Original Article

Evaluation of a Bedside Test for Phosphorylated Insulin-like Growth Factor Binding Protein-1 in Preterm Labour

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Abstract

Objective: The objective of this study was to assess the efficacy of a bedside test kit for phosphorylated insulin-like growth factor binding protein-1 (IGFBP-1) in the diagnosis of preterm labour and the prediction of subsequent preterm delivery. Materials and Methods: We performed a bedside test for IGFBP-1 in 47 women who presented to the delivery suite in suspected preterm labour between 23 and 33 weeks. Tocolysis and steroid therapy were administered in all cases. Results: Twenty-nine women (61.7%) tested negative and 18 women tested positive (38.3%). There was no statistical significance between the 2 groups except that the test-positive group had a greater median cervical dilatation (2.0 cm) compared to the test-negative group (1.0 cm) (P <0.05). The women who tested positive had a statistically significant longer median duration of hospitalisation, stay in delivery suite and tocolytic therapy (5.0 days, 56.0 hours and 34.5 hours respectively) compared to women who were test-negative (3.0 days, 19.0 hours and 10.0 hours respectively) (P <0.05). In addition, 91.7% of the patients in the IGFBP-1 negative group had a delay of more than 7 days between the onset of contractions and delivery, while only 44.4% of the women in the pIGFBP-1 positive group experienced such a delay. Conclusion: These results suggest that there may be a role for cervical IGFBP-1 test in the management of women presenting with suspected preterm labour. It may allow us to focus our efforts on women who are more likely to have a preterm delivery and perhaps allow us to avoid unnecessary treatment and to contain healthcare costs.

Ann Acad Med Singapore 2004;33:780-3

Key words: Accurate, Cost-effective, Delivery, Prediction

Introduction

The diagnosis of preterm labour poses a problem. Preterm labour accounts for about 50% of preterm births; however, most data reveal that only about 20% of women presenting with suspected preterm labour actually deliver preterm. A test to better predict who is most likely to deliver preterm would allow us to direct therapy more appropriately.[1] Tocolytic and steroid therapy as well as in utero transfer could be offered to those women who stand to benefit the most. Clinicians would also be able to confidently withhold therapy in women who are assessed to be unlikely to deliver preterm. This is important both in terms of avoiding the not insignificant risk of adverse effects associated with tocolytic therapy as well as in controlling healthcare costs. The detection of phosphorylated insulin-like growth factor binding protein-1 (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.[2,3]

IGFBP-1 belongs to the superfamily of insulin-like binding proteins.[2,4-6] There are 6 subtypes of IGFBP distributed widely throughout the body. A highly phosphorylated form (pIGFBP-1) is found in decidual tissues.[7,8] The process of labour is hypothesised to disrupt the chorio-decidual interface, releasing pIGFBP-1 into the cervical secretions. The identification of pIGFBP-1 would thus be indicative of the occurrence of the labour process and predictive of preterm delivery.[3,9] Developments in biomedical engineering have allowed the development of a commercial bedside test kit for the qualitative detection of pIGFBP-1 above the level of 10 μg/L. In this prospective study we evaluated the efficacy of the bedside test kit for pIGFBP-1 in predicting premature delivery in symptomatic women.

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Materials and Methods

We recruited 47 consecutive patients who presented with suspected preterm labour requiring tocolysis between 23 and 33 weeks amenorrhoea. All these patients had complaints of regular intermittent painful contractions occurring at least once in 10 minutes with regular uterine activity on cardiotocographic monitoring. All these patients were assessed to be in preterm labour, and a clinical decision had been made to initiate tocolytic therapy and to administer corticosteroids before they were recruited into the study.

Patients with the following conditions were excluded: antepartum haemorrhage, cervical dilatation of more than 3 cm, ruptured membranes, insertion of a cervical cerclage or a contraindication to tocolysis.

Upon admission to the delivery suite, clinical evaluation was performed, including a digital cervical assessment. After the patient was recruited, a speculum examination was done, and the bedside pIGFBP-1 test performed on the cervical secretions. Subsequent obstetric care was left to the discretion of the attending obstetrician who was informed of the pIGFBP-1 test results. All cases were administered a course of corticosteroids to enhance fetal pulmonary maturation as well as tocolysis as per the departmental protocol. These women were subsequently followed prospectively to assess the success of tocolysis and pregnancy outcome.

Statistical tests were used to assess whether the differences observed between the women who tested positive and negative were statistically different. The continuous variables within the 2 groups were compared using the Mann-Whitney U test, with a *P* value of less than 0.05 being considered statistically significant. Data were expressed as median result and range. The chi-square test was used to compare proportions in the 2 groups.

The bedside test kit for pIGFBP-1 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. The product is marketed by Medix Biochemica 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 occur. 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. A single operator conducted all tests in order to prevent any bias in the interpretation of the test results.

Results

A total of 47 women were recruited for the study. The average maternal age was 28 years and the range of gestational age was between 23 and 33 weeks. Eighteen women (38.3%) tested positive for pIGFBP-1 while 29 women (61.7%) tested negative. Of all the women recruited, 5 defaulted subsequent antenatal care in our hospital and were lost to follow up. All of these 5 women were test-negative and were discharged after their symptoms subsided. Table 1 summarises the demographics of the women recruited. All the patients in both groups received antenatal steroids and tocolytic therapy according to existing clinical protocols. Intravenous salbutamol was the tocolytic agent used in 46 women, while 1 woman received successful tocolysis with oral nifedipine alone.

The women who tested negative for IGFBP-1 had a significantly shorter stay in the delivery suite, as well as a reduced requirement for tocolysis and a shorter hospitalisation. A significantly greater proportion of women who tested negative remained undelivered after 4 days and 7 days. There was, however, no statistical significance in the number of women remaining undelivered after 48 hours. Less than a quarter of the women who tested negative delivered before 36 weeks, compared to more than 75% of the women who tested positive. This result was statistically significant. These results are summarised in Tables 2 and 3.

The 2 women who were delivered within 7 days of presentation in the test-negative group were delivered by lower segment Caesarean section within 24 hours of admission. Both of these women presented with symptoms suggestive of preterm labour, and were subsequently found to have severe pre-eclampsia upon evaluation in the delivery suite. The indication for the Caesarean section was severe pre-eclampsia in both cases, with no sign of labour having

Table 1. Patient Characteristics of Study Population

	Age (y)	Median gestational age* (wks)	Nulliparous	Median cervical dilation (cm)
Positive pIGFBP-1 (n = 18)	25.5 (range, 17-39)	31.5 (range, 23-33)	9 (50.0%)	2.0 (range, 0-3)
Negative pIGFBP-1 (n = 29)	29.0 (range, 20-40)	31.0 (range, 24-33)	18 (62.1%)	1.0 (range, 0-2.5)
P value	>0.05	>0.05	>0.05	<0.05

* Gestational age reflected is based on the working expected date of delivery
pIGFBP-1: phosphorylated insulin-like growth factor binding protein-1

Table 2. Duration of Hospital Stay, Delivery Suite Stay and Tocolytic Therapy of Patients

	Median hospital stay (days)	Median delivery suite stay (h)	Median tocolytic therapy (h)
Positive pIGFBP-1 (n = 18)	5.0 (range, 4-24)	56.0 (range, 18-444)	34.5 (range, 6-396)
Negative pIGFBP-1 (n = 29)	3.0 (range, 2-18)	19.0 (range, 6-184)	10.0 (range, 1-110)
P value	<0.05	<0.05	<0.05

pIGFBP-1: phosphorylated insulin-like growth factor binding protein-1

Table 3. Preterm Delivery and pIGFBP-1 Results

	Median GA at delivery (wks)	Delivery before 36 weeks	Undelivered after 2 days	Undelivered after 4 days	Undelivered after 7 days
Positive pIGFBP-1 (n = 18)	33	14 (77.8%)	14 (77.8%)	10 (55.6%)	8 (44.4%)
Negative pIGFBP-1 (n = 24*)	37	5 (20.8%)	22** (91.7%)	22** (91.7%)	22** (91.7%)
P value	<0.05	<0.05	>0.05	<0.05	<0.05

* 5 women lost to long-term follow-up

** Urgent lower segment caesarean section was performed in 2 women within 24 hours of presentation for severe pre-eclampsia

GA: gestational age; pIGFBP-1: phosphorylated insulin-like growth factor binding protein-1

progressed at the time of delivery.

The results show that the bedside test for pIGFBP-1 has a sensitivity of 73.7% and a specificity of 82.6% for the prediction of preterm delivery before 36 weeks. The positive predictive value of the test is 77.8% and the negative predictive value is 79.2%. In other words, a woman who tested positive for pIGFBP-1 has roughly a 78% chance of delivering preterm while a woman who tested negative has roughly 79% chance of not delivering her baby preterm. The main limitation of this study is its small sample size. However, the results suggested that this test may have an important role in the management of women presenting with symptoms suggestive of preterm labour.

Discussion

Preterm labour and delivery is a major cause of perinatal morbidity and mortality. However, the accurate diagnosis of preterm labour has been subjective, with much reliance on clinical symptoms and signs. As such, we may be over-treating patients with suspected preterm labour. Tocolysis is not entirely innocuous, with each tocolytic drug being associated with a significant risk of adverse effects.[10,11] Only about 20% of symptomatic women actually deliver preterm, and clinical parameters alone cannot reliably predict early delivery. As such, it is important that we are able to distinguish between inconsequential abdominal pain or uterine activity and true premature labour with the associated morbidity and mortality of premature delivery.

IGFBP-1 belongs to the superfamily of insulin-like binding proteins and the phosphorylation status of IGFBP-1 in decidual tissues is different from that in amniotic fluid. The highly phosphorylated form (pIGFBP-1) is found in decidual tissues and was previously designated as Placental Protein 12. The hypothesis is that labour disrupts the chorio-decidual interface, releasing pIGFBP-1 into the cervical secretions. The identification of pIGFBP-1 would thus be indicative of the occurrence of the labour process.

Kekki et al[9] showed that women with a pIGFBP-1 concentration of at least 10 μg/L in a cervical swab sample had a 10-fold risk of preterm delivery compared with women in whom the concentration of pIGFBP-1 concentration was less than 10 μg/L. In our study, we used a bedside fast-reacting test kit, which yielded qualitative results with a similar sensitivity of 10 μg/L. This immuno-enzymatic test relies on the monoclonal antibody 6303, the detecting antibody specific for the phosphorylated form of IGFBP-1. The bedside test has the advantage of allowing the results to be known within 5 minutes thereby having a direct impact on clinical management.

Lembet et al[12] 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 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, positive and negative predictive values of the rapid phIGFBP-1 test for preterm delivery were 89.5%, 94.1%, 94.4% and 88.9%, respectively.

Our current results show a test with a very reasonable accuracy and which is easy to use. The test results were all readable within 5 minutes of sampling. The women who tested negative for IGFBP-1 experienced a reduced need for hospitalisation and tocolysis, as well as a substantial prolongation in pregnancy, compared to the women who tested positive. These data suggest that this bedside test has a role in the diagnosis or exclusion, of premature labour and

delivery, in symptomatic women. In cases where premature labour is suspected, a negative test could exclude the diagnosis, thereby rendering obstetric intervention with tocolysis or in utero transfer unnecessary. This could have the additional benefits of reducing the risks associated with intervention as well as the costs of inpatient treatment.

There have existed several other objective predictive tests, including fetal fibronectin.[1,13-15] Lockwood et al[13] first proposed the detection of fetal fibronectin in vaginal or cervical secretions based on the theory that it is released from the decidua or membranes in response to mechanical or inflammatory-mediated insult to the membranes.[13] Faron et al[14] reported the high accuracy of this test, with a positive test likelihood ratio (LR) of 3.5-7.5, and a negative test LR of 0.4. However, Benattar et al[15] reported that the test may not be as reliable. Further limitations include its high cost and inaccuracy after sexual intercourse or digital examination.

As all of the women in our study received tocolysis, there is a possibility that the test serves to identify women less likely to respond to tocolysis. The next step would be to assess the effect of withholding tocolytic therapy in women who tested negative.

In conclusion, the bedside fast-reacting test kit for pIGFBP-1 shows promising results, and is clinically useful in the diagnosis and exclusion of premature labour and delivery in symptomatic women. If larger studies confirm our initial results, the test may replace cervical ultrasound and fetal fibronectin tests in the future, or at least serve as a useful adjunct to these tests. It will allow us to focus our efforts on women who are more likely to deliver preterm and perhaps allow us to avoid unnecessary treatment and to contain healthcare costs.

REFERENCES

1. Goldenberg RL, Mercer BM, Meis PJ, Cooper RL, Das A, McNellis D. The preterm prediction study: fetal fibronectin testing and spontaneous preterm birth. NICHD Maternal Fetal Medicine Units Network. Obstet Gynecol 1996;87:643-8.
2. Rutanen EM, Karkkainen TH, Lehtovirta J, Uotila JT, Hinkula MK, Hartikainen AL. Evaluation of a rapid strip test for insulin-like growth factor binding protein-1 in the diagnosis of ruptured fetal membranes. Clin Chim Acta 1996;253:91-101.
3. Nuutila M, Hiilesmaa V, Karkkainen T, Ylikorkala O, Rutanen EM. Phosphorylated isoforms of insulin-like growth factor binding-1 in the cervix as a predictor of cervical ripeness. Obstet Gynecol 1999;94: 243-9.
4. Rutanen EM. Insulin-like growth factors in obstetrics. Curr Opin Obstet Gynaecol 2000;12:163-8.
5. Rajaram S, Baylink DJ, Mohan S. Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and function. Endocr Rev 1997;18:801-31.
6. Julkunen M, Koistinen R, Aalto-Setala K, Seppala M, Janne OA, Kontula K. Primary structure of human insulin-like growth factor binding protein/placental protein 12 and tissue-specific expression of its mRNA. FEBS Lett 1988;236:295-302.
7. Martina NA, Kim E, Chitkara U, Wathen NC, Chard T, Giudice LC. Gestational age-dependent expression of insulin-like growth factor binding protein-1 phosphoforms (IGFBP-1) in human extraamniotic cavities, maternal serum, and decidua suggests decidua as the primary source of IGFBP-1 in these fluids during early pregnancy. J Clin Endocrinol Metab 1997;82:1894-8.
8. Rutanen EM, Bohn H, Seppala M. Radioimmunoassay of placental protein 12: levels in amniotic fluid, cord blood, and serum of healthy adults, pregnant women and patients with trophoblastic disease. Am J Obstet Gynecol 1982;144:460-3.
9. Kekki M, Kurki T, Karkkainen T, Hiilesmaa V, Paavonen J, Rutanen ME. Insulin-like growth factor-binding protein-1 in cervical secretion as a predictor of preterm delivery. Acta Obstet Gynecol Scand 2001;80: 546-51.
10. Main DM, Gabbe SG, Richardson D, Strong S. Can preterm deliveries be prevented? Am J Obstet Gynecol 1985;151:892-8.
11. King JF, Grant A, Keirse MJ, Chalmers I. Beta-mimetics in preterm labor: an overview of the randomized controlled trials. Br J Obstet Gynecol 1988;95:211-22.
12. Lembet A, Eroglu D, Ergin T, Kuscu E, Zeyneloglu H, Batioglu S, et al. New rapid bed-side test to predict preterm delivery: phosphorylated insulin-like growth factor binding protein-1 in cervical secretions. Acta Obstet Gynecol Scand 2002;81:706-12.
13. Lockwood CJ, Senyei AE, Dische MR, Casal D, Shah KD, Thung SN, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. N Engl J Med 1991;325:669-74.
14. Faron G, Boulvain M, Irion O, Bernard PM, Fraser WD. Prediction of preterm delivery by fetal fibronectin: a metaanalysis. Obstet Gynecol 1998;92:153-8.
15. Benattar C, Taieb J, Fernandez H, Lindendaum A, Frydman R, Ville Y. Rapid fetal fibronectin swab-test in preterm labour patients treated by betamimetics. Eur J Obstet Gynecol Reprod Biol 1997;72:131-5.