Journal of Obstetrics and Gynaecology, July 2010; 30(5): 456–460

informa
healthcare

OBSTETRICS

Role of phIGFBP-1 and ultrasound cervical length in predicting pre-term labour

M. I. NOR AZLIN[1], H. KEE BANG[1], L. JOE AN[1], S. N. MOHAMAD[1], N. A. MANSOR[1], B. SEE YEE[1], N. H. ZULKIFLI[1] & A. MOHD TAMIL[2]

Departments of [1]Obstetrics and Gynaecology and [2]Epidemiology and Biostatistics, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Summary
This prospective observational study was to evaluate the efficacy of combining phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) and transvaginal ultrasound cervical length (CL) compared with either indicator alone in predicting pre-term labour (PTL). Women with singleton pregnancy between 24 and 36 weeks' gestation with evidence of PTL were subjected to phIGFBP-1 and CL tests. Of the 51 women, five were tested positive (phIGFBP-1 positive and CL <2.5 cm) for combination of phIGFBP-1 and CL (four delivered within 1 week), whereas 46 tested negative, of which, only one delivered. A much higher negative predictivity (NP), positive predictivity (PP) and specificity (SP) in the combination test was seen compared with phIGFBP-1 or CL alone (NP: 97.8% vs 97.7% vs 97.1%; PP: 80.0% vs 51.1% and CL 23.5%; SP: 97.8% vs 93.5% vs 71.1%, respectively). The cervical os dilatation of 2 cm with combined positive test ($p = 0.001$) indicated a higher likelihood of PTL.

Keywords
Cervical length, combination, IGFBP-1, pre-term labour, ultrasound

Introduction

Pre-term delivery occurs between 7 and 10% of all pregnancies (Berkowits and Papoermik 1993) and has been reported up to 22.5% in some hospitals (Bittar 2007), which remains a challenge to obstetrician worldwide. The majority of these are caused by spontaneous pre-term labour (Terzidou 2002). Pre-term delivery is a major issue globally, as it is the main cause of neonatal deaths (Guyer 1996), long-term disability and a health economics burden. As the consequences of pre-term labour involve adverse outcomes including neonatal intensive care, drugs and surfactant therapy, an accurate diagnosis is essential (Herbst and Nilsson 2006). Similarly, a false diagnosis of pre-term labour may predispose the patient and her fetus to unnecessary intervention, creating emotional stress and financial burden, not only to family members but also the health providers.

Nevertheless, a correct diagnosis is not always easy to achieve. Over previous years many studies (Lembert 2002; Schmitz et al. 2006; Celik 2008) have been conducted to improve the accuracy of predictors for pre-term labour. Among the markers used were detection of fetal fibronectin in cervicovaginal fluids (Schmitz et al. 2006), transvaginal ultrasonographic measurement of cervical length (Berkowits and Papoermik 1993), and most recently was the phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretions (Lembert 2002). Each method showed promising results in improving the accuracy of predicting pre-term delivery (Schmitz et al. 2006).

A transvaginal assessment of cervical length is proven to be one of the best tests for predicting pre-term labour. Studies showed that a single transvaginal ultrasound examination of the uterine cervix early in pregnancy can identify pregnancies with higher risk of premature delivery (Celik 2008). The risk of pre-term labour is inversely related to cervical length (Bergelin and Valentin 2001) with cut-off points of 25 mm at <32 weeks' gestation.

IGFBP-1, which is present in cervical secretion, is also available as a rapid bedside test (Actim Partus®, Medix Biochemica, Kauniainen, Finland), and is one of the recognised markers in predicting pre-term labour with high sensitivity (80.0%), specificity (87.5%) and negative predictive value (93.3%) (Ng 2005). However, the positive predictivity is still not satisfactory. A combination of various conventional and newer markers was proposed to improve the accuracy and efficacy of the predictors (Lembert 2002; Herbst and Nilsson 2006; Schmitz et al. 2006; Celik 2008). The aim of this prospective observational study is to evaluate the efficacy of combining phIGFBP-1 and transvaginal ultrasound cervical length, comparing with each indicator alone in predicting pre-term labour in symptomatic women. The methods were chosen because they were reproducible, easily accessible and affordable.

Correspondence: M. I. Nor Azlin, Department of Obstetrics and Gynaecology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia. E-mail: azlinm@ppukm.ukm.my

ISSN 0144-3615 print/ISSN 1364-6893 online
DOI: 10.3109/01443615.2010.489162

Methods and clinical materials

A prospective observational study was carried out on all pregnant women with a gestational age between 24 and 36 weeks, with evidence of pre-term labour (PTL). Approval was granted from the Institutional Research and Ethical Board. Informed written consent was given from all patients participating in this study.

The inclusion criteria included all patients with a singleton pregnancy between 24 and 36 weeks' gestation, presenting with signs and symptoms of labour. Women with pre-term premature rupture of membranes, cervical incompetence or a cervical cerclage suture, placenta praevia or abruptio placenta, multiple pregnancies and those with cervical dilatation $\geq$3 cm on vaginal examination were excluded.

History-taking and physical examinations were done by the attending medical officers. Evidence of uterine contractions without strict criteria on frequency and strength was confirmed by external tocography. Speculum examinations were performed to ensure no leaking liquor. A phIGFBP-1 test was carried out before the digital vaginal examination. This test was by a one step dipstick test kit for detecting the presence of phIGFBP-1 in cervical secretions. A cervical specimen was taken with a Dacron swab and extracted with the specimen extraction. The test was performed by placing a dipstick in an extracted specimen of cervical secretions. A blue line (positive line) would have appeared in the result area if the concentration of phIGFBP-1 in the sample exceeded the cut-off value for the test. A second blue line confirmed correct performance of the test. If no line was seen on the dipstick, then it was taken that the test had not worked properly. The phIGFBP-1 results were not blinded to the clinician managing these patients, as this test was routinely done in the centre.

The measurement of cervical length was taken using transvaginal ultrasound scan on the same women, according to the standardised technique practiced as per guideline in our centre. A Tosbee Toshiba (Tokyo, Japan) SSH-1404 ultrasonography machine with a 6.5 MHz transvaginal transducer was used. The transducer was inserted into the vagina and the cervical length was measured in the sagittal plane. Prior to the examination, the bladder was emptied in order to avoid an elongated image, which can lead to an inaccurate result. The anatomical position of the internal cervical os, cervical canal and external cervical os were identified. The result of the cervical length was then recorded (a positive test for cervical length measured $<$25 mm and a negative test for cervical length was $\geq$25 mm). This was blinded from the managing team that further managed the women. The subsequent management of the women was then carried out as per standard protocol of the hospital. After discharge, all women were followed up at 1 week and subsequently, until delivery.

In order to achieve 80% power and 95% confidence interval (CI), the calculated sample was 51, considering 6% (Ng 2005) prevalence of pre-term labour in our centre. Demographic parameters of the pregnancy, intervention during admissions and timing of delivery were analysed. The kappa (κ) estimate, ROC curve, central tendency, Student t-test and χ^2-test were used for statistical analysis. The level of significance was taken as $p < 0.05$.

Results

A total of 51 women were included in this study. Comparisons of demographic data of patients testing positive and negative for phIGFBP-1, cervical length measurement and combination of both tests did not show any significant difference, except for the gravida and previous history of miscarriage in cervical length measurement alone group (Tables I and II).

Of the 51 women, seven were proven to have a positive phIGFBP-1 result, while the remaining 44 had negative results. When assessing the efficacy of the phIGFBP-1 test, four out of the seven women who had a positive result delivered within 1 week, while the remaining three delivered after 1 week (Table III). Of the women who had tested negative, only one out of 44 delivered within 1 week, with the remainder being delivered after 1 week. This gave a sensitivity of 80.0%, a specificity of 93.4%, a positive predictive value (PPV) of 57.1% and negative predictive value (NPV) of 97.7% (Table IV). The κ-value is 0.624, which was moderately strong in clinical agreement in this study.

However, 17 had a cervical length $<$25 mm (positive result), while the remaining 34 had a measurement of $>$25 mm (negative result) (Table III). Four out of 17 women who had a cervical length of $<$25 mm delivered within 1 week, while the remaining 13 women delivered beyond the 1-week interval. Of the women who had tested negative, only one woman out of 34 delivered within 1 week, while the remaining 33 did not deliver within the 1-week interval. This gave sensitivity, specificity, positive and negative predictive values of 80%, 87.5%, 23.5% and 96.7%, respectively (Table IV). The κ-value obtained from this study is 0.250, which indicates a weak clinical agreement between measurements of cervical length and timing of delivery, as compared with the κ-value of the phIGFBP-1 result.

It was found that only five out of 51 women had both phIGFBP-1 positive results and cervical length $<$25 mm,

Table I. Demographic data of test subjects.

	phIGFBP-1 (mean $\pm$ SD)		p value	Cervical length (mean $\pm$ SD)		p value
	Positive	Negative		Positive	Negative	
Age	29.57 $\pm$ 3.99	28.34 $\pm$ 4.32	0.475	27.29 $\pm$ 3.33	29.12 $\pm$ 4.58	0.113
Gravidity	2.43 $\pm$ 1.27	2.59 $\pm$ 1.59	0.769	1.94 $\pm$ 0.90	2.88 $\pm$ 1.70	0.038
Parity	1.00 $\pm$ 1.16	0.91 $\pm$ 0.96	0.849	0.82 $\pm$ 0.73	0.97 $\pm$ 1.09	0.570
Miscarriage	0.43 $\pm$ 1.13	0.68 $\pm$ 1.25	0.603	0.12 $\pm$ 0.33	0.91 $\pm$ 1.42	0.028
POA	32.96 $\pm$ 3.07	32.38 $\pm$ 2.64	0.652	33.37 $\pm$ 2.25	32.01 $\pm$ 2.79	0.068
Income	3,142.86 $\pm$ 1,651.12	3,352.27 $\pm$ 1,441.01	0.760	2,882.35 $\pm$ 1,515.85	3,544.12 $\pm$ 1,394.62	0.142

while the remaining 46 women had negative phIGFBP-1 results and/or a cervical length ≥25 mm (Table III). Out of the five women who had delivered within 1 week, four (80.0%) had both phIGFBP-1 positive results and cervical length <25 mm, however, only one woman (20.0%) was without positive results. The combination of the positive result of phIGFBP-1 and cervical length had produced better sensitivity of 80.0%; specificity of 97.8%; PPV of 80.0% and NPV of 97.8% (Table IV). The κ-value from the result was higher than the phIGFBP-1 and cervical length alone, which was 0.778. This produced moderately strong clinical agreement in the study.

The receiver-operating characteristic (ROC) curve had shown that the combined use of phIGFBP-1 and CL had a better result in predicting PTL compared with either phIGFBP-1 or CL alone in balance between sensitivity and specificity (Figure 1). This was supported by the largest area under the ROC curve for combined used (0.889) vs either phIGFBP-1 (0.867) or CL (0.759). Table V shows that 25 mm gave the best balance between sensitivity and specificity for cervical length, which meant the best cut-off point of CL for our sample from 24–36 weeks.

Other signs and symptoms associated with labour that had been recorded were per-vaginal discharge, show, fever, uterine contractions and cervical dilatations, for which the details of the combined test are shown in Table VI. Those with combined positive tests on both phIGFBP-1 and cervical os dilatation of 2 cm had shown a higher likelihood of PTL ($p = 0.001$).

Of 51 women, only 12 (23.53%) had tocolysis. Out of these, only two women (16.67%) had positive results for both phIGFBP-1 and cervical length <25 mm. The majority of the women ($n = 34$, 66.67%) were admitted for further management, while 16 (31.37%) were discharged. Only one woman (1.96%) was admitted twice for signs and symptoms of PTL.

The majority of the women ($n = 36$, 70.60%) had delivered via spontaneous vertex delivery; seven women (13.73%) underwent elective lower segment caesarean section and four women (7.84%) underwent emergency lower segment caesarean section. The remaining four women (7.83%) were not contactable, as they had delivered in other hospitals.

Table II. Demographic data of combination phIGFBP-1 and cervical length.

	Positive (mean ± SD)	Negative (mean ± SD)	*p* value
Age	28.60 ± 2.70	28.50 ± 4.42	0.944
Gravidity	1.80 ± 0.84	2.65 ± 1.58	0.091
Parity	0.80 ± 0.84	0.93 ± 1.00	0.750
Miscarriage	0.00 ± 0.00	0.72 ± 1.28	0.210
POA	34.34 ± 1.90	32.26 ± 2.69	0.068
Income	3,200.00 ± 1987.46	3,336.96 ± 1414.43	0.887

Table III. Diagnosing methods vs delivery time.

Variables	Delivery <1 week		Delivery >1 week	
	n	(%)	*n*	(%)
phIGFBP-1				
+ve	4	7.84	3	5.88
−ve	1	1.96	43	84.31
Cervical length				
<25 mm	4	7.84	13	25.49
≥25 mm	1	1.96	33	64.71
Both phIGFBP-1 and CL positive				
Yes	4	7.84	1	1.96
No	1	1.96	45	88.24

Discussion

Many studies (Bergelin and Valentin 2001; Lembert 2002; Ness 2007; Crane and Hutchens 2008) had shown an inverse relationship of cervical length measurements and pre-term delivery. Despite extensive studies on cervical length, no one consensus has been agreed for optimal cut-off cervical length for a given gestational age, with, instead, various adjustments made following individual study samples (Crane and Hutchens 2008; Berghella 2009). In the current study, women of gestational age from 24–36 weeks were included, and a cut-off point of 25 mm was taken to be most appropriate in our population (Table V), which is similar to other studies (Berghella 2009).

Table IV. Comparisons of phIGFBP-1, cervical length and the combination of both with previous studies.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	κ-value
phIGFBP-1					
Current study (2009)	80.0	93.5	57.1	97.7	0.624
Rahkonen et al. (2009)	71.4	87.0	13.9	99.0	
Ng et al. (2005)	80.0	87.5	66.7	93.3	
Lembert et al. (2002)	93.8	85.0	83.3	94.1	
Akerkan et al. (2004)	78.0	87.0	73.0	90.0	
Kwek et al. (2004)	73.7	82.6	77.8	79.2	
Cervical length (CL)					
Current study (2010)	80.0	71.7	23.5	97.1	0.250
Rahkonen et al. (2009)	57.1	94.1	22.2	98.7	
Palacio et al. (2007)	70.0	24.5	NA	96.8	
Schmitz et al. (2006)	87.0	61.0	13.0	99.0	
phIGFBP-1+ CL					
Current study (2010)	80.0	97.8	80.0	97.8	0.778
Rahkonen et al. (2009)	42.9	99.6	75.0	98.3	

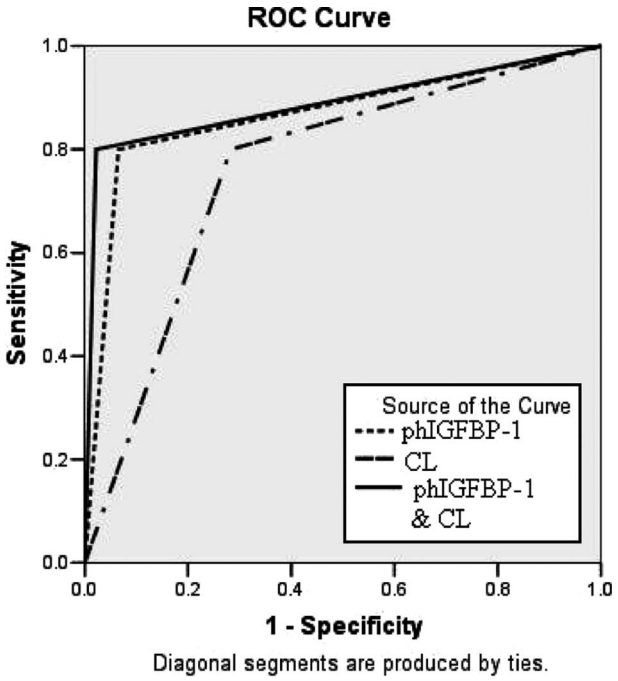

Figure 1. Comparison of sensitivity and specificity of each method.

Table V. Cervical length vs specificity and sensitivity.

CL	Specificity	1-Specificity	Sensitivity	Area
15 mm	0.978	0.022	0	0.717
20 mm	0.913	0.087	0.2	0.715
25 mm	0.717	0.283	0.8	0.759
30 mm	0.63	0.37	0.8	0.557
35 mm	0.435	0.565	1	0.567

Table VI. Signs and symptoms of labour for combined test.

	Positive		Negative		
	n	(%)	*n*	(%)	*p* value
Strength of contraction					
Irregular	1	1.96	14	27.45	
Weak	1	1.96	26	50.98	
Moderate	3	5.88	6	11.76	
Strong	0	0.00	0	0.00	
No. of contraction per 10 min (mean ± SD)	1.20 ± 0.45		1.17 ± 0.54		0.883
1	4	7.84	38	74.51	
2	1	1.96	7	13.73	
3	0	0.00	1	1.96	
Other sign and symptoms					
Show	1	2.44	6	14.64	
Per-vaginal discharge	1	2.44	30	73.17	
Fever	0	0.00	3	7.32	
Cervical dilatation (mean ± SD)	1.96 ± 0.09		0.29 ± 0.54		0.001
0 (Os close)	0	0.00	35	68.63	
1–2	5	9.80	11	21.57	

Transvaginal sonography for cervical length may be difficult for screening asymptomatic women, due to its low positive predictive values, however it may be a useful indicator for triage of symptomatic women (Ness 2007). In this current study, the predictive values obtained for sensitivity, specificity, positive and negative predictive values of cervical length alone were 80.0%, 71.7%, 23.5% and 97.1%, respectively. The figures were in accordance with a previous study, which gave more reliable negative predictivity but instead a contrast to results of positive predictive values (Schmitz et al. 2006).

As for usage of phIGFBP-1 alone, previous studies (Lembert 2002; Kwek 2004; Ng 2005) had shown a high sensitivity, specificity and negative predictive value, especially for predicting pre-term delivery within 1 week of presentation, as found in the current study (see Table IV). All studies except one (Kwek 2004) had also shown a high negative predictive value, in which women presenting with threatened pre-term labour and with negative phIGFBP-1 result predicted unlikely-to-progress into labour. The bedside test has the advantage of allowing results to be known within 5 min, which is directly applicable for clinical management. In the local setting, usage of phIGFBP-1 is preferred as compared to other biochemical markers, such as fetal fibronectin. Although cervicovaginal fetal fibronectin assay has been studied and reported to be effective, its application is limited due to its high expenses and unavailability in local settings (Kwek 2004; Ng 2005).

In this current study, the combination of phIGFBP-1 and transvaginal ultrasound cervical length has been shown to be effective for prediction of pre-term birth in symptomatic women from 24 to 36 weeks' gestation (κ-value = 0.778; Table IV). A similar study was carried out to test the combination of both methods, however it was focusing on asymptomatic women with a previous history of pre-term delivery. They concluded that screening of pregnant women with a history of pre-term birth improved with the combination of both methods (Bittar 2007). A recent study by Rahkonen et al. (2009) has shown that the phIGFBP-1 test has a high negative predictive value for pre-term labour, which was comparable with the cervical length measurement (Table IV).

All the predictive values were increased, especially the specificity and positive predictive value with the combination of phIGFBP-1 and cervical length. The sensitivity and negative predictive values still remain at a high value, which means a negative result of cervical length will support the negative values of phIGFBP-1 and gives reassurance to the clinician that the patient is unlikely to progress into labour. Also, positive predictive value has significantly increased the focus towards risk of progressing into labour and with the subsequent anticipation, management can be done to improve the outcome of pre-term labour. Thus, screening by the combination of these two methods can be reliably used in symptomatic women.

During the vaginal examination, it was noted that women with a cervical os of 2 cm would be statistically significant and were identified more frequently with the combined diagnostic method and more likely to progress into advanced labour. The subsequent management after the women were diagnosed for pre-term labour was carried out by the managing team, depending on the findings of physical examination and other investigations. Whether interventions (e.g. tocolysis and antenatal steroid) were needed could then be decided – there were 12 patients undergoing tocolysis and only two of them had a positive result on phIGFBP-1 and cervical length <2.5 cm. The

other 10 women were also given tocolysis, despite having a negative result for phIGFBP-1, although it has been shown by previous studies (Ng 2005) to have a strong negative predictive value. This may be due to the uncertainty of the phIGFBP-1 result alone.

With the current study result, combination usage of phIGFBP-1 and cervical length measurements provides more reassurance of its specificity towards pre-term labour which can now be applied with certainty, preventing unnecessary intervention. Being more specific in the anticipation of pre-term birth, the necessary preparation can then be made towards receiving premature babies, with regard to the neonatal intensive care units and for counselling parents of possible complications.

The cervical length measurements were taken by different levels of clinicians, within the standard guidelines of the study. Although this is reproducible, there may be some impact to the accuracy of the results with inter- and intra-observer variability of transvaginal CL being reported to be $<10\%$ (Berghella et al. 1997).

The combination of phIGFBP-1 and transvaginal ultrasound cervical length measurement can be easily implemented, as they are both readily accessible and reproducible. The combined used of phIGFBP-1 and transvaginal ultrasound cervical length showed a higher efficacy in predicting PTL as compared with either indicator alone. Thus, implementation of the combined methods in women with suspicion of pre-term labour has potential to improve the prediction of pre-term labour and thus, treatment can be more directed.

Acknowledgement

This study was financially supported by a UKMMC Fundamental Research Grant (FF-240–2008). The authors wish to thank medical staff of the department and the patients who had volunteered.

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

References

Akercan F, Kazandi M, Sendag F, Cirpan T, Mgoyi L, Terek MC, et al. 2004. Value of cervical phosphorylated insulinlike growth factor binding protein-1 in the prediction of preterm labor. Journal of Reproductive Medicine 49:368–372.

Bergelin I, Valentin L. 2001. Patterns of normal change in cervical length and width during pregnancy in nulliparous women: a prospective, longitudinal ultrasound study. Ultrasound in Obstetrics and Gynecology 18:217–222.

Berghella V, Tolosa JE, Kuhlman KA, Weiners, Botognese RJ, Wapner RJ. 1997. Cervical ultrasonography compared to manual examination as a predictor of pre-term delivery. American Journal of Obstetrics and Gynecology 177:723–730.

Berghella V. 2009. Novel developments on cervical length screening and progesterone for preventing pre-term birth. British Journal of Obstetrics and Gynaecology 116:182–187.

Berkowits GS, Papoermik E. 1993. Epidemiology of pre-term birth. Epidemiologic Reviews 15:414–443.

Bittar RE, Da Fonseca EB, De Carvalho MHB, Martinelli S, Zugaib M. 2007. Predicting pre-term labour in asymptomatic patients with prior pre-term delivery by measurement of cervical lengths and phosphorylated insulin-like growth factor binding protein-1. Ultrasound in Obstetrics and Gynecology 29:562–567.

Celik E, To M, Gajewska K, Smith GCS, Nicolaides KH. 2008. Cervical length and obstetric history predict spontaneous pre-term birth: development and validation of a model to provide individualized risk assessment. Ultrasound in Obstetrics and Gynecology 31:549–554.

Crane JMG, Hutchens D. 2008. Use of transvaginal ultrasonography to predict pre-term birth in women with a history of pre-term birth. Ultrasound in Obstetrics and Gynecology 32:640–645.

Guyer B, Martin JA, MacDorman MF, Anderson RN, Strobin DM. 1997. Annual summary of vital statistics 1996. Pediatrics 100:905–918.

Herbst A, Nilsson C. 2006. Diagnosis of early pre-term labour. British Journal of Obstetrics and Gynaecology 113:60–67.

Kwek K, Khi C, Ting HS, Yeo GSH. 2004. Evaluation of bed-side test for phosphorylated insulin-like growth factor binding protein-1 in pre-term labour. Annals of the Academy of Medicine, Singapore 33:780–783.

Lembert A, Eroglu D, Ergin T. 2002. New rapid bed-side test to predict pre-term delivery: phosphorylated insulin-like growth factor binding protein-1 in cervical secretions. Acta Obstetricia et Gynecologica Scandinavica 81:706–712.

Ness A, Visintine J, Ricci E, Bergella V 2007. Does knowledge of cervical length and fetal fibronectin affect management of women with threatened pre-term labor? A randomized trial. American Journal of Obstetrics and Gynecology 197:426.e1–e7.

Ng PH, Vijayan P, Mahdy ZA, Ng SP, MA Jamil. 2005. The Actim Partus bedside test to predict pre-term labour. Malaysian Journal of Obstetrics and Gynaecology 8:24–32.

Palacio M, Sanin-Blair J, Sánchez M, Crispi F, Gómez O, Carreras E, et al. 2007. The use of a variable cut-off value of cervical length in women admitted for preterm labor before and after 32 weeks. Ultrasound in Obstetrics and Gynecology 29:421–426.

Rahkonen L, Unikila-Kallio L, Nuutila M, Sainio S, Saisto T, Rutanen EM, et al. 2009. Cervical length measurement and cervical phosphorylated insulin-like growth factor binding protein-1 testing in prediction of pre-term birth in patients reporting uterine contractions. Acta Obstetricia et Gynecologica Scandinavica 88:901–908.

Schmitz T, Maillard F, Bessard-Bacquaert S, Kayem G, Fulla Y, Cabrol D, et al. 2006. Selective use of fetal fibronectin detection after cervical length measurement to predict spontaneous pre-term delivery in women with pre-term labour. American Journal of Obstetrics and Gynecology 194:138–143.

Terzidou V, Bennet PR. 2002. Preterm labour. Current Opinion in Obstetrics and Gynecology 14:105–113.