFBP-1 and fetal fibronectin results, the median ( $\pm$ SD) gestational age at delivery was 32.9 weeks ( $\pm 4.0$  weeks) and 34.2 weeks ( $\pm 4.2$  weeks), respectively. The  $P$  value was  $< 0.001$  for both the pIGFBP-1 and fetal fibronectin tests.

Table 1. Demographic and Clinical Characteristics of the Study Population

|                        | Maternal age (y) | Gestational age at admission (wks) | Parity | Gravidity | Os (cm) |
|------------------------|------------------|------------------------------------|--------|-----------|---------|
| pIGFBP-1 test          |                  |                                    |        |           |         |
| Positive (n = 28)      | 27.0             | 30.5                               | 0.5    | 2.0       | 1.00    |
| Negative (n = 66)      | 27.0             | 32.2                               | 1.0    | 2.0       | 0.00    |
| Fetal fibronectin test |                  |                                    |        |           |         |
| Positive (n = 28)      | 26.5             | 30.9                               | 0.5    | 2.0       | 1.00    |
| Negative (n = 66)      | 27.0             | 31.7                               | 1.0    | 2.0       | 0.00    |

Table 2. Gestational Age at Delivery and Admission-to-delivery Interval for Both pIGFBP-1 Test and Fetal Fibronectin Test

|                        | Gestational age at delivery (wks) | Admission-to-delivery interval (wks) |
|------------------------|-----------------------------------|--------------------------------------|
| pIGFBP-1               |                                   |                                      |
| Positive (n = 28)      | 32.9 ( $\pm 4.0$ )                | 2.3 ( $\pm 2.8$ )                    |
| Negative (n = 66)      | 37.4 ( $\pm 1.8$ )                | 5.1 ( $\pm 3.2$ )                    |
| <i>P</i>               | <0.001                            | <0.001                               |
| Fetal fibronectin test |                                   |                                      |
| Positive (n = 28)      | 34.2 ( $\pm 4.2$ )                | 3.3 ( $\pm 2.8$ )                    |
| Negative (n = 66)      | 37.4 ( $\pm 2.1$ )                | 5.1 ( $\pm 3.3$ )                    |
| <i>P</i>               | <0.001                            | 0.002                                |

The admission-to-delivery interval was 2.8 weeks shorter in the group with positive pIGFBP-1 results (2.3 weeks compared with 5.1 weeks) ( $P < 0.001$ ). It was 1.8 weeks shorter in the groups with positive fetal fibronectin results (3.3 weeks compared with 5.1 weeks) ( $P = 0.002$ ).

Both pIGFBP-1 and fetal fibronectin tests have a high negative predictive value (NPV) in predicting risk of delivery within 48 hours, 7 days or 14 days (1.00; 0.92; 0.92 and 0.97; 0.89; 0.89, respectively) (Table 3). pIGFBP-1 has the highest NPV of 1.00 in predicting risk of delivery within 48 hours.

## Discussion

An accurate diagnosis of preterm labour is clinically difficult. Only about 20% of women presenting with signs and symptoms of preterm labour would actually deliver preterm.<sup>3</sup> Various tools have been devised for the identification of women at risk of preterm delivery. These include risk scoring systems, biochemical markers of inflammation, and fetal fibronectin.<sup>14-17</sup> These aim to decrease the unnecessary interventions for patients with symptoms of preterm labour and to identify patients who might benefit from aggressive therapy including tocolysis, corticosteroids, and intra-uterine transfer to a tertiary care facility.

Table 3. The Sensitivity, Specificity, PPV and NPV for both IGFBP-1 Test and Fetal Fibronectin Test

|                        | Sensitivity | Specificity | PPV  | NPV  |
|------------------------|-------------|-------------|------|------|
| pIGFBP-1 test          |             |             |      |      |
| 48 hours               | 1.00        | 0.74        | 0.18 | 1.00 |
| 7 days                 | 0.69        | 0.78        | 0.39 | 0.92 |
| 14 days                | 0.72        | 0.80        | 0.46 | 0.92 |
| Fetal fibronectin test |             |             |      |      |
| 48 hours               | 0.60        | 0.72        | 0.11 | 0.97 |
| 7 days                 | 0.56        | 0.76        | 0.32 | 0.89 |
| 14 days                | 0.61        | 0.78        | 0.39 | 0.89 |

NPV: negative predictive value; PPV: positive predictive value

Lockwood et al<sup>8</sup> was the first to show the association between the presence of fetal fibronectin in preterm labour patients and subsequent preterm delivery. It showed that a negative result would rule out labour within 7 days with a very high NPV (97% to 99.5%), whereas a positive result does not necessarily predict the onset of labour [positive predictive value (PPV) 15% to 25%]. Therefore, a negative result indicates a low likelihood of delivery, but a positive test should not be interpreted as an indication of labour or a reason for admission on its own.

Kekki et al<sup>5</sup> showed that women with a pIGFBP-1 concentration of at least 10 mg/L in a cervical swab sample had a 10-fold risk of preterm delivery compared with women in whom the concentration of pIGFBP-1 was less than that. Lembed et al<sup>6</sup> carried out a prospective study on 36 women between 20 and 36 weeks of gestation with regular contractions. Eighteen patients had a positive Actim Partus test and 18 had a negative test. Among the 18 patients with a positive test, only 1 delivered at term and the other 17 patients delivered preterm (<37 weeks). Among the 18 women with a negative test, only 2 delivered preterm ( $P < 0.05$ ). Sensitivity, specificity, PPV and NPV of the rapid pIGFBP-1 test for preterm delivery were 89.5%, 94.1%, 94.4% and 88.9%, respectively.

Our study aimed to compare the effectiveness of pIGFBP-1 versus fetal fibronectin test in predicting preterm delivery. We studied the gestational age at delivery and the admission-to-delivery interval for the 2 tests. Our study showed that among those with negative pIGFBP-1 and fetal fibronectin results, the median ( $\pm$ SD) gestational age at delivery was 37.4 weeks ( $\pm 1.8$  weeks) and 37.4 weeks ( $\pm 2.1$  weeks) respectively. Among those with positive pIGFBP-1 and fetal fibronectin results, the median ( $\pm$ SD) gestational age at delivery was 32.9 weeks ( $\pm 4.0$  weeks) and 34.2 weeks ( $\pm 4.2$  weeks), respectively. The  $P$  value was <0.001 for both the pIGFBP-1 and fetal fibronectin tests. The 2 tests have very similar results. We also performed a Kappa analysis to ascertain the measure of agreement between the

2 tests. The Kappa was 0.75, with  $P = 0$ . This means 75% of the time the 2 tests are in agreement with each other and it is statistically significant.

The admission-to-delivery interval was 2.8 weeks shorter in the group with positive pIGFBP-1 results (2.3 weeks compared with 5.1 weeks) ( $P < 0.001$ ). It is 1.8 weeks shorter in the groups with positive fetal fibronectin results (3.3 weeks compared with 5.1 weeks) ( $P = 0.002$ ). Again, the results are comparable.

We also looked at the sensitivity, specificity, PPV and NPV for both tests in the prediction of delivery within 48 hours, 7 days and 14 days. The 48-hour time interval was chosen because this is the crucial period for the completion of corticosteroid therapy.

As expected, both pIGFBP-1 and fetal fibronectin have high NPVs. In our study, the NPV for fetal fibronectin in predicting delivery within 7 days was somewhat lower than that published in Lockwood's (89% compared to 97%). The study showed that pIGFBP-1 has a higher NPV than fetal fibronectin in predicting preterm delivery within 48 hours, 7 days and 14 days (100%; 92%; 92% and 97%; 89%; 89%, respectively).

In conclusion, both pIGFBP-1 and fetal fibronectin tests are effective adjuvant bedside test kit for the prediction of preterm delivery in patients presenting with signs or symptoms of preterm delivery. However, pIGFBP-1 has a higher NPV of 1.00 in predicting risk of delivery within 48 hours.

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#### Footnote:

*Fibronectin test costs about US\$50 each.*

*Actim Partus test costs about US\$12 each.*

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