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Contraction-based uterine artery Doppler velocimetry: novel approach for prediction of preterm birth in women with threatened preterm labor

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KEYWORDS: Doppler; preterm delivery; uterine artery; uterine contraction; velocimetry

ABSTRACT

Objective *To evaluate whether uterine artery (UtA) Doppler velocimetry during peak uterine contraction is a useful marker for the prediction of preterm delivery.*

Methods *In this prospective cohort study, 172 patients admitted with preterm (24–35 weeks' gestation) uterine contractions were evaluated by UtA Doppler velocimetry during peak uterine contraction and by common obstetric measurements including cervical length. For UtA Doppler velocimetry, flow-velocity waveforms during peak uterine contraction (determined visually on tocodynamometry) were recorded during three consecutive heart cycles, and the mean UtA pulsatility index (UtA-PI) was calculated.*

Results *UtA-PI during the peak of contractions was significantly higher in patients who delivered within 7 days than in those who did not ($P < 0.001$). On receiver–operating characteristics curve analysis of UtA-PI on contraction, the areas under the curve for prediction of delivery within 48 h, 7 days or 14 days, ≤ 35 weeks and ≤ 37 weeks were 0.92, 0.88, 0.81, 0.83 and 0.74, respectively. Multiple regression analysis identified UtA-PI on contraction ($P < 0.001$) and cervical length ($P < 0.001$) as predictors of admission-to-delivery interval. The corresponding adjusted odds ratios for delivery within 7 days were 16.5 (95% CI, 5.7–47.2) for UtA-PI on contraction ≥ 1.32, and 14.7 (95% CI, 5.2–41.8) for cervical length ≤ 28 mm.*

Conclusion *Use of UtA Doppler velocimetry during peak uterine contraction for patients exhibiting symptoms of preterm labor might be effective for the identification of pregnant women at risk of preterm delivery.* Copyright © 2016 ISUOG. *Published by John Wiley & Sons Ltd.*

INTRODUCTION

Threatened preterm delivery is the most common diagnosis that leads to hospitalization during pregnancy. Although at least half of women admitted for threatened preterm labor will eventually deliver at term, nearly 20% of symptomatic women who are diagnosed as not being in preterm labor will deliver prematurely[1–3]. Therefore, assessing the probability of preterm delivery is important because clinical interventions, such as tocolysis, steroid administration and transfer to a tertiary-care facility, may lead to improved neonatal outcome[4]. However, the diagnostic performances of the methods that are currently available for assessing the likelihood of preterm delivery are limited[5–7], and access to new biochemical markers is not always available in routine clinical practice[8–10]. New strategies are thus needed to identify accurately those women who are at high risk of preterm delivery.

Women with symptoms of preterm labor who ultimately deliver preterm might have stronger uterine contractions than those who do not. However, information regarding the intensity of contractions is difficult to obtain without using a gold-standard intrauterine pressure catheter, which requires ruptured membranes[11]. It has been shown in previous studies that increased uterine artery pulsatility index (UtA-PI) in the second trimester of pregnancy is associated with an increased risk of preterm delivery[12,13]. Additionally, several UtA blood-flow studies have demonstrated a correlation between the intensity of uterine contractions and low end-diastolic flow in term patients during labor[14–17]. The intramyometrial and placental arteries are downstream of the UtAs. Consequently, compression of the arteries during labor due to uterine contractions results in a reduction or even disappearance of the diastolic component[14–16]. Based on these studies,

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UtA Doppler measurements that show greater pulsatility due to a decreased end-diastolic component might be related to the strength of the uterine contractions. Hence, UtA Doppler measurement during peak uterine contractions may predict true *vs* false preterm labor.

This pilot study aimed at investigating whether UtA Doppler velocimetry during peak uterine contraction is a useful marker for the prediction of preterm delivery in women with preterm uterine contractions and intact membranes.

METHODS

This was a prospective cohort study performed at the Dokuz Eylul University Hospital from June 2010 to September 2011. The criteria for entry into the study were: (1) singleton pregnancy; (2) gestational age between 24 and 35 weeks; (3) uterine contractility of 3 in 30 min; (3) cervical dilatation of at most 3 cm and effacement of less than 80%; (4) intact membranes, as determined by sterile speculum examination; and (5) signed informed consent. Patients with multiple pregnancy, preterm prelabor rupture of membranes, abnormal presentation, uterine anomaly, placenta previa, abnormal placentation, chronic heart disease, inflammatory or infectious disease, gestational hypertension, pre-eclampsia, fetal growth restriction, congenital abnormality, oligohydramnios, polyhydramnios, known cervical insufficiency, acute chorioamnionitis or medically indicated preterm delivery before 35 weeks' gestation were excluded from the study. The study was approved by the institutional review board of Dokuz Eylul University, Izmir, Turkey (approval number 2010/1331).

On admission, fetal heart rate monitoring was performed, and the existence of uterine contractions was confirmed by external tocodynamometry. Contractions on tocodynamometry (by summing the individual contraction duration over a 10-min period) were calculated for each patient. Digital examination was performed to evaluate cervical dilatation, cervical ripening and Bishop score. Transvaginal ultrasound was performed shortly after admission, approximately at the time of digital examination, using a 5–7.5-MHz transvaginal probe. In the absence of uterine contractions, measurements were obtained by orienting the transducer such that the endocervical canal and the internal cervical os were visualized in the same sagittal plane. Three images were obtained, and the one showing the shortest cervical length was used to determine the cervical biometric parameters. Significant cervical funneling was considered to be present when the lateral border of the funnel was at least 3 mm in length[18]. Each measurement was performed on women with an empty bladder.

Tocodynamometer measurements and UtA Doppler velocimetry were carried out simultaneously by a single obstetrician (S.O.) within an hour of admission, before the start of tocolytic administration (Figure 1). A Voluson V730 Expert Doppler ultrasound machine (GE Healthcare Ultrasound, Milwaukee, WI, USA) was used for this analysis. All examinations were performed with the patient in a flat supine position. The iliac arteries and UtAs were identified by Doppler color-flow mapping,

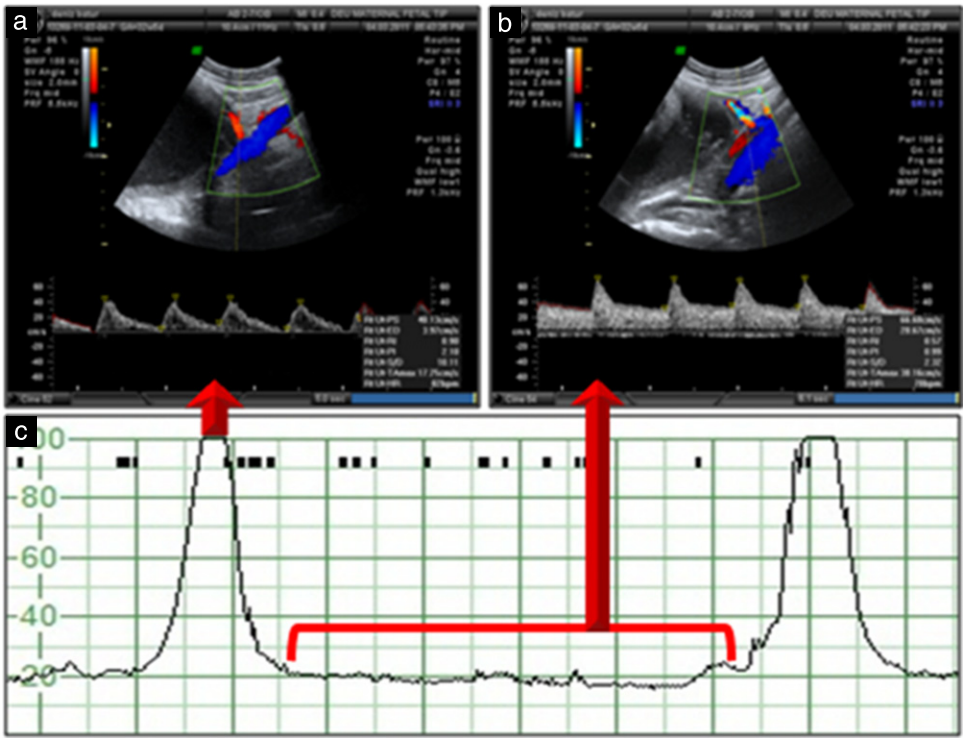


Figure 1 Flow-velocity waveforms during peak uterine contraction (a) and uterine inertia (b), determined visually from tocodynamometer (c), recorded during three consecutive heart cycles. Mean pulsatility index was calculated in each case.

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and the UtA flow-velocity waveforms were recorded at an insonation angle of less than 25° just cranial to the crossing with the external iliac artery[19]. To ensure that the Doppler shift sampling volume was maintained in the UtA during the procedure, rapid switches between velocimetry and color-flow mapping were performed. Peak uterine contraction and uterine inertia (basal) were determined visually from the tocodynamometer recording of the cardiotocogram. Flow-velocity waveforms during peak uterine contraction and uterine inertia were recorded during three consecutive heart cycles, and the mean PI was calculated for each. The measurement was repeated at the peak of a consecutive contraction, and the one with the highest UtA-PI was selected for final analysis. For cases with a laterally positioned placenta, the PI value obtained from the ipsilateral UtA was chosen to best represent the uteroplacental circulation. For cases with a centrally positioned placenta, the artery with the lowest PI was chosen to best represent the uteroplacental circulation.

Members of the obstetric team were blinded to the UtA Doppler velocimetry results but not to the cervical length or funneling, Bishop score and contractions on tocodynamometry. Therefore, the UtA Doppler velocimetry results did not influence the subsequent patient management protocol. The patients were initially recommended bed rest and were hydrated with 500 mL of lactated Ringer's solution. If a progressive cervical change was documented or if contractions persisted for at least 2 h after intravenous hydration, tocolytic therapy was started. Calcium channel blockers were used as first-line tocolytic therapy. No combined tocolytic therapy was used. Maternal corticosteroid was administered (two doses of 12 mg of intramuscular betamethasone at a 24-h interval) for fetal lung maturation. Tocolytics were discontinued 48 h after the first dose of steroids. No tocolytics and maternal steroids were used after 34 weeks' gestation.

After the initial evaluation of the clinical course of each patient in the study, patient data were recorded prospectively until birth. Gestational age at enrollment, gestational age at delivery, time interval between admission and delivery and delivery within 48 h, 7 days, 14 days, ≤ 35 weeks and ≤ 37 weeks were recorded.

Statistical analysis

The data were analyzed by the χ^2 or Mann–Whitney *U*-test. Receiver–operating characteristics (ROC) curve analysis was used to assess the accuracy of UtA-PI on contraction, basal UtA-PI, cervical length, Bishop score and contractions on tocodynamometry in the prediction of preterm delivery. Additionally, the differences between the area under the ROC curves (AUC) of UtA-PI on contraction and of cervical length were analyzed. The diagnostic indices (sensitivity and specificity) and positive and negative predictive values (PPV and NPV) were calculated. Relationships between the methods were investigated using the Spearman rank-order correlation coefficient. Multiple regression analysis was used to assess variables that were found to be associated with preterm delivery. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Univariable and multivariable logistic regression analysis was performed to investigate the relationship between the occurrence of preterm delivery and explanatory variables, including UtA-PI on contraction and cervical length. The Hosmer–Lemeshow test for the goodness of fit of the models was applied. Kaplan–Meier analysis was performed to assess the admission-to-delivery interval according to the UtA-PI on contraction and the transvaginal cervical length results. The Mann–Whitney *U*-test and intraclass correlation coefficient (ICC) were used to assess intraobserver reproducibility; $P < 0.05$ was considered to be statistically significant. Data were analyzed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA) and MEDCALC 13.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Between June 2010 and September 2011, 328 women presented to Dokuz Eylul University Hospital with preterm labor. After exclusion of 32 women with multiple pregnancy, 33 with preterm prelabor rupture of membranes, three with placenta previa, one with a unicornuate uterus, six with chronic heart disease, inflammatory or infectious disease, 20 with gestational hypertension or pre-eclampsia, 14 with intrauterine growth restriction, eight with oligohydramnios or polyhydramnios, two with cervical insufficiency and four with chorioamnionitis, 205 women were eligible for the study. Ten of the patients were excluded from the analysis since the obstetrician (S.O.) was not available to take the measurements. Two of the women declined participation in the study. In addition, four, 14 and three women were retrospectively excluded from the analysis because of induction of labor, planned Cesarean delivery before 35 weeks' gestation and incomplete data, respectively. The final study population consisted of the remaining 172 patients. The rates of delivery within 48 h, 7 days and 14 days of admission were 16.9% (29/172), 22.1% (38/172) and 26.7% (46/172), respectively. The prevalence of preterm delivery was 29.7% (51/172) at ≤ 35 weeks and 41.9% (72/172) at ≤ 37 weeks.

The clinical background variables are summarized in Table 1. A history of previous preterm delivery ($P = 0.016$) and vaginal bleeding ($P < 0.001$) were significantly higher in women delivering within 7 days. The patients who delivered within 7 days had significantly higher gestational age at enrollment ($P = 0.007$) and lower gestational age at delivery ($P < 0.001$).

UtA-PI measurements at both the peak of contractions and between contractions were found to be significantly higher in patients who delivered within 7 days than in those who delivered after this period ($P < 0.001$) (Table 2, Figure 2). A shorter cervical length ($P < 0.001$) and higher Bishop score ($P < 0.001$) were also found to be associated with delivery within 7 days. The rate of cervical funneling

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Table 1 Demographic and clinical characteristics of study population of women with preterm uterine contractions

Variable	*Delivery after 7 days* (n = *134*)	*Delivery within 7 days* (n = *38*)	P*
Maternal age (years)	29.0 (18.0–42.0)	29.0 (18.0–39.0)	0.938
Nulliparous	76 (56.7)	18 (47.4)	0.310
Previous preterm delivery	7 (5.2)	7 (18.4)	0.016
Preterm delivery in first-degree relative	12 (9.0)	3 (7.9)	0.840
ART pregnancy	7 (5.2)	1 (2.6)	0.695
Smoker	16 (11.9)	5 (13.2)	0.844
BMI (kg/m^2)	22.9 (15.6–33.2)	23.4 (17.1–29.0)	0.712
GA at enrollment (weeks)	32 + 0 (24 + 0 to 34 + 6)	33 + 1 (24 + 0 to 34 + 6)	0.007
GA at enrollment:			0.013
24 to 27 + 6 weeks	17 (12.7)	4 (10.5)	
28 to 31 + 6 weeks	49 (36.6)	5 (13.2)	
32 to 34 + 6 weeks	68 (50.7)	29 (76.3)	
GA at delivery (weeks)	38 + 1 (29 + 4 to 41 + 4)	33 + 2 (24 + 0 to 35 + 0)	< 0.001
Admission-to-delivery interval (days)	44 (8–107)	1 (0–7)	< 0.001
Vaginal bleeding	17 (12.7)	15 (39.5)	< 0.001
Tocolytic treatment	94 (70.1)	27 (71.1)	0.912
Antenatal corticosteroids	47 (35.1)	25 (65.8)	0.001
Birth weight (g)	3140 (1271–3980)	2250 (595–3470)	< 0.001
Birth-weight centile by GA	43 (11–87)	34 (20–86)	0.262

Data are given as median (range) or *n* (%). *Pearson chi-square test or Mann–Whitney *U*-test. ART, assisted reproductive technology; BMI, body mass index; GA, gestational age.

Table 2 Uterine artery pulsatility index (UtA-PI) on Doppler velocimetry and common obstetric measures in women with preterm uterine contractions

Variable	*Delivery after 7 days* (n = *134*)	*Delivery within 7 days* (n = *38*)	P*
UtA-PI (contraction)	1.03 ± 0.64	2.66 ± 1.05	< 0.001
UtA-PI (basal)	0.76 ± 0.22	0.98 ± 0.37	< 0.001
Cervical length (mm)	34.2 ± 10.1	19.7 ± 9.9	< 0.001
Cervical funneling	22 (16.4)	18 (47.4)	< 0.001
Cervical dilatation (cm)	0.8 ± 0.7	1.8 ± 0.9	< 0.001
Cervical effacement (%)	7.3 ± 17.1	42.1 ± 29.2	< 0.001
Bishop score	2.7 ± 1.6	5.3 ± 1.9	< 0.001
Contractions on tocodynamometry	3.9 ± 1.6	4.3 ± 1.5	0.391

Data are given as mean ± SD or *n* (%). *Mann–Whitney *U*-test or Pearson chi-square test.

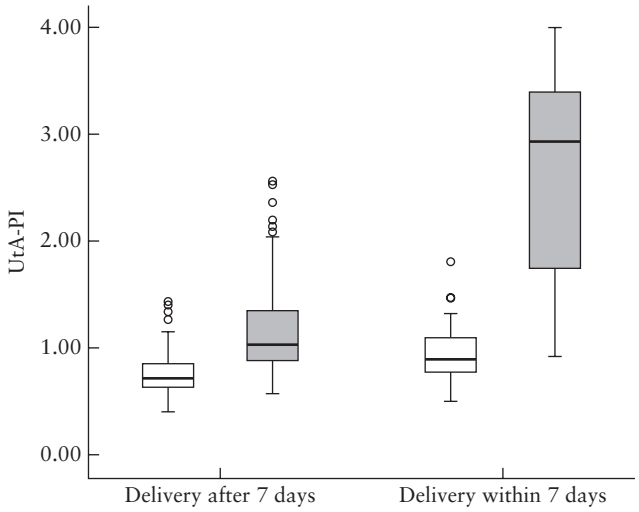


Figure 2 Box-and-whisker plot comparing basal uterine artery pulsatility index (UtA-PI) (□) and UtA-PI on contraction (■) in preterm patients delivering within 7 days of measurement compared with those delivering more than 7 days from measurement. Boxes and internal lines show interquartile range and median, whiskers show range and circles indicate outliers.

was significantly higher in patients who delivered within 7 days than in those who delivered after this period ($P < 0.001$) (Table 2).

The relationship between UtA-PI on contraction, basal UtA-PI, cervical length, Bishop score and contractions on tocodynamometry were analyzed using the Spearman rank-order correlation coefficient (Table 3). There was a large positive correlation between UtA-PI on contraction and basal UtA-PI ($\rho = 0.598$, $P < 0.001$) and a statistically significant moderate negative correlation between UtA-PI on contraction and cervical length ($\rho = -0.388$, $P < 0.001$). There was no significant correlation between UtA-PI on contraction and gestational age at enrollment ($P > 0.05$).

ROC-curve analysis (Figure 3) showed a significant relationship between UtA-PI on contraction (AUC, 0.88 (95% CI, 0.82–0.94)), basal UtA-PI (AUC, 0.72 (95% CI, 0.62–0.81)), cervical length (AUC, 0.85 (95% CI, 0.77–0.93)) and Bishop score (AUC, 0.83 (95% CI, 0.76–0.91)), and the occurrence of preterm delivery within 7 days ($P < 0.05$ for all). However, there was no significant relationship between contractions

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Table 3 Spearman rank-order correlations between uterine artery pulsatility index (UtA-PI) on Doppler velocimetry and common obstetric measures in women with preterm uterine contractions

	UtA-PI (contraction)	*UtA-PI (basal)*	*Cervical length*	*Cervical funneling*	*Bishop score*	*Contractions on tocodynamometry*
UtA-PI (basal)	0.598*					
Cervical length	−0.388*	−0.251*				
Cervical funneling	0.240*	0.197*	−0.555*			
Bishop score	0.278*	0.132	−0.600*	0.383*		
Contractions on tocodynamometry	0.139	0.093	−0.085	0.068	0.011	
GA at enrollment (days)	0.123	−0.237*	−0.201*	0.064	0.189†	−0.009

Spearman's rho values are presented. *Correlation significant at 0.01 level (two-tailed). †Correlation significant at 0.05 level (two-tailed). GA, gestational age.

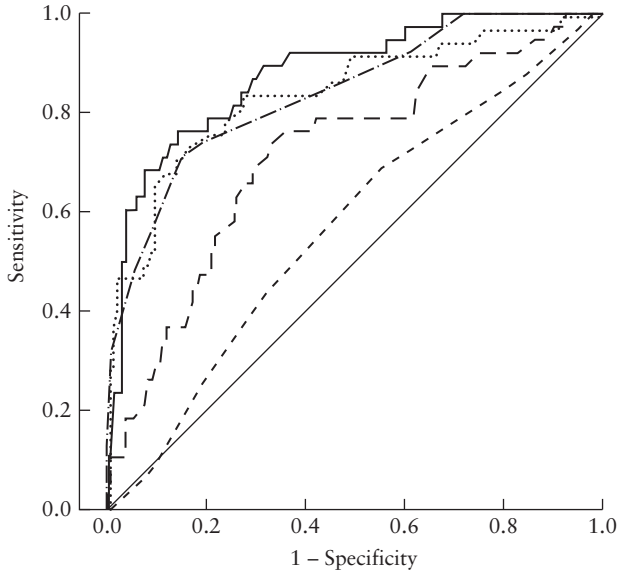


Figure 3 Receiver–operating characteristics curves for prediction of preterm delivery within 7 days in women with preterm uterine contractions by uterine artery pulsatility index (UtA-PI) on contraction (——) and by currently used clinical methods: basal UtA-PI (— —), cervical length (·····), contractions on tocodynamometry (- - -) and Bishop score (—·—).

on tocodynamometry and the occurrence of preterm delivery within 7 days (AUC, 0.57 (95% CI, 0.47–0.67); $P = 0.173$).

Multiple regression analysis was used to assess the ability of variables that were found to be associated with preterm delivery on the Mann–Whitney *U*-test to predict the admission-to-delivery interval (Table 4). The prediction model was statistically significant ($F_{7,163} = 58.9$, $P < 0.001$) and accounted for approximately 68% of the variance in the admission-to-delivery interval ($R^2 = 0.689$, adjusted $R^2 = 0.676$). In the final model, UtA-PI on contraction ($P < 0.001$), cervical length ($P < 0.001$), previous preterm delivery ($P < 0.001$), vaginal bleeding ($P = 0.001$) and gestational age at enrollment ($P < 0.001$) were found to be statistically significant.

The predictive performance measures of UtA-PI on contraction and cervical length for delivery within 48 h, 7 days or 14 days, or ≤ 35 weeks or ≤ 37 weeks, are given in Table 5. The differences between AUC values for UtA-PI on contraction and those for cervical length were non-significant when considering delivery within 48 h, 7 days or 14 days or ≤ 35 weeks ($P > 0.05$). However, the AUC value for cervical length was significantly higher than that for UtA-PI on contraction for delivery ≤ 37 weeks ($P = 0.043$).

Univariable logistic regression analysis was carried out using predictive variables dichotomized using the optimal cut-offs as reported in Table 5; we first analyzed high UtA-PI on contraction alone, then short cervical length alone and, lastly, the combination of high UtA-PI on contraction with short cervical length. Additionally, multivariable logistic regression analysis was used to assess the ability of these two indicators (high UtA-PI on contraction and short cervical length) to predict preterm delivery after controlling for the influence of previous preterm delivery, vaginal bleeding and gestational age at enrollment. We found that the combined model including high UtA-PI on contraction and short cervical length had the highest adjusted/unadjusted odds ratios for delivery within 48 h, 7 days or 14 days and ≤ 35 weeks (Table 6).

Kaplan–Meier analysis was performed to assess the admission-to-delivery interval of the following groups: (1) cervical length > 25 mm and UtA-PI on contraction < 1.93 ($n = 96$); (2) cervical length ≤ 25 mm and UtA-PI on contraction < 1.93 ($n = 31$); (3) cervical length > 25 mm and UtA-PI on contraction ≥ 1.93 ($n = 20$); and (4) cervical length ≤ 25 mm and UtA-PI on contraction ≥ 1.93 ($n = 25$). The mean admission-to-delivery interval and 95% CIs were as follows: (1) 46.0 (41.4–50.5) days; (2) 30.5 (21.2–39.7) days; (3) 35.2 (20.2–50.2) days; and (4) 4.4 (0.5–8.4) days, respectively. A log-rank test was performed to determine if there were differences in the distribution according to UtA-PI on contraction and cervical length. The distributions for the groups were found to be statistically significantly different ($\chi^2 = 103.359$; $P < 0.001$) (Figure 4).

The frequency of preterm delivery according to UtA-PI on contraction and cervical length is given in Figure 5 and Table S1. For each outcome variable, the highest frequency of preterm delivery was observed in patients with both a short cervix and a high UtA-PI during contraction. The frequency of preterm delivery was similar in patients with only a short cervix or only a high UtA-PI on contraction, with the exception of the outcome

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Table 4 Multiple regression analysis of variables associated with preterm delivery in women with preterm uterine contractions, with admission-to-delivery interval (days) as dependent variable

	Unstandardized coefficients		*Standardized coefficient*	
Variable	*B-value*	*Standard error*	*Beta*	P
UtA-PI on contraction	−0.067	0.014	−0.251	< 0.001
Cervical length (mm)	0.675	0.286	0.276	< 0.001
Cervical funneling	1.362	3.462	0.021	0.695
Bishop score	−0.674	0.850	−0.049	0.429
Previous preterm delivery	−16.019	4.478	−0.159	< 0.001
Vaginal bleeding	−11.238	3.228	−0.159	0.001
GA at enrollment (days)	−0.831	0.063	−0.494	< 0.001

$R^2 = 0.689$, adjusted $R^2 = 0.676$. GA, gestational age; UtA-PI, uterine artery pulsatility index.

Table 5 Predictive performance, in women with preterm uterine contractions, of uterine artery pulsatility index during peak uterine contraction (UtA-PI) and cervical length (CL) with respect to different outcomes relating to preterm delivery

	Delivery within 48 h		*Delivery within 7 days*		*Delivery within 14 days*		*Delivery ≤ 35 weeks*		*Delivery ≤ 37 weeks*	
Parameter	*UtA-PI*	*CL*	*UtA-PI*	*CL*	*UtA-PI*	*CL*	*UtA-PI*	*CL*	*UtA-PI*	*CL*
AUC (95% CI)	0.92 (0.87–0.96)	0.86 (0.78–0.93)	0.88 (0.82–0.94)	0.85 (0.77–0.93)	0.81 (0.73–0.89)	0.83 (0.76–0.91)	0.83 (0.76–0.90)	0.80 (0.72–0.87)	0.74 (0.66–0.82)	0.84 (0.77–0.90)
Best cut-off	1.93	25.0 mm	1.32	28.0 mm	1.26	28.0 mm	1.26	28.3 mm	1.11	30.0 mm
Sens (%)	82.8	79.3	81.6	81.6	76.1	76.1	78.4	72.5	69.4	79.2
Spec (%)	85.3	76.9	74.6	73.1	73.8	74.6	76.9	74.4	66.0	84.0
PPV (%)	53.3	41.1	47.7	46.3	51.5	52.2	58.8	54.4	59.5	78.1
NPV (%)	96.1	94.8	93.5	93.3	89.4	89.5	89.4	86.5	75.0	84.8
LR+	5.6	3.4	3.2	3.0	2.9	3.0	2.9	2.8	2.0	5.0
LR−	0.2	0.3	0.2	0.3	0.3	0.3	0.3	0.4	0.5	0.2

AUC, area under receiver–operating characteristics curve; LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

Table 6 Relationship between uterine artery pulsatility index (UtA-PI) on contraction and cervical length, and different outcomes relating to preterm delivery, as analyzed by both univariable and multivariable logistic regression

	Preterm delivery:				
Parameter	*Within 48 h (n = 29)*	*Within 7 days (n = 38)*	*Within 14 days (n = 46)*	*≤ 35 weeks (n = 51)*	*≤ 37 weeks (n = 72)*
Univariable models					
High UtA-PI (contraction)	27.9 (9.8–81.2)	13.0 (5.3–32.3)	9.0 (4.1–19.7)	12.1 (5.5–26.6)	4.4 (2.3–8.5)
Short cervical length	12.8 (4.8–34.0)	12.1 (4.9–29.8)	9.3 (4.3–20.5)	7.7 (3.7–16.1)	19.9 (9.1–43.5)
High UtA-PI (contraction) + short cervical length	61.3 (18.7–201.5)	20.2 (8.3–49.2)	12.4 (5.4–28.1)	14.3 (6.2–32.9)	15.7 (6.4–38.5)
Multivariable models*					
High UtA-PI (contraction)	37.4 (10.7–130.4)	16.5 (5.7–47.2)	9.4 (4.0–22.2)	14.1 (5.7–34.6)	3.9 (2.0–7.8)
Short cervical length	12.1 (4.2–34.7)	14.7 (5.2–41.8)	10.4 (4.3–24.9)	8.3 (3.6–18.8)	23.7 (9.9–56.2)
High UtA-PI (contraction) + short cervical length	65.1 (16.6–255.7)	30.1 (10.2–92.1)	17.0 (6.4–45.2)	16.3 (6.5–41.0)	15.4 (6.0–39.4)

Results shown are odds ratio (95% CI); $P < 0.01$ in all cases. Cut-off points for UtA-PI on contraction and cervical length are as shown in Table 5. *Adjusted for previous preterm delivery, vaginal bleeding and gestational age at enrollment.

'delivery ≤ 37 weeks', for which a higher frequency was observed in patients with a short cervix only.

There were no significant differences in UtA-PI on contraction between repeated measures obtained by the same observer ($P = 0.319$); the ICC (0.90 (95% CI, 0.86–0.93)) indicated a high correlation between UtA-PI on contraction obtained by the same examiner.

DISCUSSION

Although UtA resistance to blood flow during uterine inertia was higher in patients who delivered preterm, the reliability of this approach in predicting preterm delivery was found to be low. On the other hand, much better results were obtained when UtA Doppler velocimetry was

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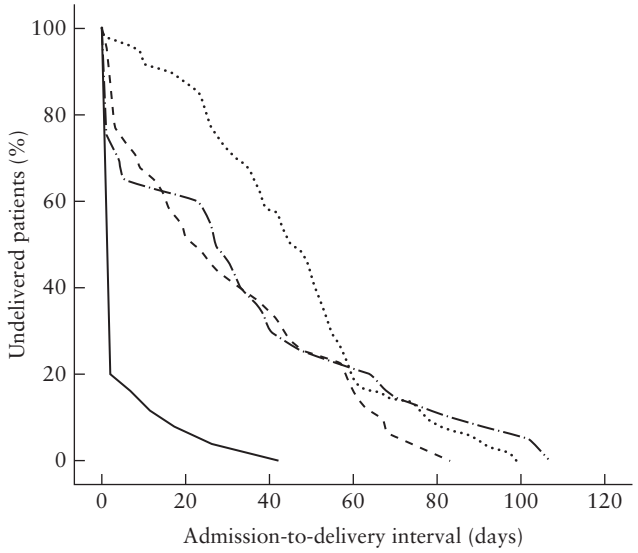


Figure 4 Kaplan–Meier curve of admission-to-delivery interval in women with preterm uterine contractions according to uterine artery pulsatility index (UtA-PI) on contraction and cervical length (CL) (log-rank test, $P < 0.001$; linear interpolation was applied): ·····, CL > 25 mm and UtA-PI on contraction < 1.93 ($n = 96$); - - -, CL ≤ 25 mm and UtA-PI on contraction < 1.93 ($n = 31$); —·—, CL > 25 mm and UtA-PI on contraction ≥ 1.93 ($n = 20$); ——, CL ≤ 25 mm and UtA-PI on contraction ≥ 1.93 ($n = 25$).

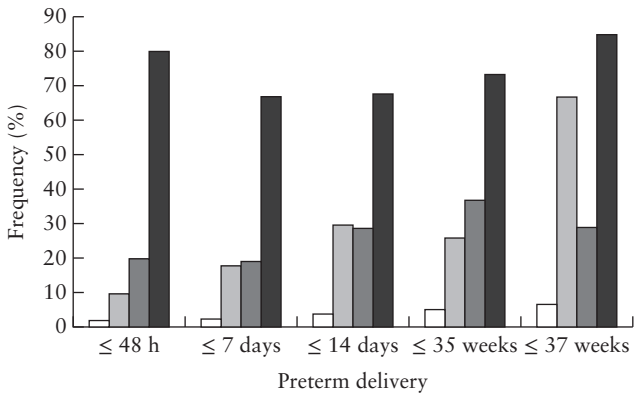


Figure 5 Frequency of preterm delivery in women with preterm uterine contractions according to uterine artery pulsatility index (UtA-PI) on contraction and cervical length (CL) (categorized according to cut-off points from Table 5): □, long CL and low UtA-PI on contraction; ▫, short CL and low UtA-PI on contraction; ▪, long CL and high UtA-PI on contraction; ■, short CL and high UtA-PI on contraction.

measured during peak uterine contraction. The low level of correlation observed between basal UtA-PI and gestational age is not an issue for UtA-PI on contraction and gestational age. These findings might show that UtA-PI on contraction depends mostly on a dynamic process, i.e. myometrial contraction itself, without being affected by gestational age. The evidence so far suggests that the use of cervical-length measurement is an objective tool and can be used to better identify women with preterm labor likely to have an imminent preterm delivery[7,20]. Similarly, we observed that both UtA-PI on contraction and cervical length were independent predictors of admission-to-delivery interval. We therefore further expanded the analysis using the cervical length results.

Our analysis revealed that the clinical utility for predicting preterm delivery was comparable between UtA-PI on contraction and cervical length. Since these methods are likely to detect different components of a preterm labor syndrome, myometrial contractility or cervical ripening, UtA Doppler velocimetry during peak uterine contractions might enable us to identify patients who have not been diagnosed previously as being at high risk for preterm delivery based on cervical length. Additionally, unlike UtA-PI on contraction, cervical length is associated with gestational age at measurement. Therefore, on the basis of this result, there seems to be a clinical advantage to the use of UtA Doppler velocimetry over cervical-length measurement. It is of interest that analysis of the Bishop scores showed better results than values reported in the literature[6]. However, unlike those of previous reports, our study population consisted mostly of women at high risk for preterm delivery, and all clinical examinations were performed by a single obstetrician.

The results obtained in the present study, in which the most appropriate cut-off values for cervical length were obtained from the ROC curves, are comparable with those from previous studies. In accordance with previous research studies, a cut-off of 25 mm for cervical length predicted 87.0% (95% CI, 71.9–95.6%) of preterm births within 48 h with a specificity of 72.2% (95% CI, 69.1–75.2%)[21,22]. Across studies, both sensitivity and specificity show considerable heterogeneity, despite the theoretical similarity in cervical-length assessment methodology and the lack of obvious disparities in the selection and exclusion criteria. Sotiriadis *et al.*[7] reported pooled positive and negative likelihood ratio estimates of 5.92 (95% CI, 4.91–7.13) and 0.35 (95% CI, 0.15–0.82), respectively. An interesting finding of our study was that cervical length in particular is better at predicting preterm birth ≤ 37 weeks when compared with UtA-PI on contraction. These findings raise an important question regarding the clinical utility of cervical length for predicting preterm delivery within a short time interval. Similarly to our results, there are compelling data to suggest that cervical length is a good predictive marker for preterm birth over a long rather than a short time interval[18].

The predictive performance measures for UtA-PI on contraction were found to be highest for delivery within 48 h. We therefore believe that UtA-PI on contraction might be a better tool for detecting preterm birth in a short rather than a long time interval. UtA-PI on contraction could be used alone or in combination with cervical-length measurement in all patients presenting with preterm uterine contractions and intact membranes. However, it is of interest that high UtA-PI on contraction improved the predictive performance of ultrasonographically determined cervical-length measurement when the cervix was short. The practical consequence of this finding is that patients could be screened with cervical sonography, with additional UtA Doppler velocimetry restricted to those with a short cervix. When the cervical

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length (≤ 25 mm) was considered in combination with the UtA-PI on contraction (PI ≥ 1.93), the predictive value of the test increased, particularly for delivery within 48 h (sensitivity = 87.0%, specificity = 84.8%, PPV = 80.0% and NPV = 90.3%).

The advantage of the method proposed in this study is that it is a non-invasive single measurement that yields rapid, objective and quantitative results that are easy to interpret and applicable in all clinics. However, it should be borne in mind that, in the setting of placental insufficiency (intrauterine growth restriction, oligohydramnios, maternal hypertension, pre-eclampsia, diabetes mellitus or vascular disease), UtA-PI would already be elevated during uterine inertia (basal) and would obviously be elevated during uterine contractions. Moreover, increased intrauterine pressure attributable to multiple pregnancy or polyhydramnios may also independently affect UtA impedance to blood flow. Consequently, in patients with concomitant pathology, the optimal values of UtA-PI on contraction should be redetermined to avoid false-positive results for each group. Alternatively, the percentage flow differences between inertia and contraction might also be used as a predictive marker in those cases instead of contraction-based velocimetry alone.

Our study has a few drawbacks, which include the lack of assessment of interobserver variability in measuring UtA Doppler velocimetry. Since this was a pilot study and the primary objective was to demonstrate the relationship between UtA Doppler velocimetry during peak uterine contraction and preterm labor, we decided not to conduct the study by different observers.

Our study demonstrates that the use of UtA Doppler velocimetry during peak uterine contraction for patients exhibiting symptoms of preterm labor might be effective for the identification of pregnant women at risk for preterm delivery. We believe that this information may provide essential clues for evaluating preterm delivery, as it relates directly to the characteristics of uterine contractions. However, further long-term prospective studies on this novel field of research are required to test our preliminary results.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Frequency of preterm delivery according to uterine artery pulsatility index on contraction and cervical length dichotomized by optimal cut-offs

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