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Placental α-microglobulin-1 in cervicovaginal fluid and cervical length to predict preterm birth by Thai women with symptoms of labor

Saifon Chawanpaiboon[1,*], Vitaya Titapant[1], Julaporn Pooliam[2]

Abstract

Background: Presence of placental α microglobulin-1 (PAMG-1) in cervicovaginal fluid is a bedside test to predict preterm delivery.

Objective: To determine whether the accuracy of a positive PAMG-1 test result to predict preterm birth within 7 days and 14 days in our hospital setting can be improved by adding cervical length.

Methods: We recruited 180 pregnant women who attended the labor ward of Siriraj Hospital, Thailand, from 2016 to 2018 for this prospective observational study of diagnostic accuracy. We used data from 161 women who met inclusion criteria including symptoms of preterm labor between $20^{0/7}$ and $36^{6/7}$ weeks' gestation without ruptured membranes and with cervical dilatation <3 cm and effacement <80%. Presence of PAMG-1 in cervicovaginal fluid was tested using a PartoSure kit, cervical length was measured by transvaginal ultrasound, and the time to spontaneous delivery was calculated.

Results: Pregnant women with labor pain who had cervical length <30 mm (45/161; 28%) went into delivery within 7 days, and women with a cervical length <15 mm (11/14; 79%) went into delivery within 7 days. When the PAMG-1 test result was positive and cervical length was ≤15 mm, the positive predictive value (PPV) was 83%; and when cervical length was ≤30 mm the PPV was 69%. The optimal cut off from receiver operating characteristic curve analysis showed that a cervical length <25 mm and PAMG-1 positive result has a PPV of 80% to predict preterm birth within 7 days and 90% within 14 days. The area under the curve (95% confidence interval) for a positive PAMG-1 result and cervical length ≤25 mm to predict preterm birth <7 days was 0.61 (0.50, 0.73) and <14 days was 0.60 (0.49, 0.70).

Conclusions: Cervical length ranging 15–30 mm combined with a positive PAMG-1 test result has a high accuracy to predict imminent spontaneous delivery within 7 days by women with preterm labor and cervical dilatation <3 cm in clinical practice.

Keywords: cervical length measurement; IGFBP1 protein, human; PAMG-1 protein, human; premature birth; term birth

Preterm or premature birth remains a major problem worldwide, and the trend of preterm birth has increased in many developed countries at least up to 2007 [1]. The World Health Organization (WHO) defines preterm birth as all births before 37 completed weeks of gestation [2]. Short and long-term complications of prematurity are reported [3]. The statistical

***Correspondence to: Saifon Chawanpaiboon,** Maternal Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand, email: saifon.cha@mahidol.ac.th

[1] Department of Obstetrics and Gynaecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

[2] Office for Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

unit of the Department of Obstetrics and Gynecology at Siriraj Hospital has reported that the annual incidence of preterm births steadily increased from 9.4% in 2004 to 13.7% in 2010 [4]. The 2015 preterm birth rate for the USA (based on obstetric estimate of gestational age) was 9.63% [5]. Spontaneous preterm birth in the UK occurs in 7%–12% of pregnancies before 37 weeks' gestation and in about 4% of pregnancies before 34 weeks' gestation [6]. In most developed countries, 60%–80% of neonatal mortality and 75% morbidity are from preterm birth [6]. There is support for steroid therapy to reduce respiratory morbidity [7–9] and tocolytic agents to inhibit uterine contraction and postpone delivery [7]. Corticosteroid treatment shows maximum benefit from 24 h after administration [8]. However, preterm birth is difficult to diagnose and this results in overtreatment of threatened preterm labor, which was modeled to have a high cost of 4,653 EUR per case in 2013 (USD 6,179; Federal Reserve Foreign Exchange Rate G.5A), at least in The Netherlands [10]. Several agents with different modes of action have been used to inhibit uterine contractility with a maximum time of 136 days in Germany [11]. In 50%–80% of pregnant women, preterm labor does not lead to preterm birth within 7 days and 50%–70% of women in this group who received a placebo gave birth close to term [12]. The sign of preterm labor alone has a false positive rate >50% [13], which may lead to unnecessary hospital admission for preterm labor management.

Methods to predict spontaneous preterm birth include cervical examination for dilatation and length [14–16], and testing cervicovaginal fluid for fetal fibronectin [6, 10], prolactin [17], and phosphorylated insulin-like growth factor binding protein 1 (phIGFBP-1), also known as placental α microglobulin-1 (PAMG-1) [18, 19], are effective in excluding spontaneous preterm delivery within 7–14 days. An ideal predictor would be a test that identifies who would deliver within 48 h to 7 days with the purpose of guiding the rational use of antenatal corticosteroids and tocolytic agents, decreasing unnecessary admissions, and correcting triage of patients that need in utero transfer [14, 15].

PAMG-1 was initially referred to as a specific α-1 globulin of the placenta [20, 21], then as phIGFBP-1 [19], and was first isolated from human amniotic fluid as reported by Petrunin et al. in 1976 (cited by reference 1 in [22]). PAMG-1 is found in the amniotic fluid, blood, and vaginal discharge of pregnant women [18, 23]. The concentration of PAMG-1 is several thousand-fold higher in amniotic fluid than it is in cervicovaginal secretions [22]. Therefore, PAMG-1 is an important biomarker for premature rupture of the fetal membrane (PROM). Moreover, during uterine contractions, PAMG-1 passes through chorioamniotic pores in fetal membranes, and through microperforations from degradation of the extracellular matrix of fetal membranes, possibly as a result of the inflammatory processes of labor or infection [18, 22].

The predictive accuracy of PAMG-1 is similar to that of qualitative fetal fibronectin [21, 24, 25]. However, to our knowledge, only one study has shown PAMG-1 to have a higher positive predictive value (PPV) than fetal fibronectin for predicting preterm labor [24]. A systematic review and meta-analysis showed that PAMG-1 is highly predictive of preterm birth within 7–14 days of preterm labor [25].

Cervical length measurement in symptomatic women can be used to predict preterm labor to shorten hospital stay without compromising patient care [26]. Cervical length measurement, fetal fibronectin, and uterine contraction monitoring during pregnancy have been proposed to predict preterm delivery, but their practical beneficial remains uncertain [16, 26]. A cervical length >30 mm or a negative fibronectin obtained from a patient with possible preterm labor can avoid overdiagnosis and unnecessary treatment [27]. However, a woman with a cervical length <25 mm has a 6-fold increased risk of preterm delivery [27]. Combining cervical length of 15–30 mm with fetal fibronectin testing to predict delivery by women with symptoms of preterm labor improved identification of women with a low risk to deliver spontaneously within 7 days [28]. A high negative predictive value (NPV), but low PPV, make fetal fibronectin a good test to exclude premature delivery, but not a good test to predict it [29]. For a subgroup of symptomatic patients with a cervical length 15–30 mm, the PPV of fetal fibronectin remains poor [28].

Currently used methods to predict preterm labor include cervical length measurement, and presence of cervicovaginal fetal fibronectin or PAMG-1 [14, 16]. However, the accuracy of PAMG-1 and fetal fibronectin to diagnose preterm labor within 7 days is not significantly different [30]. When cervical length of 15–30 mm is combined with a PAMG-1 test, the accuracy to predict imminent spontaneous delivery is better than that when combining cervical length and fetal fibronectin [25, 31, 32]. However, to date there is no data from Thailand for its use in clinical practice.

We hypothesized that a test of cervicovaginal fluid for PAMG-1 using a commercial kit combined with cervical length would provide better accuracy to predict preterm birth within 7–14 days of preterm labor than either method alone.

Methods

The present prospective observational study was approved by the Ethics Committee of the Siriraj Institutional Review Board (Si 625/2016) and was conducted in full compliance with international guidelines for human research protection

including the principles outlined in the contemporary revision of the Declaration of Helsinki 1964 (World Medical Association) incorporating the most recent (2013) and earlier amendments, the Belmont Report, Council for International Organizations of Medical Sciences Guidelines, and the International Conference on Harmonization in Good Clinical Practice. We retrospectively registered the study in the Thai Clinical Trials Registry (TCTR20180703002), although we note this was an observational study. We used guidelines in the STARD 2015 list of essential items to ensure appropriate reporting of studies of diagnostic accuracy [33].

A sample of 163 pregnant women was needed based on the expected 85% sensitivity of the tool and an estimated 15% preterm in the study setting [4]. From March 2016 to September 2018, we recruited a total of 180 pregnant women in a consecutive series who attended the labor ward at Siriraj Hospital, a tertiary care, primary teaching hospital of the Faculty of Medicine, Mahidol University, with a capacity of >2,000 beds in Bangkok, Thailand. All participants provided their written informed consent before entering the study.

The included patients were those with a singleton pregnancy who had symptomatic painful uterine contraction every 4 times in 20 min or 8 times in 60 min with a cervical opening <3 cm, effacement <80%, and a gestational age from $20^{0/7}$ weeks to $36^{6/7}$ weeks without ruptured membranes.

Excluded patients were those who had received a digital examination, had bleeding per vagina, had abruption placentae, suspected placenta previa, had been exposed to tocolytic drugs, cervical cerclage, trauma, urinary tract infection, girls <18 years, and those with fetal anomaly.

All patients recruited underwent a full clinical examination by the attending physicians. This included collecting the sample for the PAMG-1 test, sterile speculum examination, transvaginal ultrasound, and digital examination. The sample for the PAMG-1 test was taken before the cervical examination. If cervical opening was ≥3 cm, effacement ≥80%, the patient was excluded from the study. Parameters recorded at presentation included cervical length, cervical dilatation, contraction frequency, cervical effacement, patient history, and PAMG-1 test result. Data regarding the gestational age of delivery, timing of delivery, neonatal Apgar score, and body weight and possible complication after delivery were also recorded.

PAMG-1 test

The PAMG-1 test was performed using a kit (PartoSure PTL time-to-delivery test; Parsagen Diagnostics, a Qiagen company), following the instructions from the manufacturer [31, 32]. Before speculum examination, digital examination, or transvaginal ultrasound, a sterile vaginal swab was inserted into the vagina for 30 s. The swab was then inserted into a vial with solvent for 30 s and agitated by rotating using the thumb and forefinger. The swab was then removed from the vial, and a test strip was inserted into the sample to allow migration along the membranes through capillary action. When two lines were visible, the result was interpreted as positive. Using another method, the test was interpreted after the test strip had been inserted into the sample vial for 5 min. The positive and negative PAMG-1 results were determined by the presence of two lines or one line, respectively [31, 32]. If no line was seen, the test was undetermined and the patient data were excluded from the study. The treatment of the patients was followed by a decision of the attending physician without concern for the PAMG-1 test results.

Cervical length measurement by transvaginal ultrasound

A cervical length measurement of 30 mm was used as cut-off point. A patient with a cervical length >30 mm, or a negative PAMG-1 test result, was not considered be at risk of imminent spontaneous delivery within 2 days, 7 days, or 14 days, and by contrast, those patients with a cervical length of ≤30 mm, or a positive PAMG-1 test result, were considered to be at risk of imminent spontaneous delivery within 7 days or 14 days.

Statistical analysis

We estimated the sample size for adequate sensitivity and specificity with a 95% confidence interval (CI) and 15% error of detected sensitivity using in house software from Mahidol University, Bangkok, Thailand. All other statistical analyses were completed using PASW Statistics for Windows (version 18.0; SPSS). Data are expressed as mean ± standard deviation (SD), median (range) for continuous variables, and frequency (percentages) for categorical variables. The diagnostic accuracy of PAMG-1, cervical length, and a combination of the 2 indicators for predicting preterm birth was assessed using receiver operating characteristic (ROC) curves and determining the area under the curve (AUC). The sensitivity, specificity, PPV, NPV, and accuracy with 95% CI were calculated.

Results

From the total of 180 pregnant patients recruited, 19 were excluded from the study because of indicated deliveries (10 patients), incomplete data for cervical assessment (5 patients), and loss to follow-up (4 patients). Therefore, we included 161 patients in the study (**Figure 1**). All 161 patients underwent a PAMG-1 test and cervical length measurement. Their mean age was 28.9 years with an average body weight of 65 kg. Most of the patients were primigravid. Gestational age was calculated from ultrasound in about 43%. Some 145 (91%) patients went into spontaneous vaginal delivery; other deliveries were assisted or by cesarean section (**Table 1**).

Of the 161 symptomatic pregnant women with cervical length ≤30 mm, 34 (21%) went into spontaneous delivery within 7 days and 11 (7%) went into spontaneous delivery within 14 days (**Table 2**). Of the 14 symptomatic pregnant women with a cervical length ≤15 mm, 11 (79%) went into spontaneous delivery within 7 days (**Table 3**).

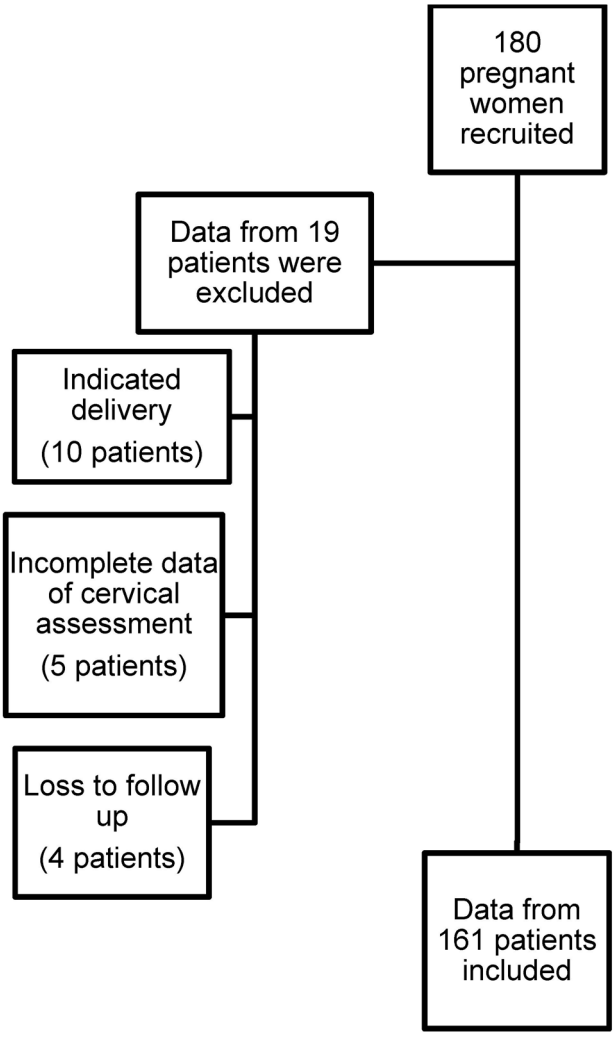

Figure 1. Flow of participants.

Table 1. Patient demographic characteristics

Demographic data	n = 161
Maternal age (years)	28.9 ± 6.9
Body weight (kg)	65.0 ± 12.5
Height (cm)	157.7 ± 6.2
BMI (kg/m²)	26.2 ± 4.8
Income (Thai baht per month)*	20,000 (0–70,000)
Occupation	
Government	19 (12%)
Housewife	35 (22%)
Labor	86 (53%)
Merchant	11 (7%)
Own business	4 (3%)
Student	6 (4%)
Gravida	1 (1, 6)
Parity	0 (0, 5)
Abortion	0 (0, 3)
Gestational age at first visit (weeks)	10 (4, 34)
Gestational age at admission (weeks)	33.2 (21.1, 36.3)
Number of antenatal care	10 (0, 12)
Calculate gestational age by source	
LMP	34 (21%)
LMP/ultrasound	58 (36%)
Ultrasound	69 (42%)
Maternal medical illness	
None	144 (89%)
Gestational diabetes mellitus	2 (1%)
Hypertension	3 (2%)
Pulmonary disease	5 (3%)
Thyroid disease	7 (4%)
Iron deficiency	13 (8%)
Hemoglobinopathy	
None	121 (75%)
α-Thalassemia trait	8 (5%)
β-Thalassemia trait	1 (1%)
Hemoglobin E trait	28 (17%)
Homozygous hemoglobin E	3 (2%)
VDRL reactive†	1 (1%)
Anti-HIV positive‡	2 (1%)
HBS Ag positive§	25 (16%)
Maternal complication	
None	137 (85%)
Gestational diabetes mellitus	11 (7%)
Gestational hypertension	5 (3%)
Mild preeclampsia	2 (1%)
Severe preeclampsia	6 (4%)

(*continued*)

Table 1. Continued

Demographic data	n = 161
Mode of delivery	
Cesarean section	8 (5%)
Spontaneous vaginal delivery	147 (91%)
Vacuum extraction	6 (4%)

Data are presented as n (%), mean ± SD, and median (range).
*U.S. Federal Reserve Foreign Exchange Rate G.5A. 1 USD = 35.26 (2016), 33.91 (2017), 32.30 (2018). Participants recruited March 2016 to September 2018.
†VDRL reactive means positive screening test for syphilis.
‡HBS Ag positive means positive screening test for antibodies to hepatitis B surface antigen.
§Anti-HIV positive means positive screening test for antibodies to HIV.
BMI, body mass index; HBS Ag, hepatitis B surface antigen; HIV, human immunodeficiency virus; LMP, last menstrual period; SD, standard deviation; VDRL, venereal disease research laboratory test.
Some patients may have more than one type of thalassemia.

Table 2. Symptomatic patients with cervical length <30 mm and delivery within 7 days and 14 days

All 161 patients included (symptomatic with cervical length <30 mm)	
Delivery <14 days	45 (28%)
Delivery <7 days	34 (21%)
Delivery 7–14 days	11 (7%)
Delivery ≥14 days	116 (72%)
Total	161 (100%)

Table 3. Symptomatic patients with various cervical lengths and delivery within 7 days and 14 days

All symptomatic patients with cervical length <30 mm	Delivery <7 days n (%)	Delivery <14 days n (%)
Cervical length <15 mm (n = 14)	11 (79)	11 (79)
Cervical length 15 to 30 mm (n = 50)	14 (28)	18 (36)
Cervical length >30 mm (n = 97)	9 (9)	16 (16)

When PAMG-1 testing was combined with cervical length measurement <30 mm, the NPV was 83% to predict preterm birth within 7 days, and 77% to predict preterm birth within 14 days (**Table 4**). When PAMG-1 testing and cervical length measurement ≤15 mm was used, the PPV was 83% (**Table 5**). The optimal cut-off from ROC curve analysis shows that a cervical length <25 mm and a PAMG-1 positive result has a PPV of 80% to predict preterm birth within 7 days and 90% to predict preterm birth within 14 days (**Tables 6–8; Figures 2 and 3**).

Discussion

We sought to determine whether testing cervicovaginal fluid for PAMG-1 could be used with cervical length to improve the predictability of preterm delivery within 7 days or 14 days in our hospital setting. The 161 patients in our present study were all treated with the same protocol, which did not affect the time to delivery. Of the 161 pregnant women with labor pain who had a cervical length <30 mm, 45 (28%) went into delivery within 7 days, and of those, 14 women with cervical length <15 mm, 11 (79%) went into delivery in <7 days. A positive PAMG-1 test result had a high NPV of 82% for preterm birth within 7 days and 76% within 14 days. When a cervical length <30 mm was combined with a PAMG-1 positive result, the NPV increased to 83% for preterm birth within 7 days, and 77% within 14 days. When a cervical length <15 mm was combined with a PAMG-1 positive result, the PPV was higher than it was when using cervical length alone. Cervical length <15 mm alone is a good predictor of preterm birth within both 7 days and 14 days and explains this finding [25]. Nikolova et al. [31] found that a positive PAMG-1 test result has a higher PPV than fetal fibronectin, or cervical length <25 mm. When

Table 4. Performance of a positive PAMG-1 test result and cervical length <30 mm in symptomatic patients to predict preterm birth within 7 days and 14 days

Indicator	Preterm birth <7 days				Preterm birth <14 days			
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity	Specificity	PPV	NPV
PAMG-1	10/34 (29)	112/127 (88)	10/25 (40)	112/136 (82)	12/45 (27)	103/116 (89)	12/25 (48)	103/136 (76)
95% CI	15, 48	81, 93	21, 61	75, 88	15, 42	82, 94	28, 69	68, 83
Cervical length <30 mm	25/34 (74)	88/127 (69)	25/64 (39)	88/97 (91)	29/45 (64)	81/116 (70)	29/64 (45)	81/97 (84)
95% CI	56, 87	61, 77	27, 52	83, 96	49, 78	61, 78	33, 58	75, 90
PAMG-1 and cervical length <30 mm	9/34 (26)	123/127 (97)	9/13 (69)	123/148 (83)	11/45 (24)	114/116 (98)	11/13 (85)	114/148 (77)
95% CI	13, 44	92, 99	39, 91	76, 89	13, 40	94, >99	55, 98	69, 83
PAMG-1 or cervical length <30 mm	26/34 (77)	77/127 (61)	26/76 (34)	77/85 (91)	30/45 (67)	70/116 (60)	30/76 (40)	70/85 (82)
95% CI	59, 89	52, 69	23, 46	82, 96	51, 80	50, 69	28, 51	73, 90

CI, confidence interval; NPV, negative predictive value; PAMG-1, positive placental α microglobulin-1 test result; PPV, positive predictive value.

Table 5. Performance of a positive PAMG-1 test result and cervical length <15 mm in symptomatic patients to predict preterm birth within 7 days and 14 days

Indicator	Preterm birth <7 days				Preterm birth <14 days			
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PAMG-1	10/34 (29)	112/127 (88)	10/25 (40)	112/136 (82)	12/45 (27)	103/116 (89)	12/25 (48)	103/136 (76)
95% CI	15, 48	81, 93	21, 61	75, 88	15, 42	82, 94	27, 69	68, 83
Cervical length <15 mm	12/34 (35)	122/127 (96)	12/17 (71)	122/144 (85)	12/45 (27)	111/116 (96)	12/17 (71)	111/144 (77)
95% CI	20, 54	91, 99	44, 90	78, 90	15, 42	90, 99	44, 90	69, 83
PAMG-1 and cervical length <15 mm	5/34 (14)	126/127 (>99)	5/6 (83)	126/155 (81)	5/45 (11)	115/116 (>99)	5/6 (83)	115/155 (74)
95% CI	5, 31	96, >99	36, >99	74, 87	4, 24	95, >99	36, >99	67, 81
PAMG-1 or cervical length <15 mm 95% CI	17/34 (50)	108/127 (85)	17/36 (47)	108/125 (86)	19/45 (42)	99/116 (85)	19/36 (53)	99/125 (79)
	32, 68	78, 91	30, 65	79, 92	28, 58	78, 91	36, 70	71, 86

CI, confidence interval; NPV, negative predictive value; PAMG-1, positive placental α microglobulin-1 test result; PPV, positive predictive value.

Table 6. ROC curve analysis of a positive PAMG-1 test result and cervical length to predict preterm birth within 7 days and 14 days

Indicator	Preterm birth <7 days				Preterm birth <14 days			
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PAMG-1	10/34 (29)	112/127 (88)	10/25 (40)	112/136 (82)	12/45 (27)	103/116 (88)	12/25 (48)	103/136 (76)
95% CI	15, 48	81, 93	21, 61	75, 88	15, 42	82, 94	28, 69	68, 83
Cervical length <25 mm	23/34 (68)	107/127 (84)	22/43 (54)	107/118 (91)	24/45 (53)	97/116 (84)	24/43 (56)	97/118 (82)
95% CI	50, 83	77, 90	38, 69	84, 95	38, 68	76, 90	40, 71	74, 89
PAMG-1 and cervical length <25 mm	8/34 (24)	125/127 (98)	8/10 (80)	125/151 (83)	9/45 (20)	115/116 (>99)	9/10 (90)	115/151 (76)
95% CI	11, 41	94, >99	44, 98	76, 88	10, 35	95, >99	56, >99	69, 83
PAMG-1 or cervical length <25 mm	25/34 (74)	94/127 (74)	25/58 (43)	94/103 (91)	27/45 (60)	85/116 (73)	27/58 (47)	85/103 (83)
95% CI	56, 87	66, 81	30, 57	84, 96	44, 74	64, 81	33, 60	74, 89

CI, confidence interval; NPV, negative predictive value; PAMG-1, positive placental α microglobulin-1 test result; PPV, positive predictive value; ROC, receiver operating characteristic.

Table 7. ROC curve analysis of cervical length (<25 mm) to predict preterm birth within 7 days and 14 days

Measurement	Preterm birth <7 days Value (95% CI)	Preterm birth <14 days Value (95% CI)
Area under curve	0.78 (0.68, 0.88)	0.73 (0.64, 0.82)
Sensitivity (%)	68 (50, 83)	53 (38, 68)
Specificity (%)	84 (77, 90)	84 (76, 90)
PPV (%)	54 (38, 69)	56 (40, 71)
NPV (%)	91 (84, 95)	82 (74, 89)
Accuracy (%)	81 (74, 87)	75 (68, 82)

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

Table 8. AUC (95% CI) for PAMG-1, cervical length <25 mm, PAMG-1 and cervical length <25 mm, and PAMG-1 or cervical length <25 mm

Indicator	Preterm birth <7 days AUC (95% CI)	Preterm birth <14 days AUC (95% CI)
PAMG-1	0.59 (0.47, 0.70)	0.58 (0.48, 0.68)
Cervical length <25 mm	0.76 (0.66, 0.86)	0.69 (0.59, 0.78)
PAMG-1 and cervical length <25 mm	0.61 (0.49, 0.73)	0.60 (0.49, 0.70)
PAMG-1 or cervical length <25 mm	0.74 (0.64, 0.83)	0.67 (0.57, 0.76)

AUC, area under the receiver operating characteristic curve; CI, confidence interval; PAMG-1, positive placental α microglobulin-1 test result.

cervical length is used as an initial screen and later combined with PAMG-1 testing, it has the greatest utility to predict delivery within 7 days in patients with cervical length 15–35 mm [31, 32]. Without cervical length screening, a positive PAMG-1 test result is more accurate than fetal fibronectin even when fetal fibronectin is combined with cervical length [31, 32]. The present study found combining a cervical length <15 mm with a positive PAMG-1 test result was the best predictor for

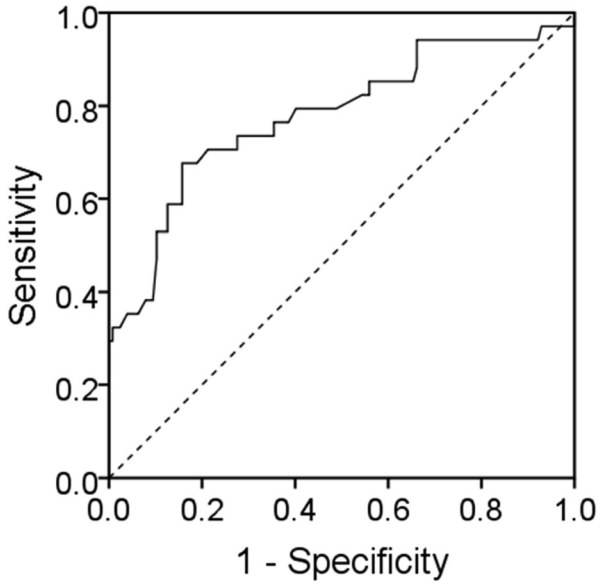

Figure 2. Receiver operating characteristic curve analysis of cervical length <25 mm and a PAMG-1 positive result to predict preterm birth ≤ 7 days. Diagonal segments are produced by ties. PAMG-1, placental α microglobulin-1.

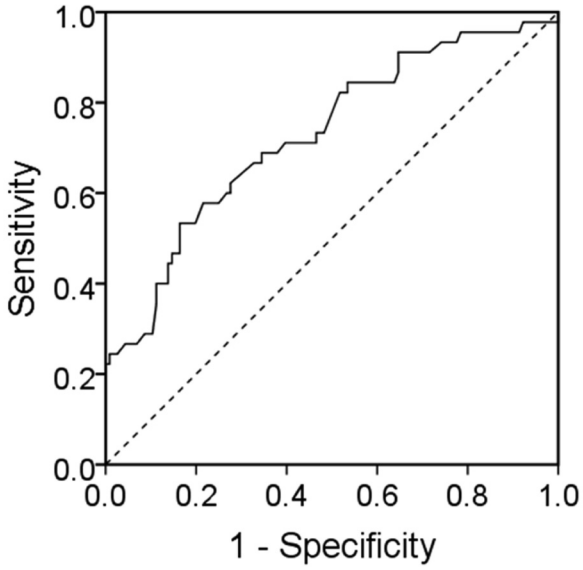

Figure 3. Receiver operating characteristic curve analysis of cervical length <25 mm and a PAMG-1 positive result to predict preterm birth ≤14 days. Diagonal segments are produced by ties. PAMG-1, placental α microglobulin-1.

delivery within 7 days in women with preterm labor. Combining the cervical length with the PAMG-1 test result increases the accuracy of the test to predict delivery within 7 days, achieving our goal of guiding the rational use of antenatal corticosteroids and tocolytic agents, decreasing unnecessary admissions, and correcting triage of patients that are need in of utero transfer [14, 15, 31, 32]. Therefore, the pregnant women who are not at risk of premature delivery can be advised to stay at home without unnecessary tocolytics or admissions. Patients who are at risk of premature delivery can be referred for tertiary care at specialized perinatal centers. The test allows physicians time to make the best decision to support their patients and manage them optimally. Psychological and physical burdens, the length of hospital stay, and health care costs can be reduced.

The lower cervical length cutoff point is associated with the highest specific prediction of imminent delivery within either 7 days or 14 days. A higher cervical length cutoff point lowers the specificity of the test. We sought to determine whether there is a specific cervical length range in which the PAMG-1 test would be most applicable and found that when a cervical length ≤15 mm was combined with a positive PAMG-1 result, 122/144 patients (85%) delivered within 7 days. When cervical length >30 mm was combined with a positive PAMG-1 result, 9/97 patients (9%) delivered within 7 days. However, patients with cervical length measurements between these two cutoffs had varying rates of delivery within 7 days. In our present study, 14/50 (28%) patients with cervical length 15–30 mm delivered within 7 days of testing.

The present study suggests that a PAMG-1 test result is useful when combined with a cervical length of 15–30 mm. The ROC curve analysis found that an optimal cut off of cervical length <25 mm with a positive PAMG-1 result has a PPV of 80% to predict preterm birth within 7 days, and 90% within 14 days.

A limitation of the study is that patients with any bleeding per vagina, rupture of membranes, or who had undergone a vaginal examination had to be excluded. Therefore, the target population is not fully representative and the test can only be used in a limited population excluding those with the conditions described. Another limitation is that we did not meet our expected sample size target of 163 patients because of an unexpectedly high loss to follow up. Nevertheless, the sample size of 161 patients obtained did not unduly affect the results of the present study.

It is already known that a short cervix or cervical length <15 mm is a good predictor of imminent spontaneous preterm delivery within 7 days. When cervical length measurement 15–30 mm was used as a cutoff, it was the least accurate predictor of imminent spontaneous preterm delivery within 7 days. This study adds that a cervical length 15–30 mm combined with a positive PAMG-1 test result will provide a higher predictor of imminent spontaneous preterm delivery within 7 days than either method alone, and should be considered for clinical practice. Our present findings support those of Nikolova et al. [31] and Bolotskikh and Borisova [32], who

reported predictive results for a cervical length 15–35 mm combined with a positive PAMG-1 test result.

Conclusion

Cervical length 15–30 mm combined with testing cervicovaginal fluid for PAMG-1 has a high accuracy to predict imminent spontaneous delivery within 7 days by pregnant women with preterm labor and cervical dilatation <3 cm in our clinical practice setting.

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Conflicts of interest statement. The authors have each completed the International Committee of Medical Journal Editors Form for Uniform Disclosure of Potential Conflicts of Interest. Julaporn Pooliam has no potential conflict of interest to disclose. Saifon Chawanpaiboon and Vitaya Titapant disclose the gift of the PartoSure test kits from the representatives of Parsagen Diagnostics (the manufacturer), but have no other financial relationship to disclose. The authors declare they had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement. Statistical summaries of data generated and analyzed for the present report are included in this published article. Further details of data that support the findings of the present study are also available in figshare, with identifier https://doi.org/10.6084/m9.figshare.14751717; and all data are available on reasonable request for noncommercial purposes after deidentification from any patients whose data are included in this report.

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