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The role of phosphorylated insulin-like growth factor binding protein-1 in predicting pre-term labour in twin pregnancies

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Summary
This was a retrospective study, carried out at Yeovil District Hospital, UK, from January 2006 to December 2008, looking at 40 patients with twin pregnancies. The aim was to evaluate the role of phosphorylated insulin-like growth factor binding protein-1 (IGFBP-1) test in the prediction of pre-term delivery in twin pregnancies. All the patients had a transvaginal ultrasound scan for cervical length at 24 weeks, followed by a high vaginal swab for IGFBP-1 at 26 weeks. A total of 95% of women screened negative for the IGFBP-1 test. None of these women delivered before 30 weeks; 7.50% delivered between 30 and 33+6 weeks; 87.5% delivered after 34 weeks. Two women (5.00%) screened positive for phosphorylated insulin-like growth factor binding protein-1; one had a spontaneous pre-term delivery at 30 weeks, while the other patient delivered at 38 weeks. It was concluded that women with twin pregnancies that have negative phosphorylated insulin-like growth factor binding protein-1 have a low risk of delivery before 34 weeks in the absence of other obstetric complications.

Keywords
Phosphorylated insulin-like growth factor binding protein-1, pre-term labour, twin pregnancies

Introduction

The prediction of pre-term delivery is a vital aspect of antenatal care for twin pregnancies. Testing for phosphorylated insulin-like growth factor binding protein-1 (IGFBP-1) from human decidual cells have a strong negative predictive value for pre-term delivery mostly in singleton pregnancies. Phosphorylated insulin-like growth factor binding protein-1 is based on immuno-chromatography and it involves two monoclonal antibodies to human IGFBP-1.

Pre-term labour and delivery occurs in nearly 57% of all twin pregnancies (Gardner et al. 1995) and, it remains the most serious complication among this high risk group. An increase in multiple pregnancies accounts for some of the recent rise in pre-term birth rate and low birth weight infants. Although twin pregnancies account for only 2.6% of births, they represent 12.2% of premature deliveries and 15.4% of neonatal deaths (Gardner et al. 1995). The prediction of pre-term birth is a vital aspect of antenatal care for twin pregnancies.

Insulin-like growth factor (IGF) system (including IGF-I, IGF-II, their receptors and the binding proteins) is involved in the control mechanism of fetal and placental growth and development. IGFBP-1 is mainly secreted from fetal and adult liver. The phosphorylated form is predominantly secreted from human decidual cells up to 18 weeks. It is uncommon to leak these substances after 20 weeks (Martina et al. 1997; Nuutila et al. 1999).

This test is an immuno-chromatographic dipstick test that detects the presence of the phosphorylated form of IGFBP-1 in cervical secretions. It has been previously shown that the detection of phIGFBP-1 in cervical secretions of symptomatic patients is a good marker for prediction of pre-term delivery (Lembet et al. 2002; Akercan et al. 2004).

The aim of this study was to assess the value of a rapid test for IGFBP-1 in cervico-vaginal secretions for predicting pre-term delivery among twin pregnancies.

Method

This was a retrospective study, carried out at Yeovil District Hospital, UK over 3 years from January 2006 to December 2008. A total of 52 women with twin pregnancies booked for antenatal care; two women (3.84%) had spontaneous miscarriage and 50 women (96.16%) delivered in our hospital during the study period. Of these, 10 women did not have the rapid IGFBP-1 test. A total of 40 women (80%) with twin pregnancies were included in this study. Antenatal and delivery records were extracted from hospital notes. Gestational age was confirmed by early dating scan.

After consent, cervical length was assessed by standard transvaginal ultrasound at 24 weeks, and the result was recorded in the patient's notes. Women with cervical length <25 mm were kept under close surveillance and given antenatal steroids if appropriate.

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The IGFBP-1 test was performed at 26 weeks. After passing a vaginal speculum under aseptic condition, a Dacron swab (provided in the kit) was applied to the external cervical os for 10–15 seconds to allow it to absorb the cervical secretions.

The specimen was analysed by using a rapid, one-step dipstick bed-side test (Actim partus test, Medix Biochemica, Finland) to detect cervical phIGFBP-1. The test is based on immuno-chromatography and it involves two monoclonal antibodies to human IGFBP-1. The concentration of phIGFBP-1 in the extracted sample higher than 30 μg/l gives the strong positive result. A single line on IGFBP was regarded as negative. A positive result appeared in 2–5 min as two blue lines on the dipstick, but if no line was seen, it was taken that the test had not worked properly.

The primary outcome measure was delivery before 34 weeks' gestation.

Table I. Maternal obstetric and demographic characteristics in the study ($n = 40$).

	Study group	
Parameters	*n*	(%)
Age (years), mean	29	
Parity, mean	1	
Ethnic background		
Caucasian	38	96.36
Non-Caucasian	2	3.64
Booking		
Gestational age ≤12 weeks	29	72.73
Gestational age >12 weeks	11	27.27
Conception		
Spontaneous	39	97.50
Assisted	1	2.50
Chorionicity		
Monochorionic	13	32.25
Dichorionic	27	67.75
Other risk factors for pre-term delivery		
Alcohol consumption	17	42.5
Smoking	13	32.5%
Previous pre-term delivery	3	7.5
Previous cervical surgery	1	2.5
None	15	37.5
Significant antenatal complications		
Proteinuric hypertension	9	22.5
Anaemia	8	20
Threatened pre-term labour	4	10
Intrauterine growth restriction	4	10
Others*	7	17.5*
None	16	40
Mode of delivery		
Normal vaginal delivery	22	55
Caesarean section	18	45

*Antepartum haemorrhage (APH), group B Strep. positive, obstetric cholestasis, premature pre-labour rupture of membranes (PPROM) and severe twin to twin syndrome (TTTS).

Results

Maternal obstetric and demographic characteristics are shown in Table I. A total of 13 women (32.25%) had monochorionic twin pregnancies, while 27 (67.75%) had dichorionic twin pregnancies. Cervical length and the IGFBP-1 test were both negative in 38 women (95%). One woman (2.50%) had positive results for both tests and one woman (2.50%) screened negative for cervical length and positive for IGFBP-1. Of the 38 women that screened negative for both tests, none delivered before 30 weeks and three (7.50%) delivered between 30 weeks and 33+6 weeks. All three had major obstetric complications: two had severe twin-twin transfusion syndrome and one had major antepartum haemorrhage.

Of the two women with a positive phIGFBP-1, one delivered between 30–33+6 weeks and the other delivered after 37 weeks. None of the 40 women in the study delivered before 30 completed weeks (Table II).

There were no babies with APGAR scores <5 at 5 min. A total of 35 babies (43.75%) were admitted to the special care baby unit (SCBU) for prematurity; 32 babies (40%) spent >5 days in the SCBU for premature-related problems. One baby (1.25%) was transferred to a tertiary hospital for severe sepsis, pneumothorax and jaundice. Other significant neonatal morbidities were jaundice (5%), small for gestational age, ABO incompatibility, congenital hypothyroidism, neonatal anaemia and polycythaemia (1.25% each).

Discussion

The findings of this study show that phIGFBP-1 testing at 26 weeks' gestation is useful for the prediction of pre-term birth. It has a comparable negative predictive value to transvaginal cervical length assessment at 24 weeks. Both tests accurately identify the majority of patients who will not deliver before 34 weeks. Most patients with twin pregnancies who have other risk factors for pre-term delivery, e.g. previous pre-term birth, will not deliver before 34 weeks. Therefore, there is a need for additional tests to identify those who are truly at risk.

An accurate diagnosis of pre-term labour is clinically difficult. Only about 20% of women presenting with signs and symptoms of pre-term labour actually deliver pre-term

Table II. Cervical length, phIGFBP-1 and gestational age at delivery ($n = 40$).

	<30 weeks		30–33+6 weeks		34 weeks		35 weeks		36 weeks		≥37 weeks		Total	
Test	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Negative cervical length and phIGFBP-1	0		3	7.50*	4	10.00	7	17.50	4	10.00	20	50.00	38	95.00
Positive cervical length and phIGFBP-1	0		1	2.50	0		0		0		0		1	2.50
Positive phIGFBP-1 and negative cervical length	0		0		0		0		0		1	2.50	1	2.50

*Severe TTTS (2) and APH (1).

(Goldenberg et al. 1996). Various tools have been devised for the identification of women at risk of pre-term delivery. These include risk-scoring systems, biochemical markers of inflammation and fetal fibronectin (Creesy et al. 1980; Owen et al. 1990; Mercer et al. 1996; Honest et al. 2002). These aim to decrease the unnecessary interventions for patients with symptoms of pre-term labour and to identify women who might benefit from interventions like tocolysis, corticosteroids, and intrauterine transfer to a tertiary care facility.

Lembet et al. (2002) reported that the detection of phIGFBP-1 in cervical secretions by immuno-chromatography is a rapid and easily applicable test that highly anticipates pre-term delivery < 37 weeks in singleton pregnancies. Kekki et al. (2001) showed that women with a phIGFBP-1 concentration of at least 10 mg/l in a cervical swab sample had a 10-fold risk of pre-term delivery compared with women in whom the concentration of phIGFBP-1 was less than that.

Our study demonstrates the negative predictive value of phIGFBP-1 in pre-term delivery in twin pregnancies. We studied the results of phIGFBP-1 at 26 weeks and the gestational age at delivery. Our study showed that among those women with negative phIGFBP-1, 92.1% delivered after 34 weeks. Among the two women with positive phIGFBP-1, one delivered before 34 weeks.

Eroglu et al. (2007) in a study of 52 symptomatic women and 90 asymptomatic women, demonstrated that both fetal fibronectin and rapid phIGFBP-1 tests had an approximately equivalent ability (NPV 91.9% vs 92.3%) to predict pre-term delivery at < 35 weeks in singleton pregnancies. IGFBP-1 has the additional advantages that it is unaffected by urine and seminal plasma and it is cheaper and quicker than the fibronectin test (Rutanen 2000). However, vaginal bleeding and cervico-vaginal infection may adversely affect the results of both tests.

When compared with cervical length assessment in twin pregnancies, phIGFBP-1 has a similar strong negative predictive value for pre-term delivery (Lembet et al. 2002; Skentou et al. 2001; Goldenberg et al. 1996). Our study shows that both tests have similar negative predictive values (92.11%).

Detection of cervical phIGFBP-1 by a rapid test seems to be a future promising tool in the prediction of pre-term delivery in twin pregnancies. Women with twin pregnancies who have a negative phIGFBP-1 have a low risk of delivery before 34 weeks in the absence of other obstetric complications.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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