Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2017, 7, 358-368
http://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

Comparison of PAMG-1 and phIGFBP-1 Tests for the Prediction of Preterm Delivery in Patients with Preterm Labor

Marija Hadzi-Lega[1*], Josephine Theresia Maier[2], Hanns Helmer[3], Lars Hellmeyer[2], Ana Daneva Markova[1], Anastasika Poposka[4]

[1]Department of Obstetrics and Gynecology, State University Hospital of Skopje, Skopje, Republic of Macedonia
[2]Department of Obstetrics and Gynecology, Vivantes Klinikum im Friedrichshain, Berlin, Germany
[3]Division of Obstetrics and Maternal-Fetal Medicine, Medical University Vienna, Vienna, Austria
[4]Department of Orthopedics, State University Hospital of Skopje, Skopje, Republic of Macedonia
Email: *marijahadzilega@yahoo.com

How to cite this paper: Hadzi-Lega, M., Maier, J.T., Helmer, H., Hellmeyer, L., Markova, A.D. and Poposka, A. (2017) Comparison of PAMG-1 and phIGFBP-1 Tests for the Prediction of Preterm Delivery in Patients with Preterm Labor. *Open Journal of Obstetrics and Gynecology*, **7**, 358- 368.
https://doi.org/10.4236/ojog.2017.73037

Received: March 4, 2017
Accepted: March 26, 2017
Published: March 29, 2017

Abstract

Objective: To compare PAMG-1 and phIGFBP-1 tests in predicting impending spontaneous preterm delivery within 7 days upon presentation in pregnant women with symptoms of preterm labor. **Study Design**: From September 2014 to April 2015 women with singleton gestation, symptoms of preterm labor, GA 22 - 35, participated in this prospective cohort study upon admission. Recruited patients had intact membranes and a minimal cervical dilatation of ≤3 cm. Vaginal swabs for phIGFBP-1 and PAMG-1 were taken in addition to routine treatment. Biochemical test results were blinded and had no effect on management of patients. **Results**: A total of 96 patients were screened for inclusion into the trial; 57 met the inclusion criteria for final analysis. The PAMG-1 test was positive in 5.7% of patients, while phIGFBP-1 test was positive in 29.8% of patients. The prediction of spontaneous preterm delivery within 7 days of admission in patients with a cervical length < 25 mm (30%), the PAMG-1 test and phIGFBP-1 test showed a SN of 100% and 100%; SP of 83.3% and 50.0%, ($p \leq 0.05$); PPV of 71.4% and 45.5%; and NPV of 100% and 100%. 89.5% of women who received corticosteroids and 84.2% of women who received tocolysis did not go into preterm labor within one week. **Conclusion**: Our study supports the high negative predictability of biochemical tests to rule out spontaneous preterm labor in patients with a short cervix. However, our study strongly suggests that the PAMG-1 test is more accurate for predicting imminent spontaneous preterm delivery as compared to phIGFBP-1. These findings can significantly reduce economic burden caused by unnecessary admission and treatment of patients suspected of preterm labor. Such a reduction in the use of corticosteroids and tocolytics would lead to a reduction in the short and long term health effects associated with the use of

therapeutic drugs like corticosteroids, antibiotics and tocolytics.

Keywords

Preterm Labour/Labor, Preterm Birth, phIGFBP-1, Parto Sure, PAMG-1

1. Introduction

The worldwide preterm birth rate ranges from about 5% in several European countries to 18% in some African countries [1]. Up to 50% of preterm births are directly preceded by preterm labor (PTL). As many as 28% of pregnant patients presenting with signs and symptoms of PTL are admitted to the hospital [2], but only as few as 5% of these women will deliver within 7 days [3] [4]. Therefore, approximately 85% of patients admitted to the hospital for impending PTL do not deliver within the next 7 days [5]. This statistic highlights the urgent need for more accurate ways to identify those women with a true risk of impending spontaneous preterm birth (PTB), defined as birth prior to the completion of the 37th week of gestation, to avoid unnecessary administration of potentially harmful therapeutics. Use of tocolytics, particularly beta-mimetic drugs, is known to have serious side effects such as tachycardia, cardiac arrhythmia and pulmonary oedema [6]. Corticosteroids are administered for lung maturation and can lead to unwanted long-term effects if administered multiple times [7]. Therefore, it is important to time their administration within seven days of delivery to have the optimal impact on the fetus.

Traditionally, the diagnosis of imminent spontaneous PTB includes suggestive symptoms of PTL, such as suspected amniorrhexis (or rupture of the fetal membranes [ROM]), uterine activity, abdominal discomfort, change in vaginal discharge, bleeding, or cramping. Patients who have a confirmed diagnosis of ROM, typically deliver within 7 days of presentation [8]. However, in patients who have clinically intact membranes prognosis of delivery that is not as obvious. Clinical symptomatology alone is usually insufficient for prediction [9] and therefore rarely used alone. In general, research has shown that the shorter the cervix, the higher the risk for preterm delivery and vice versa [10]. Consequently, in many European countries transvaginal ultrasound (TVU) for the measurement of cervical length is frequently used to assess the risk of preterm birth in patients with impending preterm birth [11]. The use of biochemical tests, therefore, often depends on whether cervical length falls in the non-obvious 15 to 30 mm range, which accounts for roughly 55% of patients presenting with suspicion of PTL [12] [13].

As a result of such drawbacks, both biophysical and biochemical markers have been employed to help reduce the level of uncertainty in predicting imminent spontaneous PTB among these symptomatic patients. The extent to which they are used varies widely by geography and institution. The American College of Obstetrics & Gynecology (ACOG) reported that the positive predictive value of a posi-

tive fetal fibronectin test result or a short cervix alone is so poor that neither should be used exclusively to direct management in the setting of acute symptoms [14].

To date, several studies have investigated commercially available biochemical marker tests including the fetal fibronectin test (fFN; QuikCheck/Rapid fFN™, Hologic, USA), phosphorylated insulin-like growth factor binding protein test (phIGFBP-1; Actim Partus™, Oy Medix Biochemica Ab, Finland), and the placental alpha microglobulin-1 test (PAMG-1; PartoSure™, Parsagen Diagnostics, USA) [9] [15] [16]. The tests are designed to detect the presence of specific biochemical markers associated with preterm birth at concentrations higher than those found in background cervicovaginal fluids. A smaller subset of studies has compared directly the performance of these tests to each other, and while the fFN and phIGFBP-1 tests have proven comparable in several studies [17], the PAMG-1 test was found to be significantly more accurate than the fFN test [18].

The purpose of the present investigation was to compare the PAMG-1 and the phlIGFBP-1 tests in predicting impending spontaneous preterm delivery within 7 days upon presentation of pregnant women with symptoms of preterm labor, with and without a short cervix.

2. Methods

Patients were eligible to participate in this prospective cohort study upon admission at a tertiary perinatal centre (University Hospital Gynecology and Obstetrics, Skopje, Macedonia) between 22 and 34 6/7 gestational weeks. They were admitted to the High Risk Pregnancy Unit with symptoms or complaints suggesting preterm labor including uterine contractions and intermittent lower abdominal pain at the time of admission. A total of 96 patients were screened for inclusion into the trial. Recruited patients had intact amniotic membranes determined by speculum examination and a cervical dilatation of ≤3 cm determined by digital examination. Women were excluded if they had multiple pregnancies, ruptured membranes, antepartum hemorrhage, active labor, or cervical cerclage. As the primary endpoint of the study was spontaneous preterm delivery within 7 and 14 days, defined as preterm birth after premature rupture of membranes or spontaneous labor irrespective of mode, subjects with non- spontaneous deliveries within 14 days were excluded from the final analysis. Patients were recruited between September 2014 and April 2015. The study was approved by the Local Ethics Committee, and all patients gave informed consent before enrollment.

Consenting women were treated according to the standard of care at the hospital which follows Royal College of Obstetricians and Gynecologists (RCOG) guidelines and includes hospitalization, discharge, administration of tocolytic agents including beta mimetics and calcium channel blockers, and/or administration of corticosteroids (betamethasone). The only additional procedures administered for the purposes of research were the vaginal swabs taken for the phIGFBP-1 (Actim Partus) and PAMG-1 (Parto Sure) tests. Women were asked to empty their bladders and were seated in dorsal lithotomy position. Prior to

the sterile speculum examination, a blind vaginal sample was collected for the PAMG-1 test. After the introduction of the sterile speculum, a sample of cervical fluid was collected from the external os for the phIGFBP-1 test. Sample elution was performed according to the manufacturer indications by placing the vaginal specimens into the buffer solution corresponding to each test. After the extraction process, the swabs were removed and the respective rapid test strips were placed into the sample-solvent matrix. Test results were read and recorded. Following specimen collection, the patients underwent a digital examination to measure cervical dilation and a transvaginal ultrasound examination to measure cervical length. Results of all examinations and tests were recorded on the study datasheets by the respective operators. Biochemical test results were not known by the attending clinicians managing the care of patients, nor were the results of the digital and ultrasound examinations known to the reader of the biochemical tests.

Sensitivity (SN), specificity (SP), negative predictive value (NPV), and positive predictive value (PPV) for the prediction of imminent spontaneous delivery within 7 and 14 days, respectively, were calculated for the PAMG-1, phIGFBP-1, and cervical length (CL) tests independently. For patients with a short cervix, defined as cervical length of less than 25 mm, the same performance measures were calculated for the same time periods for the biochemical tests. McNemar's Test was used to compare measures (sensitivity, specificity, NPV, and PPV) of the two tests, considering results from subjects with paired data available for the given measure of interest. SAS version 9.3 was used to analyze the results.

3. Results

A total of 96 patients were screened for inclusion into the trial. 72 (75%) of these patients met initial inclusion criteria. Upon review of the final delivery records of these 72 patients, an additional 15 (21%) patients whose delivery was not proceeded by either premature rupture of membranes or spontaneous labor within 14 days of presentation were excluded. Thus, 57 of 72 patients (79%) who met the initial inclusion criteria were included in the final analysis.

The median maternal age of patients included in the final analysis was 27 years. The median gestational age at presentation was 31 weeks, whereas the median gestational age at delivery was 37 weeks. The median cervical length via transvaginal ultrasound was 28 mm. While 38 (67%) patients received tocolytic therapy and 38 (67%) patients received corticosteroids, not all patients who received one received the other. While only 6 (11%) patients delivered spontaneously within 7 days of presentation, 16 (28%) patients delivered spontaneously prior to the completion of the 33rd week of gestation. Table 1 outlines these patient characteristics. In the overall study group (n = 57), the PAMG-1 test was positive in 10 (5.7%) patients, while the phIGFBP-1 test was positive in 17 (29.8%) patients. In the group of patients with cervical length < 25 mm (n = 17), the PAMG-1 test was positive in 7 (41.2%) patients, while the phIGFBP-1 test was positive in 11 (64.7%) patients.

Table 1. Patient characteristics (n = 57).

Characteristic	Value
Maternal age (median, interquartile)	27 [23.0, 30.5]
Gestational age at presentation (median, interquartile)	31 [28.8, 32.4]
Gestational age at delivery (median, interquartile)	37 [33.5, 38.6]
Cervical length at presentation (median, interquartile)	28 [20.0, 31.0]
Cervical length < 25 mm at presentation (count/percent)	17 (30%)
Corticosteroid therapy (count/percent)	38 (67%)
Count/percent delivered within 7 days	4 (11%)
Count/percent delivered within 14 days	6 (16%)
Tocolytic therapy (count/percent)	38 (67%)
Count/percent delivered within 7 days	6 (16%)
Count/percent delivered within 14 days	7 (18%)
Delivery < 34 weeks (count/percent)	16 (28%)
Delivery ≤ 7 days of presentation	6 (11%)

For the prediction of spontaneous preterm delivery within 7 days upon admission, the PAMG-1 test, the phIGFBP-1 test, and cervical length measurement (using a cutoff of 25 mm) displayed a sensitivity (SN) of 83%, 83%, and 100%, respectively; and a specificity (SP) of 90%, 76%, and 71% (p = 0.0082), respectively. The positive predictive value (PPV) was at 50%, 29%, and 29%, respectively; and the negative predictive value (NPV) at 98%, 98%, and 100%, respectively. Table 2 illustrates these results. Figure 1 outlines the comparative performances of the PAMG-1 test and the phIGFBP-1 test in predicting spontaneous preterm birth within 7 days upon admission.

For the prediction of spontaneous preterm delivery within 14 days upon admission, the PAMG-1 test, the phIGFBP-1 test, and cervical length measurement (using a cutoff of 25 mm) displayed a sensitivity (SN) of 67%, 67%, and 78%, respectively; and a specificity (SP) of 92%, 77%, and 71%, respectively. The positive predictive value (PPV) was at 60%, 35%, and 33%, respectively; and the negative predictive value (NPV) at 94%, 93%, and 94%, respectively. Table 2 shows these performance results.

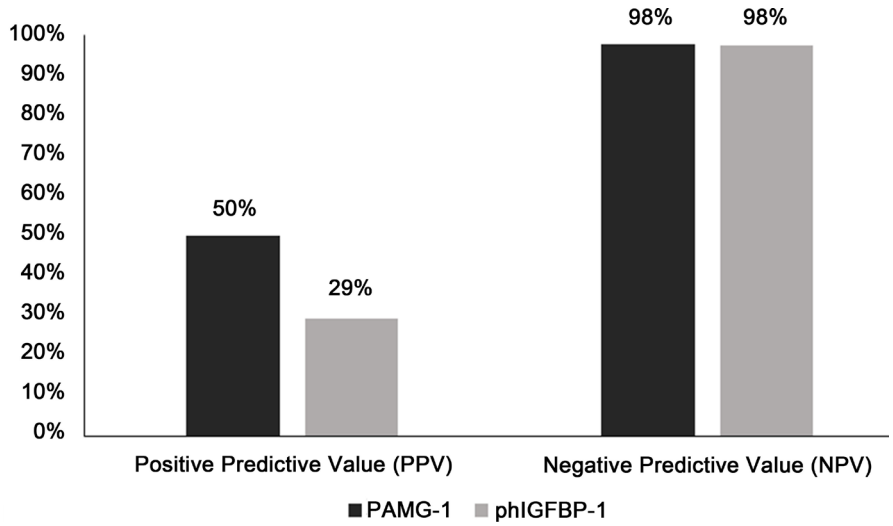
As is displayed in Figure 2, the prediction of spontaneous preterm delivery within 7 days upon admission in patients with a cervical length of less than 25 mm, the PAMG-1 test and phIGFBP-1 test showed a sensitivity (SN) of 100% and 100%, respectively; and a specificity (SP) of 83% and 50%, respectively (p = 0.0455). The positive predictive value (PPV) was at 71% and 45%, respectively; and the negative predictive value (NPV) at 100% and 100%, respectively.

In addition, Table 3 illustrates results. For the prediction of spontaneous preterm delivery within 14 days upon admission in patients with a cervical length of less than 25 mm, the PAMG-1 test and the phIGFBP-1 test displayed a sensitivety (SN) of 83% and 83%, respectively; and a specificity (SP) of 82% and 45%,

Table 2. Prediction of spontaneous preterm delivery within 7 and 14 days of presentation.

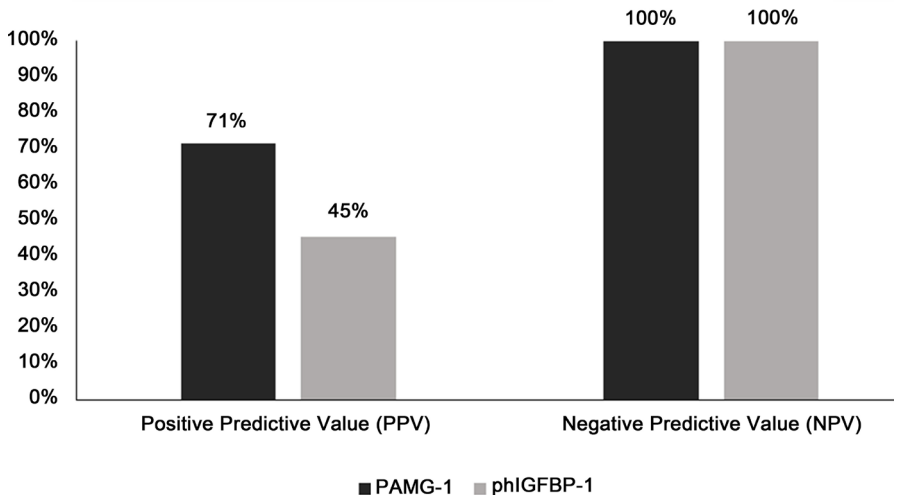
Performance Measure for 7 days	PAMG-1	phlIGFBP-1	CL (<25 mm)
Sensitivity (SN)	83%	83%	100%
Proportion	(5/6)	(5/6)	(6/6)
Confidence Interval	(35.88, 99.58)	(35.88, 99.58)	(54.07, 100)
Specificity (SP)	90%*	76%	71%
Proportion	(46/51)	(39/51)	(36/51)
Confidence Interval	(78.59, 96.74)	(62.51, 87.21)	(56.17, 82.51)
Positive Predictive Value (PPV)	50%	29%	29%
Proportion	(5/10)	(5/17)	(6/21)
Confidence Interval	(18.71, 81.29)	(10.31, 55.96)	(11.28, 52.17)
Negative Predictive Value (NPV)	98%	98%	100%
Proportion	(46/47)	(39/40)	(36/36)
Confidence Interval	(88.71, 99.95)	(86.84, 99.94)	(90.26, 100)
Performance Measure for 14 days	**PAMG-1**	**phlIGFBP-1**	**CL (<25 mm)**
Sensitivity (SN)	67%	67%	78%
Proportion	(6/9)	(6/9)	(7/9)
Confidence Interval	(29.93, 92.51)	(29.93, 92.51)	(39.99, 97.19)
Specificity (SP)	92%	77%	71%
Proportion	(44/48)	(37/48)	(34/48)
Confidence Interval	(80.02, 97.68)	(62.69, 87.97)	(55.94, 83.05)
Positive Predictive Value (PPV)	60%	35%	33%
Proportion	(6/10)	(6/17)	(7/21)
Confidence Interval	(26.24, 87.84)	(14.21, 61.67)	(14.59, 56.97)
Negative Predictive Value (NPV)	94%	93%	94%
Proportion	(44/47)	(37/40)	(34/36)
Confidence Interval	(82.46, 98.66)	(79.61, 98.43)	(81.34, 99.32)

PAMG-1: placental alpha macroglobulin-1; phlIGFBP-1: phosphorylated insulin-like growth factor binding protein; CL: cervical length 95% confidence intervals (CI) computed by the Clopper-Pearson procedure; * P-values calculated for pairwise comparisons between PAMG-1 test and phlIGFBP-1 test Specificity for Parto Sure was statistically significant (p = 0.0082)



PAMG-1: placental alpha macroglobulin-1; phlIGFBP-1: phosphorylated insulin-like growth factor binding protein.

Figure 1. Prediction of spontaneous preterm delivery within 7 days of presentation.



PAMG-1: placental alpha macroglobulin-1; phlIGFBP-1: phosphorylated insulin-like growth factor binding protein.

Figure 2. Prediction of spontaneous preterm delivery within 7 days of presentation in patients with a short cervix (<25 mm).

Table 3. Prediction of spontaneous preterm delivery within 7 and 14 days of presentation in patients with a short cervix (<25 mm).

Performance Measure for 7 days	PAMG-1	phlIGFBP-1
Sensitivity (SN) Proportion Confidence Interval	100% (5/5) (47.82, 100)	100% (5/5) (47.82, 100)
Specificity (SP) Proportion Confidence Interval	83% (10/12) (51.59, 97.91)	50% (6/12) (12.09, 78.91)
Positive Predictive Value (PPV) Proportion Confidence Interval	71% (5/7) (29.04, 96.33)	45% (5/11) (16.75, 76.62)
Negative Predictive Value (NPV) Proportion Confidence Interval	100% (10/10) (69.15, 100)	100% (6/6) (54.07, 100)
Performance Measure for 14 days	**PAMG-1**	**phlIGFBP-1**
Sensitivity (SN) Proportion Confidence Interval	83% (5/6) (35.88, 99.58)	83% (5/6) (35.88, 99.58)
Specificity (SP) Proportion Confidence Interval	82% (9/11) (48.22, 97.72)	45% (5/11) (16.75, 76.62)
Positive Predictive Value (PPV) Proportion Confidence Interval	71% (5/7) (29.04, 96.33)	45% (5/11) (16.75, 76.62)
Negative Predictive Value (NPV) Proportion Confidence Interval	90% (9/10) (55.50, 99.75)	83% (5/6) (35.88, 99.58)

PAMG-1: placental alpha macroglobulin-1; phlIGFBP-1: phosphorylated insulin-like growth factor binding protein; CL: cervical length 95% confidence intervals (CI) computed by the Clopper-Pearson procedure.

respectively; the positive predictive value (PPV) was at 71% and 45%, respectively; the negative predictive values (NPV) at 90% and 83%, respectively. **Table 3** shows these results.

In 38 (67%) of women corticosteroids were administered. Of these patients only 4 gave birth preterm within 7 days and 2 more within 14 days. Thus, 89% of patients given corticosteroids did not go into preterm labor within one week, and 84% of women within two weeks. Of 38 (67%) patients that received tocolytic therapy, 6 patients delivered preterm within 7 days and only 1 gave birth within 14 days. Thus, 84% of patients given tocolysis did not go into preterm labor within one week, and 82% within two weeks.

4. Discussion

Our study revealed that only 29% of patients presenting with (i) symptoms of preterm labor, (ii) with a sonographically short cervix (<25mm) and (iii) who were admitted to the hospital, delivered within 7 days. Of those women who did not go into preterm labor (a total of 71%) 82% received a combination of tocolysis, corticosteroids and/or antibiotics. By administering corticosteroids unnecessarily, the subsequent effect of an additional round, if administered when truly needed, may be compromised [19] [20]. Administering tocolysis needlessly can have a negative impact on maternal, fetal, and neonatal outcome [6] [21].

Thus, there is an important need for a test to accurately identify patients that are truly at risk for impending spontaneous preterm delivery. In accordance with previous literature on biochemical marker tests in high risk patients with a short cervix, our comparison of PAMG-1 and phIGFBP-1 tests showed high negative predictive values (100% for both tests for delivery within 7 days; 90% and 83% for delivery within 14 days, PAMG-1 test and phIGFBP-1 test, respectively). However, in this first ever direct comparison of the PAMG-1 and phIGFBP-1 tests, our data suggest that the PAMG-1 test is a more accurate predictor of imminent spontaneous preterm delivery with 7 days, with respect to positive predictive value (71% vs. 45%, respectively) and specificity (83% vs. 50%), which was found to be statistically significant ($p < 0.05$). This finding is supported by test performance in the entire study group (*i.e.* not only patients with a cervix less than 25 mm), wherein the PAMG-1 test was found to be more accurate than the phIGFBP-1 test across specificity ($p < 0.01$), positive predictive value and negative predictive value. This finding is further supported by previous studies investigating the PAMG-1 test specifically in patients with impending preterm labor and a cervical length less than 25 mm, which reported a positive predictive value of 75% and a specificity of 89% for the PAMG-1 test [18].

Assuming that patients with a short cervix (<25 mm) and a positive biomarker test would be admitted to the hospital, and that patients with a short cervix and a negative biomarker test would be discharged from the hospital, our data suggest that 57% of additional patients would be admitted unnecessarily to the hospital if the phIGFBP-1 test were to be used instead of the PAMG-1 test. The present

investigation could have benefited from the addition of a cost analysis to determine the financial impact of different treatment modalities and admission rates based on the contingent results of biochemical tests after ultrasound. A recent systematic review and meta-analysis conducted by Conde-Agudelo *et al.* on the phIGFBP-1 test, which reviewed 18 independent studies reporting the performance of phIGFBP-1 for predicting imminent spontaneous preterm birth within 7 days of presentation, concluded that there was insufficient evidence to recommend the routine clinical use of the phIGFBP-1 test in women with symptoms of preterm labor [22].

Despite the plethora of information in support of combining cervical length measurements and biochemical test results, the majority of non-European countries do not have the luxury of universal access to cervical length screening of symptomatic women. As a result, clinicians in these regions of the world, most of which are underdeveloped and low-resource, rely much more heavily on biochemical test results. Thus, it is for this portion of the world that this study may provide the most relevance when deciding which biochemical test to use. Further evaluation with discharging women based on biochemical test alone results and following outcomes will be interesting to research.

In conclusion, our study supports the high negative predictability of biochemical test methods to rule out spontaneous preterm labor in those patients with a short cervix, in line with previous literature. However, our study strongly suggests that the biochemical PTL test based on the detection of PAMG-1 is the more accurate test for predicting imminent spontaneous preterm delivery as compared to the phIGFBP-1 test. These findings can be applied to significantly reduce the economic burden caused today by the unnecessary admission and treatment of patients suspected of preterm labor, particularly in low resource settings where cervical length via transvaginal ultrasound is not available. Such a reduction in the use of corticosteroids and tocolytics would lead to a reduction in the short and long term health effects associated with the use of therapeutic drugs like corticosteroids, antibiotics and tocolytics.

Conflict of Interest

The authors report no conflict of interest. Parto Sure and Actim Partus test kits were obtained free of charge. The investigators do not have any financial relationship with either company.

References

[1] Blencowe, H., *et al.* (2012) National, Regional and Worldwide Estimates of Preterm Birth Rates in the Year 2010 with Time Trends Since 1990 for Selected Countries: A Systematic Analysis and Implications. *Lancet*, **379**, 2162-2172. https://doi.org/10.1016/S0140-6736(12)60820-4

[2] Grobman, W.A., Welshman, E.E. and Calhoun, E.A. (2004) Does Fetal Fibronectin Use in the Diagnosis of Preterm Labor Affect Physician Behavior and Health Care Costs? A Randomized Trial. *American Journal of Obstetrics & Gynecology*, **191**, 235-240. https://doi.org/10.1016/j.ajog.2003.11.034

[3] McPheeters, M.L., *et al.* (2005) Monoamniotic-versus Diamniotic-Monochorionic Twin Placentas: Anastomoses and Twin-Twin Transfusion Syndrome. *American Journal of Obstetrics & Gynecology*, **192**, 1325-1329. https://doi.org/10.1016/j.ajog.2004.12.055

[4] Ness, A., Visintine, J., Ricci, E. and Berghella, V. (2007) Does Knowledge of Cervical Length and Fetal Fibronectin Affect Management of Women with Threatened Preterm Labor? A Randomized Trial. *American Journal of Obstetrics & Gynecology*, **197**, 426.e1-426.e7. http://dx.doi.org/10.1016/j.ajog.2007.07.017

[5] Alfirevic, Z., Allen-Coward, H., Molina, F., Vinuesa, C.P. and Nicolaides, K. (2007) Targeted Therapy for Threatened Preterm Labor Based on Sonographic Measurement of the Cervical Length: A Randomized Controlled Trial. *Ultrasound Obstetrics & Gynecology*, **29**, 47-50. https://doi.org/10.1002/uog.3908

[6] Gyetvai, K., Hannah, M.E., Hodnett, E.D. and Ohlsson, A. (1999) Tocolytics for Preterm Labor: A Systematic Review. *Obstetrics & Gynecology*, **94**, 869-877. https://doi.org/10.1097/00006250-199911001-00043

[7] Roberts, D. and Dalziel, S. (2006) Antenatal Corticosteroids for Accelerating Fetal Lung Maturation for Women at Risk of Preterm Birth. *Cochrane Database of Systematic Reviews*, **3**, CD004454. https://doi.org/10.1002/14651858.cd004454.pub2

[8] Alexander, J.M. and Cox, S.M. (1996) Clinical Course of Premature Rupture of the Membranes. *Seminars in Perinatology*, **20**, 369-374. https://doi.org/10.1016/S0146-0005(96)80003-6

[9] Iams, J.D., *et al.* (1995) Fetal Fibronectin Improves the Accuracy of Diagnosis of Preterm Labor. *American Journal of Obstetrics & Gynecology*, **173**, 141-145. https://doi.org/10.1016/0002-9378(95)90182-5

[10] Honest, H. *et al.* (2009) Screening to Prevent Spontaneous Preterm Birth: Systematic Reviews of Accuracy and Effectiveness Literature with Economic Modeling. *Health Technology Assessment*, **13**, 1-627. https://doi.org/10.3310/hta13430

[11] Di Renzo, G.C., *et al.* (2011) Guidelines for the Management of Spontaneous Preterm Labour: Identification of Spontaneous Preterm Labour, Diagnosis of Preterm Premature Rupture of Membranes, and Preventive Tools for Preterm Birth. *The Journal of Maternal-Fetal & Neonatal Medicine*, **24**, 659-667. https://doi.org/10.3109/14767058.2011.553694

[12] Boots, A.B., *et al.* (2014) The Short-Term Prediction of Preterm Birth: A Systematic Review and Diagnostic Metaanalysis. *American Journal of Obstetrics & Gynecology*, **210**, 54.e1-54.e10. https://doi.org/10.1016/j.ajog.2013.09.004

[13] Tsoi, E., Fuchs, I.B., Rane, S., Geerts, L. and Nicolaides, K.H. (2005) Sonographic Measurement of Cervical Length in Threatened Preterm Labor in Singleton Pregnancies with Intact Membranes. *Ultrasound in Obstetrics & Gynecology*, **25**, 353-356. https://doi.org/10.1002/uog.1809

[14] ACOG Committee on Practice Bulletins-Obstetrics (2012) Practice Bulletin No. 127: Management of Preterm Labour. Clinical Management Guidelines for Obstetrician-Gynecologists. *Obstetrics & Gynecology*, **119**, 1308-1316. https://doi.org/10.1097/AOG.0b013e31825af2f0

[15] Nuutila, M., Nuutila, M., Hiilesmaa, V., Kärkkäinen, T., Ylikorkala, O. and Rutanen, E.M. (1999) Phosphorylated Isoforms of Insulin-Like Growth Factor Binding Protein-1 in the Cervix as a Predictor of Cervical Ripeness. *Obstetrics & Gynecology*, **94**, 243-249. https://doi.org/10.1097/00006250-199908000-00017

[16] Nikolova, T., Bayev, O., Nikolova, N. and Di Renzo, G.C. (2014) Evaluation of a Novel Placental Alpha Microglobulin-1 (PAMG-1) Test to Predict Spontaneous

Preterm Delivery. *Journal of Perinatal Medicine*, **42**, 473-477. https://doi.org/10.1515/jpm-2013-0234

[17] Riboni, F., *et al.* (2011) Biochemical Markers Predicting Pre-Term Delivery in Symptomatic Patients: Phosphorylated Insulin-Like Growth Factor Binding Protein-1 and Fetal Fibronectin. *Archives of Gynecology and Obstetrics*, **284**, 1325-1329. https://doi.org/10.1007/s00404-011-1839-4

[18] Nikolova, T., Bayev, O., Nikolova, N. and Di Renzo, G.C. (2015) Comparison of a Novel Test for Placental Alpha Microglobulin-1 with Fetal Fibronectin and Cervical Length Measurement for the Prediction of Imminent Spontaneous Preterm Delivery in Patients with Threatened Preterm Labour. *Journal of Perinatal Medicine*, **43**, 395-402. https://doi.org/10.1515/jpm-2014-0300

[19] Antenatal Corticosteroids Revisited: Repeat Courses. *NIH Consens Statement* 2000, **17**, 1-18.

[20] Murphy, K.E., *et al.* (2008) Multiple Courses of Antenatal Corticosteroids for Preterm Birth (MACS): A Randomised Controlled Trial. *The Lancet*, **372**, 2143-2151. https://doi.org/10.1016/S0140-6736(08)61929-7

[21] Oei, S.G., Oei, S.K. and Brölmann, H.A.M. (1999) Myocardial Infarction during Nifedipine Therapy for Preterm Labor. *The New England Journal of Medicine*, **340**, 154. https://doi.org/10.1056/NEJM199901143400219

[22] Conde-Agudelo, A. and Romero, R. (2015) Cervical Phosphorylated Insulin-Like Growth Factor Binding Protein-1 Test for the Prediction of Preterm Birth: A Systematic Review and Metaanalysis. *American Journal of Obstetrics & Gynecology*, **214**, 57-73. https://doi.org/10.1016/j.ajog.2015.06.060