

Prediction of Preterm Delivery: A Pilot Study on the Use of Rapid Phosphorylated Insulin-like Growth Factor-binding Protein 1 Test

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Objective: This was a pilot study to determine whether the rapid phosphorylated insulin-like growth factor-binding protein 1 (phIGFBP-1) bedside test can help to predict preterm delivery in women who presented with symptoms of threatened preterm labour in our local population in Hong Kong.

Methods: This prospective cohort study was conducted in a tertiary obstetrics and gynaecology unit. Pregnant women with a singleton pregnancy and intact membrane who presented with symptoms of threatened preterm labour between 24 and 34 weeks' gestation, from July 2013 to May 2014, were recruited. Cervical samples were taken for rapid phIGFBP-1 bedside testing from eligible consenting patients. Sensitivity, specificity, negative predictive value, and positive predictive value of the rapid phIGFBP-1 bedside test to predict preterm delivery within 48 hours, 7 days, 14 days, as well as at <34 and <37 weeks' gestation were measured.

Results: A total of 39 women were recruited. Of 19 (49%) who had a positive result for the phIGFBP-1 test, three (16%) delivered within 7 days. A negative phIGFBP-1 test was confirmed in 20 (51%) women of whom two delivered within 7 days and one within 48 hours. The negative predictive value for predicting delivery within 7 days and 48 hours was 90% and 95%, respectively. The delivery outcome for women with a positive and those with a negative phIGFBP-1 result showed no statistical difference.

Conclusion: The high negative predictive value in this pilot study was similar to that in other studies. Hong Kong J Gynaecol Obstet Midwifery 2016; 16(1):15-20

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Introduction

Preterm delivery (PTD) is a serious pregnancy complication that can lead to significant perinatal morbidity and mortality¹. It occurs in approximately 5% to 13% of all deliveries^{2,4}. Prediction of PTD is difficult even in symptomatic women. Only about 20% of women who present with symptoms of threatened preterm labour (TPL) will deliver preterm⁵. If the accuracy of predicting PTD can be improved, there is a possibility that treatment to reduce neonatal morbidity and mortality, such as use of antenatal corticosteroids, tocolytics and neonatal support, can be reserved for those women at high risk of PTD and thus avoid unnecessary treatment for those at low risk.

Insulin-like growth factor-binding protein 1 (IGFBP-1) is abundant in amniotic fluid, but less so in other body fluids. It is synthesised in the decidua and liver and has different phosphorylation isoforms. Decidual cells and the human liver secrete predominantly phosphorylated forms of IGFBP-1 (phIGFBP-1), whereas amniotic fluid, fetal

serum and maternal plasma contain a substantial amount of non-phIGFBP-1⁶. When delivery is approaching, fetal membranes begin to detach from the decidua parietalis. As decidual cells are damaged, phIGFBP-1 leaks into cervical secretions. Previous studies showed that a phIGFBP-1 level of ≥ 10 $\mu\text{g/L}$ was considered elevated after 22 weeks' gestation and associated with an increased risk of PTD^{7,8}. phIGFBP-1 in cervical fluid has been studied as a biochemical marker to predict PTD among symptomatic women (presenting with uterine contractions) between 23 and 37 weeks of gestation. A sensitivity of 40% to 80% and negative predictive value (NPV) of 86% to 99% in prediction of PTD have been shown in previous studies^{9,12}.

The detection of phIGFBP-1 in cervical fluid is possible using a bedside immunochromatographic

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rapid dipstick test (Actim Partus, Medix Biochemica, Kauniainen, Finland). It is based on highly unique monoclonal antibodies, and there is no effect from semen or urine⁶. It can be used from week 22 of pregnancy until term. A concentration of phIGFBP-1 in the extracted sample $>25 \mu\text{g/L}$ is a positive result. Some overseas studies have suggested that a negative phIGFBP-1 test using this bedside kit can exclude imminent delivery within 7 days in about 90% to 95% of patients¹³⁻¹⁷. Nonetheless to date no local study has been performed in Hong Kong to address this issue. This pilot study aimed to determine whether a bedside rapid phIGFBP-1 test could predict PTD in symptomatic women in our locality.

Methods

This was a prospective cohort study carried out in the Department of Obstetrics and Gynaecology, Princess Margaret Hospital, Hong Kong from July 2013 to May 2014. The study was approved by the Kowloon West Cluster Research Ethics Committee, Hospital Authority (KW/FR-13-012[62-16]).

Patients with a viable singleton pregnancy and intact membranes who presented with symptoms of TPL, defined as having regular intermittent painful contractions occurring at least once in 10 minutes with regular uterine activity on cardiotocographic monitoring, between 24 and 34 weeks of gestation were recruited.

Patients with a multiple pregnancy, ruptured membranes, cervical dilatation, antepartum haemorrhage, chorioamnionitis, intrauterine growth restriction, pre-eclampsia, or major fetal or genital tract anomaly were excluded from the study.

The gestational age of the pregnancy was calculated using the first day of the last menstrual period (LMP) and confirmed by either a first- or second-trimester ultrasound scan. The gestational age was adjusted where there was a discrepancy >7 days or 14 days between the LMP and the first-trimester or second-trimester scan, respectively. PTD was defined as delivery after 24 and before 37 weeks of gestation.

Eligible patients were invited to participate in the study and written consent was obtained. Consenting women were treated according to the hospital protocol, with the addition of a cervical swab taken to detect the presence of cervical phIGFBP-1. Each patient admitted with symptoms of preterm labour underwent sterile speculum examination to assess the length and dilatation of the cervix. A cervical

swab was taken from the cervical os using a polyester swab that came with the bedside kit (Actim Partus). It was held in place for 10 to 15 seconds. The swab was then placed in the Specimen Extraction Solution provided with the bedside kit and swirled vigorously for 10 seconds. The dipstick in the kit was placed in the Specimen Extraction Solution until the liquid front reached the result area. The result of the test was regarded as positive if two blue lines were visible. The test was read as negative if only one blue line was visible after 5 minutes. The result of the phIGFBP-1 test was read and documented by a midwife on a pre-printed form. The forms were immediately filed in a designated folder away from the patients' hospital record. The patients and managing obstetrician were thus blinded to the result and subsequent patient care was provided based on individual clinical situations according to our departmental protocol for management of TPL, irrespective of the test result. Transvaginal measurement of cervical length was then performed by obstetricians who had the Hospital Authority Obstetric and Gynaecological Ultrasonography qualification according to the standard described by the Fetal Medicine Foundation. The patient emptied her bladder prior to the ultrasound. She was then placed in the dorsal lithotomy position and the ultrasound probe (Philips HD11 XE C8-4V, California, US; or Esaote EC123, Florence, Italy) introduced into the vagina and directed at the anterior fornix. A sagittal view of the cervix was obtained. The endocervical mucus was used to guide the true position of the internal os. Calipers were used to measure the linear distance between the triangular area of echogenicity at the external os and the V-shaped notch at the internal os. Three measurements were taken and the shortest of three measurements was recorded.

Data Collection

A standardised data collection form was used. Demographic variables (age, gravidity, parity, gestational age, previous PTD, smoking) were retrieved from the antenatal record. The subsequent use of tocolytics, antenatal corticosteroids and pregnancy outcome were traced by the investigators and documented on the standardised data collection form. Phone follow-up was conducted to review the pregnancy outcome if the patient delivered outside our unit.

Statistical Analysis

All statistical analysis of data was done by PASW Statistics 18, release version 18.0.0 (SPSS, Inc., Chicago [IL], US). Fisher's exact test was used to analyse categorical data. For continuous data with normal distribution, independent-sample *t* test was used. For continuous data

with a highly skewed distribution, a non-parametric test (i.e. Mann-Whitney *U* test) was used. The critical level of statistical significance was set at 0.05.

Results

Forty-three patients were considered suitable during the study period, but four refused consent so 39 patients were recruited. The mean ($\pm$ standard deviation) maternal age was 28.8 ± 4.7 years. The median gestational age at recruitment was 30.4 (range, 28.7-32.7) weeks. The median gestational age at delivery was 38.5 (range, 37.1-39.4) weeks. Eight (20.5%) women delivered at <37 weeks, of whom five (12.8%) delivered before 34 weeks. Tocolytics were prescribed according to departmental protocol after admission to 38 (97.4%) women. A positive and negative phIGFBP-1 result was obtained in 19 (49%) and 20 (51%) women, respectively.

Table 1 shows the comparison of maternal demographics and obstetric characteristics between women with a positive and negative phIGFBP-1 test result. Their baseline characteristics were similar with no statistically significant difference.

The phIGFBP-1 result, delivery characteristics and outcome are shown in Table 2. Among the 19 women with

a positive phIGFBP-1 result, five (26%) delivered before 37 weeks, of whom three delivered within 48 hours. All five patients had a spontaneous PTD. Fourteen (73.7%) patients did not have PTD. Among the 20 women with a negative phIGFBP-1 test result, 17 (85%) delivered after 37 weeks. PTD before 37 weeks occurred in three (15%) patients. One patient delivered within 24 hours of a negative phIGFBP-1 test result at 25 weeks and 1 day of gestation. The cervical length of that patient measured by transvaginal ultrasound was only 4 mm on admission. She was prescribed antenatal corticosteroids and atosiban as tocolytics before her delivery. Another woman was delivered by emergency lower segment Caesarean section 5 days after a negative phIGFBP-1 at 34 weeks' gestation because of a pathological fetal heart tracing on the cardiotogram without onset of labour. The third woman had a negative phIGFBP-1 test at 24 weeks and 2 days of gestation. She subsequently underwent spontaneous PTD at 36 weeks and 4 days. Although 15% of women with a negative phIGFBP-1 test result delivered before 37 weeks and 26% of women with positive phIGFBP-1 delivered preterm, the delivery outcome was not statistically different between the two groups.

The sensitivity, specificity, positive predictive value (PPV), and NPV of the phIGFBP-1 test are listed in Table

Table 1. Maternal demographics and obstetric characteristics of subjects*

Characteristic	Actim Partus–negative (n=20)	Actim Partus–positive (n=19)	p Value
Age (years)	29.7 ± 4.4	28.0 ± 4.9	0.28
Parity	0 (0-1)	0 (0-1)	0.66
Gravidity	2 (1-2)	2 (1-2)	0.81
Gestation (weeks)	31.3 (29.8-32.8)	29.3 (27.6-31.6)	0.13
Previous preterm			0.11
Yes	0	3 (16)	
No	20 (100)	16 (84)	
Smoking			1
Yes	1 (5)	1 (5)	
No	19 (95)	18 (95)	
Cervical length by transvaginal ultrasound (mm)	29.2 ± 9.9	29.4 ± 10.4	0.97
Steroids			0.49
Yes	20 (100)	18 (95)	
Tocolytics			0.49
Yes	20 (100)	18 (95)	
No	0	1 (5)	

* Data are shown as mean $\pm$ standard deviation, median (interquartile range), or No. (%)

3. A negative pHIGFBP-1 test result was associated with a high NPV for delivery before 37 weeks. The NPV was 95% for delivery within 48 hours and remained as high as 90% for delivery within 14 days.

Discussion

This current study of 39 women with symptoms of TPL determined that the sensitivity, specificity, PPV, and NPV of pHIGFBP-1 in predicting PTD <37 weeks was 62.5%, 54.8%, 26.3% and 85.0%, respectively. Respective values within 7 days were 60.0%, 52.9%, 15.8%, and 90.0%.

According to the Royal College of Obstetricians and Gynaecologists, antenatal corticosteroids are most effective in reducing neonatal respiratory distress syndrome in pregnancies that deliver between 24 hours and up to 7 days following administration of a second dose of antenatal corticosteroids¹⁸. The most common regimen of

antenatal corticosteroids is two doses of betamethasone 12 mg given intramuscularly 24 hours apart or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart. Delivery within 48 hours and within 7 days were thus chosen as outcomes in this study.

Ting et al¹⁰ carried out a prospective study of 94 women between 24 and 34 weeks of gestation with symptoms suggestive of PTD. The sensitivity, specificity, PPV and NPV of IFGBP-1 rapid test for PTD within 7 days was 69%, 78%, 39% and 92%, respectively. A recent larger prospective study published by Cooper et al¹² that included 349 women with symptoms of PTD between 24 and 34 weeks found that the sensitivity, specificity, PPV and NPV of IFGBP-1 rapid test for PTD before 37 weeks were 39%, 76%, 24% and 86%, respectively.

The PPV of the test was low in our study, similar to

Table 2. Characteristics of delivery and outcome between patients with negative and positive results of phosphorylated insulin-like growth factor-binding protein 1 test*

Characteristic	Actim Partus-negative (n=20)	Actim Partus-positive (n=19)	p Value
Mode of delivery			0.24
Caesarean section	6 (30)	2 (11)	
Vaginal	14 (70)	17 (89)	
Gestation (weeks)	38.5 (37-39)	38.6 (34-40)	0.76
Cumulative delivery			
Within 24 hours	1 (5)	2 (11)	0.61
Within 48 hours	1 (5)	3 (16)	0.34
Within 7 days	2 (10)	3 (16)	0.66
Within 14 days	2 (10)	4 (21)	0.41
Delivery			
Before 37 weeks	3 (15)	5 (26)	0.45
Before 34 weeks	1 (5)	4 (21)	0.18

* Data are shown as mean $\pm$ standard deviation, median (interquartile range), or No. (%)

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value for phosphorylated insulin-like growth factor-binding protein 1 test*

	<24 Hours	<48 Hours	Within 7 days	Within 14 days	<34 Weeks	<37 Weeks
Sensitivity	66.7 (9.4-99.2)	75.0 (19.4-99.4)	60.0 (14.7-94.7)	66.7 (22.3-95.7)	80.0 (28.4-99.5)	62.5 (24.5-91.5)
Specificity	52.8 (35.5-69.6)	54.3 (36.6-71.2)	52.9 (35.1-70.2)	54.5 (36.4-71.9)	55.9 (37.9-72.8)	54.8 (36.0-72.7)
PPV	10.5 (1.3-33.1)	15.8 (3.4-39.6)	15.8 (3.4-39.6)	21.1 (6.1-45.6)	21.1 (6.1-45.6)	26.3 (9.1-51.2)
NPV	95.0 (75.1-99.9)	95.0 (75.1-99.9)	90.0 (68.3-98.8)	90.0 (68.3-98.8)	95.0 (75.1-99.9)	85.0 (62.1-96.8)

Abbreviations: NPV = negative predictive value; PPV = positive predictive value

* Data are shown in percentages (95% confidence intervals)

the findings of other published studies^{10,12}. It is consequently deduced that a positive test should not be used as a sole indicator for PTD or used in isolation to decide on the need for initiating treatment that may prove to be unnecessary. It is worth mentioning that the commonly used tocolytics and repeated dose of steroids are not without adverse effects. Beta-agonists carry a risk of palpitations, tremor, nausea and vomiting, headache and pulmonary oedema¹⁹ whereas the use of a calcium channel blocker has a risk of flushing, palpitations, and hypotension^{20,21}. Although the side-effects of atosiban are fewer, mainly nausea²², it is an expensive drug. The cost of a course of atosiban is about HK\$6000 to HK\$7000, thus unnecessary and repeated use of the medication in public hospitals will significantly drive up the overall public medical cost. A repeated dose of steroids is associated with decreased weight, length and head circumference of the fetus at birth²³. A non-significant higher risk of cerebral palsy has also been reported among children exposed to multiple doses of steroids²⁴. Therefore tocolytics and steroids should be used with caution.

Similar to other studies, the NPV in this study was as high as 90% for delivery within 7 days and 85% for delivery before 37 weeks. A negative test result should therefore be reassuring for obstetricians and pregnant women, and might avoid unnecessary use of steroids and tocolytics. Nonetheless there was no statistical difference in outcome between the positive and negative phIGFBP-1 groups. This may have been due to the small sample size, the main limitation of this pilot study. If a NPV were to be set at 85% with the margin of error being 0.05, which is the same as the present study, it is calculated that a sample size of 196 (assuming there is no dropout) or 245 (assuming there is a 20% dropout rate) would be required to have an adequately powered study to show a significant difference between the positive and negative phIGFBP-1 groups.

Although there was no statistical difference for outcome, there were differences in the absolute event rate for PTD between the negative and positive phIGFBP-1 groups (95% vs. 84% for not delivering within 48 hours; 95% vs. 79% for not delivering before 34 weeks; and 85% vs. 74% for not delivering before 37 weeks). Such data may have clinical implications or importance for the use of antenatal corticosteroids and tocolytics in women who present with symptoms of TPL, should a significant difference in pregnancy outcome be shown by a larger

prospective study.

In this study, 100% of patients in the negative phIGFBP-1 group and 95% in the positive phIGFBP-1 group were prescribed antenatal corticosteroids and tocolytics. Of 20 women with a negative phIGFBP-1 result, only one (5%) delivered within 48 hours and before 34 weeks, but all received antenatal corticosteroids and tocolytics. The application of these medications might theoretically be avoided in 95% of the women. The one patient who delivered within 48 hours and before 34 weeks of gestation had a cervical length of 4 mm measured by transvaginal ultrasound. Therefore, the addition of cervical length measurement may be of value and help to predict PTD. This needs to be addressed in a future larger prospective study.

Although the study by Cooper et al¹² showed a high NPV, it has been argued that the application of such a test result is not clinically important due to the minimal change in pre- and post-test negative probability from 84% (292/349) to 86% (95% confidence interval [CI], 82%-91%). In this current study, the pre-test and post-test negative probability for delivering preterm before 37 weeks was 79.5% (31/39) and 85% (95% CI, 62.1%-96.8%), respectively. The difference in pre-test negative probability between the current study and the one by Cooper et al¹² might be due to the use of different inclusion criteria: in the latter study¹² PTD was defined as symptoms of uterine activity judged by the assessing physician to be indicative of PTD, whereas in our study an objective assessment of uterine activity defined as regular intermittent painful contractions occurring at least once in 10 minutes with regular uterine activity on cardiotocographic monitoring was used. Nevertheless despite the small difference in the estimated pre-test negative probability, the post-test negative probability strongly supports Cooper et al's data¹² and this current study.

In conclusion, the high NPV found in this pilot study is similar to that in other studies. The clinical implications for use of tocolytics and antenatal steroids in women with a negative phIGFBP-1 test result need to be addressed in a larger prospective study.

Declaration

The Actim Partus bedside kits were provided by Nordep Healthtech.

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