Prediction of Pre-term Delivery with Phosphorylated Insulin-like Growth Factor-binding Protein-1

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Abstract

Pre-term delivery (PTD) is one of the big challenges in obstetrics having remarkable medical, health, economic and human effects. Several markers have been studied in order to identify methods to predict PTD. Ideally, a marker should predict the risk in very early pregnancy, but even when symptoms already occur, identification of women at true risk may help direct antenatal interventions to those patients that really need them. Several studies have assessed the use of the rapid phIGFBP-1 test in prediction of PTD among symptomatic women with singleton pregnancies and demonstrated that the test can efficiently rule out the risk with a high probability. Combined use of the test with cervical length (CL) measurement may also help to improve prediction of PTD risk.

Keywords

Pre-term delivery, markers, prediction, risk

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Pre-term delivery (PTD) occurs in 5–15 % of pregnancies, and in spite of several efforts to address the problem, its rate has increased over the past few decades. The phenomenon has remarkable medical, health economic and human effects. These effects are more prevalent in infants that are delivered before 34 weeks.

Approximately 75 % of all neonatal deaths are caused by pre-term delivery and it causes half of children's long term disabilities. In addition to the tremendous personal burden, the delivery of a pre-term infant brings considerable healthcare costs. Overall the majority of the costs are accounted for by infants born between 28 and 32 weeks, but individually highest costs per case occur in treating very and extremely pre-term infants.[1]

Over half of all pre-term deliveries occur for women with no apparent risk factors. Thus the cause of this complication often remains unknown, although several risk factors for PTD have been identified and some individuals seem to be more likely to deliver pre-term than others.[2,3]

One of the major focuses of PTD research has been on the search for new methods to predict it more effectively and earlier.[4,5,6] Several potential markers have been widely studied in different body fluids and tissues. The advantage of biochemical markers is that they can be performed on cervical or vaginal secretion samples that are easy and safe to obtain, with minimal discomfort for the expectant mother. The usefulness of many biomarkers, on the other hand, may be limited by the presence of many interfering factors in cervicovaginal secretions. The most extensively studied predictors are bacteriovaginosis (BV), proteins such as foetal fibronectin (FFN), insulin-like growth factor-binding protein-1 (IGFBP-1) and cytokines in cervical fluids. This article concentrates on IGFBP-1, and its use in PTD prediction.

Insulin-like Growth Factor-binding Protein-1 as a Biomarker

IGFBP-1 is synthesised and secreted by foetal and adult liver cells and by decidualised endometrial cells during pregnancy. The phosphorylation status of IGFBP-1 varies in different body fluids and tissues[7,8,9] and these different phosphorylation forms of IGFBP-1 can be distinguished by different monoclonal antibodies.[10]

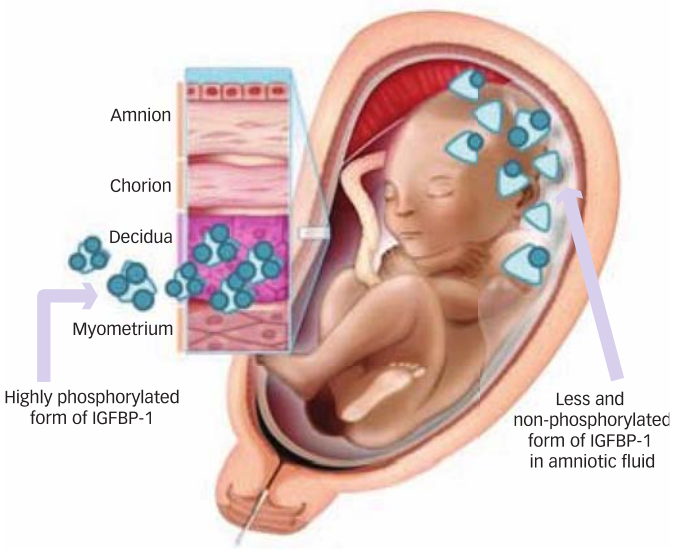
The phosphorylated form of IGFBP-1 (phIGFBP-1), produced by decidua (*see Figure 1*), can be detected by a specific monoclonal antibody (Mab 6303, Medix Biochemica, Kauniainen, Finland). When tissue disruption occurs in the choriodecidual space due to uterine contractions or infection-induced proteolysis, leakage of the decidual IGFBP-1 forms occurs into the cervical and vaginal secretions.[10] An immunochromatographic rapid bedside test for detection of phIGFBP-1 (≥10 µg/l) has been developed (Actim Partus test, Medix Biochemica) to be used for prediction of the risk of PTD. In amniotic fluid (AF), the predominant form is non-phosphorylated IGFBP-1, but other phosphorylation forms also exist. However, the most highly phosphorylated form is not found in amniotic fluid. (*see Figure 1*) The concentration of IGFBP-1 in amniotic fluid is very high, being 100–1000 times higher than in maternal serum. Very high levels of IGFBP-1 are already found in AF in very early pregnancy weeks.[10,11] The immunoenzymometric assay using a particular monoclonal antibody

Table 1: Phosphorylated Insulin-like Growth Factor-binding Protein-1 Test in Prediction of Pre-term Delivery Among Symptomatic Women

Study	n	Testing Weeks	Outcome	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Delivery within 7–14 days							
Azlin et al., 2010	51	24–36	7 days	80.0	93.5	57.1	97.7
Brik et al., 2010	276	24–34	7 days	73.1	66.2	21.8	95.0
Lembet et al., 2002	54	20–36	7 days	93.8	85.0	83.3	94.1
Eroglu et al., 2007	51	24–35	7 days	83.3	84.4	41.7	97.4
Kwek et al., 2004	47	23–33	7 days	83.3	73.3	55.6	91.7
Ting et al., 2007	94	24–34	7 days	69.0	78.0	39.0	92.0
Tanir et al., 2009	68	24–37	7 days	93.3	79.2	56.0	97.6
Rahkonen et al., 2009*	246	22–34	14 days	71.4	87.0	13.9	99.0
Tanir et al., 2009	68	24–37	14 days	60.7	80.0	68.0	74.4
Ting et al., 2007	94	24–34	14 days	72.0	80.0	46.0	92.0
Delivery before 32–37 weeks							
Brik et al., 2010	276	24–34	<32 weeks	76.2	65.5	18.4	96.4
Brik et al., 2010	276	24–34	<34 weeks	59.0	66.0	23.4	88.6
Rahkonen et al., 2009*	246	22–34	<34 weeks	50.0	86.9	13.9	97.6
Tanir et al., 2009	68	24–37	<34 weeks	70.4	74.5	48.0	88.8
Elizur et al., 2005	64	24–35	<35 weeks	81.8	64.1	32.1	94.4
Eroglu et al., 2007	51	24–35	<35 weeks	70.0	87.8	58.3	92.3
Kwek et al., 2004	47	23–33	<36 weeks	73.7	82.6	77.8	79.2
Akercan et al., 2004	77	24–36	<37 weeks	78.0	87.0	73.0	90.0
Altinkaya et al., 2009	105	24–35	<37 weeks	70.0	87.1	56.0	92.5
Elizur et al., 2005	51	24–35	<37 weeks	69.6	70.7	57.1	80.5
Lembet et al., 2002	54	20–36	<37 weeks	89.5	94.1	94.4	88.9
Paternoster et al., 2007	109	22–34	<37 weeks	69.2	90.5	50.0	95.6
Paternoster et al., 2009	210	24–34	<37 weeks	52.9	89.2	48.7	90.8

NPV = negative predictive values; PPV = positive predictive values; PROM = premature rupture of foetal membranes.
**Quantitative immunoenzymometric assay (IEMA) for phosphorylated insulin-like growth factor-binding protein-1 was used.*

Figure 1: Phosphorylation Forms of Insulin-like Growth Factor-binding Protein-1 are Different in Amniotic Fluid and in Decidual Area Enabling Different Forms to be Detected by Specific Monoclonal Antibodies



IGFBP-1 = insulin-like growth factor-binding protein-1. Illustration © Medix Biochemica Oty, reprinted with permission.

(Mab 6305, Medix Biochemica, Kauniainen, Finland) can be used to detect these non-phosphorylated and less phosphorylated forms of IGFBP-1 in vaginal samples. The detection of these forms in vaginal fluid can be used as a marker of premature rupture of foetal membranes.[12,13] The rapid bedside test (Actim PROM test, Medix Biochemica) with a detection limit of 25 µg/l can be used for this purpose.

Neither of the two tests is affected by urine and seminal plasma because IGFBP-1 is undetectable in these biological fluids, and the Actim PROM test has also been shown not to be affected by maternal bleeding.[12,14,15,16] On the other hand, maternal blood may interfere with the Actim Partus test, since the same phosphorylated forms of IGFBP-1 predominate in decidua and maternal blood.[9]

Phosphorylated Insulin-like Growth Factor-binding Protein-1 – Predictor for Pre-term Delivery

The increased concentrations of phIGFBP-1 (≥10 µg/l) in cervical secretions have been shown to predict cervical ripening in late pregnancy.[17] Several studies have assessed the use of the rapid phIGFBP-1 test in prediction of PTD among symptomatic women with singleton pregnancies (*see Table 1*).[18–29] The observed sensitivities range between 50–90 %, and the negative predictive values (NPV) between 79–98 %. The test seems to be most sensitive in predicting PTD within seven days.[18,20,24] The test has been much less studied in cases of multifoetal pregnancies and no significant difference was observed between positive and negative results.[21] A recent study, however, has shown that women with twin pregnancies who have a negative phIGFBP-1 result have a low risk of delivery before 34 weeks in the absence of other obstetric complications.[30]

One of the most widely studied markers for PTD prediction is FFN. FFN can be measured in samples obtained from the ectocervix or posterior vaginal fornix using an immunochromatographic test with a detection limit of ≥50 µg/l.[31,32] The accuracy of the FFN test in predicting spontaneous PTD varies.[6] It is most accurate in predicting spontaneous PTD within seven to ten days after testing among symptomatic women.[32,33] In direct comparison studies between the two tests, the

Table 2: Studies Comparing Rapid Tests in Prediction of Pre-term Delivery, Phosphorylated Insulin-like Growth Factor-binding Protein (Actim Partus) and Fetal Fibronectin Test

Study	n	Testing Weeks	Outcome	Test Method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Delivery within 7–14 days								
Eroglu et al., 2007	51	24–35	7 days	Actim Partus	83.3	84.4	41.7	97.4
				FFN-test	83.3	80.0	35.7	97.3
Riboni et al., 2011	210	24–34	7 days	Actim Partus	50.0	83.7	10.8	97.7
				FFN-test	50.0	80.2	9.1	97.6
Ting et al., 2007	94	24–34	7 days	Actim Partus	69.0	78.0	39.0	92.0
				FFN-test	56.0	76.0	32.0	89.0
Ting et al., 2007	94	24–34	14 days	Actim Partus	72.0	80.0	46.0	92.0
				FFN-test	61.0	78.0	39.0	89.0
Delivery before 32–37 weeks								
Riboni et al., 2011	210	24–34	<34 weeks	Actim Partus	64.3	85.7	24.3	97.1
				FFN-test	62.5	82.5	22.7	96.4
Eroglu et al., 2007	51	24–35	<35 weeks	Actim Partus	70.0	87.8	58.3	92.3
				FFN-test	70.0	82.9	50.0	91.9
Riboni et al., 2011	210	24–34	<37 weeks	Actim Partus	52.9	89.2	48.7	90.8
				FFN-test	50.0	85.9	45.5	88.0

FFN = foetal fibronectin; NPV = negative predictive values; PPV = positive predictive values.

Table 3: Combination of Phosphorylated Insulin-like Growth Factor-binding Protein-1 Results and Cervical Length in Prediction of Pre-term Delivery

Study	n	Testing Weeks	Outcome	Test Method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Delivery within 7–14 days								
Azlin et al., 2010	51	24–35	7 days	phIGFBP-1 (≥10 µg/l)	80.0	93.5	57.1	97.7
				CL <25 mm	80.0	71.7	23.5	97.1
				CL <25 mm and phIGFBP-1 (≥10 µg/l)	80.0	97.8	80.0	97.8
Eroglu et al., 2007	51	24–35	7 days	phIGFBP-1 (≥10 µg/l)	83.3	84.4	41.7	97.4
				CL <25 mm	66.7	88.9	44.4	95.2
				CL <25 mm and phIGFBP-1 (≥10 µg/l)	80.0	97.1	80.0	97.1
Rahkonen et al., 2009*	246	22–34	14 days	phIGFBP-1 (≥10 µg/l)	71.4	87.0	13.9	99.0
				CL <25 mm	57.1	94.1	22.2	98.7
				CL <25 mm and phIGFBP-1 (≥10 µg/l)	42.9	99.6	75.0	98.3
			<34 weeks	phIGFBP-1 (≥10 µg/l)	50.0	86.9	13.9	97.6
				CL <25 mm	40.0	94.1	22.2	97.4
				CL <25 mm and phIGFBP-1 (≥10 µg/l)	30.0	99.6	75.0	97.1
Paternoster et al., 2009	210	24–34	<37 weeks	phIGFBP-1 (≥10 µg/l)	52.9	89.2	48.7	90.8
				CL <26 mm	86.4	71.9	34.5	96.8
				CL <26 mm and and phIGFBP-1 (≥10 µg/l)	40.1	96.1	64.3	90.4

CL = cervical length; NPV = negative predictive values; phIGFBP-1 = phosphorylated insulin-like growth factor-binding protein-1; PPV = positive predictive values.
**Quantitative immunoenzymometric assay (IEMA) for phosphorylated insulin-like growth factor-binding protein-1 was used.*

accuracies of the phIGFBP-1 and FFN tests for predicting PTD have been shown to be similar (*see Table 2*)[22,24,34]

The predictive value of a combination of cervical ultrasonography and the use of the Actim Partus test has also been studied (*see Table 3*). One study involved cervical ultrasonography and the Actim Partus test in symptomatic women, and demonstrated that both a positive test result and a cervical length (CL) <26 mm were independent predictors of PTD.[26] Eroglu et al. demonstrated that both short CL and the Actim Partus test had similar NPV of 91.1 % and 92.3 % respectively.[22] Using the Actim Partus test in combination with the CL measurement increased the sensitivity of the CL measurement to predict delivery within the next seven days from 66.7 %–80.0 % when a cut-off of 25 mm was used for CL. In our studies, we observed that both CL measurement and Actim Partus test as a single means had a lower sensitivity to predict delivery than the physician's judgment, but that a negative phIGFBP-1 test identified patients at low risk for pre-term delivery with a high NPV comparable to that of CL >25 mm and clinical assessment including cervical ultrasonography.[29] Thus, the rapid bedside phIGFBP-1-test may provide a valuable alternative to ultrasonographic CL measurement to be used in combination with clinical assessment in prediction of pre-term delivery, especially if equipment or skills for ultrasonographic CL measurement are not available.

Phosphorylated Insulin-like Growth Factor-binding Protein-1 in Early Pregnancy

We examined for the first time the level of the phIGFBP-1 forms in cervical and vaginal samples during early pregnancy[29,35] in order to assess its potential to act as an early predictor of the risk of PTD. The study involved 5,180 asymptomatic pregnant women, examined during the first (between 12+0 and 13+6 weeks) and second (between 18+0 and 20+6 weeks) ultrasound screening visits. The study samples were taken from the vagina and cervix.

First we showed that although the range of phIGFBP-1 concentrations, as measured by immunoenzymometric assay (IEMA), was roughly similar in the vaginal and cervical samples in the first and mid-second trimester, the protein was detectable in cervical samples more than twice as often as in the vaginal samples in both trimesters and the median concentrations were significantly higher in cervical samples than in vaginal samples. Thus, our data clearly show that the site of sampling has to be defined and considered when phIGFBP-1 is used as decidual marker and data interpreted for research or clinical purposes. Secondly, we showed that elevated phIGFBP-1 (≥10 µg/l) in the first trimester increased independently the risk of subsequent spontaneous PTD. The risk for very premature birth (before 32 weeks of gestation) was nearly four-fold.

Phosphorylated Insulin-like Growth Factor-binding Protein-1 is not Released from Decidual Cells due to Intercourse

Because contaminating factors may interfere with biochemical markers, the IGFBP-1 has also been examined in body fluids that could potentially contaminate a cervical or vaginal sample. Very low or undetectable levels of IGFBP-1 have been reported in seminal plasma.[12] This finding suggested that sexual intercourse does not interfere with the use of the test, but this had not been previously examined.

In our study population, one-fifth of the women reported having had sexual intercourse within the 48 hours before sampling, and it could be demonstrated that this did not have any effect on the vaginal or cervical phIGFBP-1 concentrations. Our finding confirms that phIGFBP-1 remains a reliable marker even after intercourse.[29,35] Contrarily, high levels of FFN, another biomarker for PTD, are found in the seminal plasma, and the FFN test result may thus be affected and is not recommended if the woman has had sexual intercourse within 24 hours.[31,36]

Discussion

Pre-term delivery and its prevention remain an important challenge in obstetrics. Ideally, the more intensive antenatal surveillance and prophylactic measures should be directed to those that are most likely to benefit from prevention. In order to achieve this, accurate methods to predict PTD among asymptomatic women or those with threatened pre-term labour (PTL) would be needed.

The potential of the Actim Partus test to predict PTD in early pregnancy needs further investigation. The challenge in these studies was the low rate of pre-term deliveries as can be seen from the very low number of PTD cases; the incidence of PTD especially in non-symptomatic women is small and therefore the predictive studies require large numbers of pregnancies.

Studies on phIGFBP-1 indicate that the marker can be used as a rapid and easy to perform method to help estimate the potential risk of PTD among symptomatic patients. When the symptoms occur, there may be no way to stop the cascade that results in delivery, although it may be possible to postpone it. Therefore, even among symptomatic women, prediction of PTD is clinically helpful in certain situations. Perinatal morbidity and mortality can be reduced by appropriate application of antenatal interventions, and the success of these interventions may be increased if the diagnosis is made early. The interventions include transfer of high-risk women with PTL to a facility that can provide a neonatal intensive care unit. Secondly, timing of administration of glucocorticoids is critical, because their benefit does not last beyond seven days[37,38] and accurate prediction may help to better choose the correct time point. Thirdly, tocolytics may be administered to postpone the delivery for a few days, allowing sufficient time for transfer and treatment with antenatal steroids. Accurate diagnosis may help avoid unnecessary tocolytic treatment. This is desirable due to the significant side effects associated with the use of tocolytics.

According to the studies on phIGFBP-1, a negative Actim Partus test result is observed for the majority of symptomatic women. The high negative predictive value of the test means that those patients are highly unlikely to deliver pre-term. This helps to focus the interventions to the actual high-risk patients that will benefit from them the most. ■

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