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Sonographic Cervical Markers at the Second Trimester for the Prediction of Preterm Birth

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Abstract

Background: This study aimed to assess the diagnostic value of novel ultrasonographic markers, Anterior Uterocervical Angle (AUA), Cervical Consistency Index (CCI) and Cervical Glandular Area (CGA) in the Prediction of Preterm Birth (PTB), in a general population.

Methods: We conducted a prospective cohort study on singleton gestations between 16 -24 weeks undergoing transvaginal sonography for Cervical Length (CL) screening. AUA, CCI and CGA were evaluated. The primary outcome was prediction of spontaneous PTB before 37 weeks' gestation by UCA, CCI and CGA. The secondary outcome was evaluating performance of these markers alone and in combination with CL to predict PTB.

Results: A total of 310 women were studied. The rate of PTB in this population was 10.6 % for delivery before 37 weeks. In the PTB group, the shorter CL, the wider AUA and the lower CCI were significant, but the CGA width and area were not significantly different in term and PTB groups. The optimal cut-off based on the ROC curve was 33.15 mm for CL (sensitivity: 57%; specificity: 68%), 102.5 degrees for AUA (sensitivity: 50%; specificity: 80%), and 60.3% for CCI (sensitivity: 43%; specificity: 68%).

Conclusions: Our data indicate that the combination of CL and CCI (positive likelihood ratio:3; negative likelihood ratio:0.7) and the combination of CL and AUA (positive likelihood ratio:4.8; negative likelihood ratio:0.76) are better methods for the prediction of spontaneous PTB before 37 weeks; and can be used as a screening tool in the second trimester.

Key Words: Cervical length measurement, Preterm birth, Ultrasonography.

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1- INTRODUCTION

Preterm birth (PTB), defined as delivery before 37 completed weeks of gestation, is the leading cause of neonatal mortality and morbidity (1). It has an overall estimated prevalence of 9.2% in Iran (2). PTB occurs spontaneously in around 80% of cases, following preterm labor or preterm prelabor rupture of membranes. It is important to screen spontaneous PTB in asymptomatic women; because there are some preventive methods including progesterone supplementation, cervical cerclage and pessaries. Sonographic Cervical-Length (CL) measurement has become the standard strategy for predicting PTB in asymptomatic women and it is advised to screen women by measuring CL between 18 - 24 weeks of gestation, as a part of the second-trimester anomaly scan (3). But it is not an ideal screening test because of its low sensitivity (4, 5). Not only the length but also the capacity of cervix to preserve pregnancy until term period is important for predicting PTB (6). As PTB is a complex condition caused by different etiologies (7), evaluating several parameters for detecting the predisposing reasons may predict it better and even sooner than shortening CL below the determined cutoffs.

New ultrasound markers like anterior Uterocervical Angle (AUA), Cervical Consistency Index (CCI), and absence of Cervical Glandular Area (CGA) have been proposed as effective methods to be combined with CL (8, 9).It is suggested that a more acute AUA makes less direct loading pressure on internal os, while a wider AUA provides more pressure and may predict spontaneous PTB (10-15).

CCI, another novel ultrasound marker introduced for prediction of PTB, estimates cervical softness. Using the formula of (AP1/AP0) 100, the anteroposterior diameter of the uterine cervix before (AP0) and at maximum compression with the vaginal ultrasound probe (AP1) are measured by ultrasound and converted into a percentage. Higher cervical compressibility is evident at lower CCI values. Since cervix softens before shortening, this marker may detect early changes of cervix in order to detect PTB (16-19).

CGA is a sono morphological parameter that directly shows cervical maturation. This area can be seen in most women, whether they are pregnant or not, but it disappears with maturing cervix like when threatened preterm labor happens or in third trimester of pregnancy, when the cervix ripens (20-22).

Our objective, in the present study, was to evaluate whether UCA, CCI and CGA can predict the risk of spontaneous PTB and assess how well they perform relative to CL.

2- MATERIALS AND METHODS

This prospective cohort study was designed to evaluate the performance of UCA, CCI and CGA evaluated during routine transvaginal sonography (TVS) for CL screening in singleton gestations in predicting PTB.

2-1. Inclusion and Exclusion Criteria

The inclusion criteria encompassed singleton pregnant women between 16 and 24 gestational weeks who attended to our perinatal care centers in two teaching hospitals of Tehran University of Medical Sciences, most of them for anomaly scan, from November 2021 to June 2022. The exclusion criteria included patients with Mullerian malformations, multiple pregnancy, fetal malformations, fetal death, previous cervix surgery, surgery during pregnancy, induced or iatrogenic preterm delivery, history of cervical insufficiency and symptoms of preterm labor or preterm prelabor rupture of membranes happened before the second-trimester scan.

2-2. Procedure

Sonographic assessment of the cervix was performed by a single examiner with the FMF certificate for cervical assessment, using a Philips Affiniti 70 Ultrasound Machine, equipped with a transvaginal 3-10 MHz probe. CL measurement was performed according to the standard method described in the last International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guideline. (3) If the uterine isthmus was contracted, the procedure was repeated after a while.

AUA is the angle measured between the anterior wall of lower uterine segment and the cervical canal. To measure, the first line was placed straight from the internal os to the external os and a second line was then placed along the anterior uterine segment with electric calipers. The angle was measured by machine (**Fig. 1**).

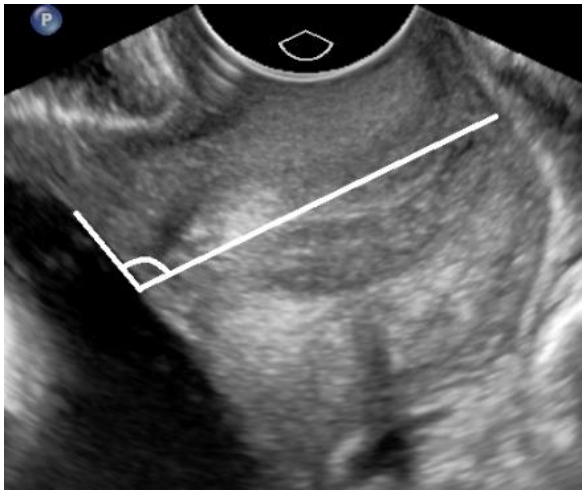

Fig. 1: Ultrasound measurement of anterior uterocervical angle

CCI is formulated as (AP1/AP0) × 100, measuring anteroposterior cervical diameter before (AP0) and after (AP1) pressure of the transducer. AP0 was measured in the sagittal view used for CL measurement. To acquire the image at maximum compression, the technique described by Parra-Saavedra et al. (16) was used. Pressure was applied softly and progressively on the cervix until no further compression in the anteroposterior direction could be observed (**Fig. 2**).

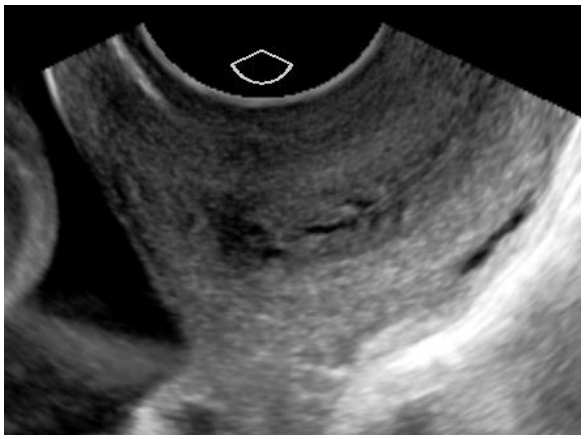

Fig. 2: Sagittal view of uterine cervix at maximum compression with vaginal probe

A perpendicular line covering the whole anteroposterior diameter of the cervix crossing through the midpoint of the same line of CL aligned with the longitudinal axis of the cervix was drawn in each view. CGA is a region with different echotexture from the uterine cervix stroma in the periphery of the cervical canal (**Fig. 3**).

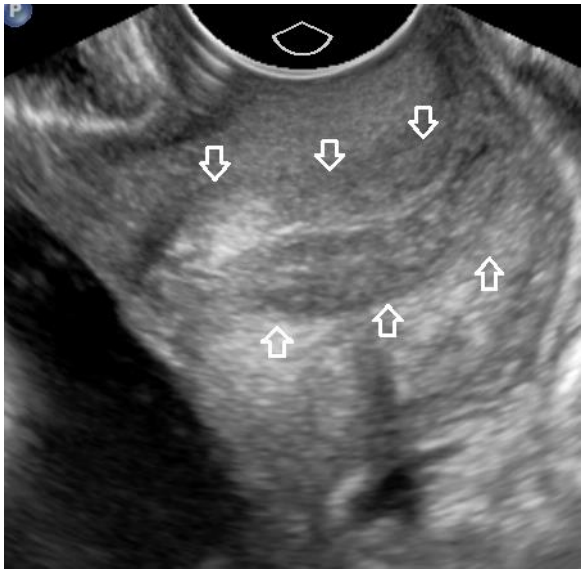

Fig. 3: Cervical glandular area surrounding the cervical canal

We measured and compared the width and area separately. Width was measured with electric calipers under a 90-degree angle from the endocervical canal, as a linear distance between bilateral outers of the deepest existence of cervical glands; and area was calculated by machine after tracing the described region.

Gestational age was based on menstrual date confirmed by first-trimester ultrasound. Demographic characteristics and obstetric history were recorded. The following variables were collected: gestational age, maternal weight and height, obstetric history, education level, gestational age at TVS, history of Dilatation and Curettage (D&C), vaginal bleeding, diabetes, receiving progesterone or Acetyl-Salicylic Acid (ASA), gestational age at delivery, Mode of delivery, birth weight, infant sex and NICU admission. Data related to pregnancy outcomes were gathered after about 20 weeks.

The primary outcome was the prediction of PTB before 37 weeks' gestation (<37 Weeks) by UCA, CCI and CGA measured during second trimester TVS for CL screening, and the secondary aim was comparison of the effectiveness of these sonographic markers alone and in combination with CL for prediction of PTB.

Data were analyzed using the IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Kolmogrov-Smirnov test. For the continuous data, as all of them were non-normally distributed, the statistical significance of differences was calculated using the Mann–Whitney test and for categorical data using the chi-square test or Fisher's exact test; $p<0.05$ was defined as the level of significance. Receiver Operating Characteristic (ROC) curves were developed to determine the optimal values for prediction of PTB <37 weeks.

Areas under the ROC curves (AUCs) and their 95% CI were calculated.

The sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and positive (LR+) and negative (LR–) likelihood ratios and their 95% CI with regard to predicting PTB <37 weeks were calculated for the optimal cut-off based on the ROC curve for CL, AUA, CCI and for the combined use of parameters. The optimal cut-off is the one corresponding to the point on the ROC curve situated farthest from the reference line.

3- RESULTS

A total of 310 women were eligible for inclusion during the study period. After removing thirty-one due to loss of follow up, eight due to medically indicated PTB, four due to cerclage and three due to delivery before 20 weeks, 264 (85%) women remained for analysis. The rate of spontaneous PTB before 37 weeks was 10.6%. Demographic characteristics, cervical measurements and perinatal outcomes according to gestational age at birth, for the women included are shown in **Table 1**.

Table-1: Demographic and clinical characteristics of patients according to the gestational age at delivery

Variable		Total n=264	Term Birth n=236	PTB <37w n=28	p-value
Maternal	Maternal Age, years	31.56 (± 6.16)	31.56 (± 6.30)	31.53 (± 4.96)	0.802
	BMI, kg/m^2	27.57(± 4.65)	27.36 (± 4.51)	29.32 (±5.46)	0.111
	Mean Gravidity	2.51 (±1.43)	2.48 (±1.45)	2.71 (±1.32)	0.262
	Mean Parity	1.04 (± 0.95)	1.01 (± 0.96)	1.25 (± 0.79)	0.123
	Previous Abortion	0.41 (± 0.72)	0.40 (± 0.73)	0.50 (± 0.63)	0.216
	Education:				
	-Under diploma	75 (28.4%)	60 (25.4%)	15 (53.6%)	0.003
	-Diploma and above	189 (71.6%)	176 (74.6%)	13 (46.4%)	
	PTB history	21 (8%)	13 (5.5%)	8 (28.6%)	0.0001
	GA at TVS, w	19.82 (±3.01)	19.99 (± 2.53)	18.43 (± 5.50)	0.465
	Prior D&C	26 (9.8%)	20 (8.5%)	6 (21.4%)	0.042
	Vaginal bleeding	52 (19.7%)	41 (17.4%)	11 (39.3%)	0.011
	Diabetes	42 (15.9%)	37 (15.7%)	5 (17.9%)	0.758
	Received progesterone	75 (28.4%)	58 (24.6%)	17 (60.7%)	0.0001
	Received ASA	104 (39.4%)	89 (37.7%)	15 (53.6%)	0.151
Measurements	Mean CL, mm	34.92 (±4.83)	35.23 (± 4.67)	32.25 (± 5.40)	0.002
	Mean AUA, Degree	84.70 (±23.37)	83.45 (22.83)	95.22 (25.61)	0.014
	Mean CCI, %	64.66 (± 11.48)	65.15 (± 11.59)	60.58 (± 9.69)	0.029
	Mean Anteroposterior diameter, mm	34.78 (4.58)	34.88 (4.68)	33.94 (3.61)	0.380
	Mean CGA width, mm	9.06 (3.22)	9.17 (3.21)	8.07 (3.16)	0.123
	Mean CGA area, cm^2	2.43 (1.11)	2.47 (1.11)	2.12 (1.09)	0.116
Delivery	GA at delivery, w	38.21 (±1.67)	38.63 (±0.95)	34.74 (±2.36)	0.000
	Mode of delivery:				

	-Vaginal	108 (40.9%)	92 (39%)	16 (57.1%)	0.071
	-Caesarian	156 (59.1%)	144 (61%)	12 (42.9%)	
Newborn	Birth weight, gr	3210 (±474)	3278 (±365)	2638 (±808)	0.0001
	NICU admission	76 (28.8%)	51 (21.6%)	25 (89.3%)	0.0001
	Female	128 (48.5%)	114 (48.3%)	14 (50%)	0.865
	Male	136 (51.5%)	122 (51.7%)	14 (50%)	-

Data are mean (± standard deviation) or n (%)
BMI: Body Mass Index, GA: Gestational Age, NICU: Neonatal Intensive Care Unit, w: weeks

Women who delivered preterm were more likely to have lower education, a prior PTB, a history of dilation and curettage (D&C), a history of vaginal bleeding, and a history of progesterone consumption.

In the PTB group, CL was significantly shorter (32.25 mm vs 35.23 mm; P=0.002), AUA was significantly wider (95.22° vs 83.45°; P=0.014) and CCI was significantly lower (60.58% vs 65.15%; P=0.029) but CGA width and area were not significantly different in the two groups.

ROC curves were generated to evaluate CL, AUA, CCI related to gestational age at delivery. The AUC for CL, AUA and CCI with regard to predicting PTB <37 weeks were 0.675 (95% CI, 0.57–0.78), 0.643 (95% CI, 0.24–0.47), and 0.626 (95% CI, 0.54–0.72), respectively.

The optimal cut-off based on ROC curve was 33.15 mm for CL (sensitivity, 57%; specificity, 68%), 102.5 degrees for AUA (sensitivity, 50%; specificity, 80%), and 60.3% for CCI (sensitivity, 43%; specificity, 68%).

Sensitivity, specificity, PPV, NPV, LR+ and LR– of CL, AUA and CCI for prediction of PTB <37 weeks, when using the optimal cut-off points based on the ROC curve as well as for some other cut-offs, are shown in **Table 2**.

Table-2: Discriminative performance of CL, AUA and CCI and the combination of the two measurements with regard to predicting spontaneous PTB <37 weeks

Parameters	Cutoff a	sensitivity	specificity	PPV	NPV	LR+	LR-
CL	< 25 mm	7	97	22	90	2.33	0.95
	< 30 mm	25	88	20	91	2.08	0.85
	< 33.15 mm	57	68	17	93	1.58	0.56
AUA	> 95 %	57	70	18	93	1.9	0.61
	> 102.5 %	50	80	23	93	2.5	0.63
	> 105 %	43	81	21	92	2.26	0.70
AUA and CL	> 102.5 % and < 33.15 mm	29	94	35	92	4.8	0.76
CCI	< 60.3	43	68	14	91	1.34	0.83
CCI and CL	< 60.3 % and < 33.15 mm	39	87	26	92	3	0.70

Optimal CCI and CL cut-offs based on receiver-operating characteristics curve
LR-: negative Likelihood Ratio; LR+: positive Likelihood Ratio; NPV: Negative Predictive Value; PPV: Positive Predictive Value

The discriminative performance of the combined use of CL and AUA, as well as CL and CCI are also shown in **Table 2**.

4- DISCUSSION

The main finding of this study is that in a general population assessed during the second-trimester, AUA and CCI but not CGA are independently associated with PTB.

The PTB rate of 10.6% in our study is consistent with the rate reported in a meta-analysis estimating overall prevalence of PTB in Iran (2).

The mean CL in the present study was 34.92 (±4.83) mm, which is similar to the mean CL of 35.98 mm calculated for Asian countries in a recent meta-analysis (23). In a prior study evaluating CL as a screening tool in the second trimester, a CL ≤25 mm yielded a sensitivity of 37% for PTB. (5) This cutoff, which is used in clinical practice (3), had a very low sensitivity in our survey but the optimal CL cutoff based on the ROC curve (33.15 mm) showed a better performance. (Sensitivity: 57%; specificity: 68%) Noticing the longer CL means in American and European countries (39 mm) in comparison to other regions based on the mentioned meta-analysis (23), it seems that exclusive cutoffs are needed for deciding about interventions in different regions. It seems logical to use a higher cutoff in countries with shorter CL means or combine other screening methods with CL for better detection of PTB.

In this prospective study, we compared the diagnostic accuracy of AUA, CCI and the combination of each of them with CL in the prediction of PTB in asymptomatic pregnancies. It is proposed that three essential elements of PTB (premature decidual activation, premature myometrial activation, and premature cervical remodeling), which are triggered by several factors, contribute independent of which one was activated first (24). This implies that investigating other mechanisms in combination with cervical assessment is suitable.

During the last years, several studies have investigated the potential impact of AUA in the prediction of PTB. We found significantly wider AUA in the PTB group, consistent with the findings of earlier research studies. The mean values of AUA in the PTB and term groups are different among studies, probably due to different population characteristics, techniques of measurement and study designs. Dziadosz et al. (10) observed that a second trimester AUA of >95° was significantly associated with PTB <37 weeks. Khamees et al. (15) showed that an AUA greater than 105°, provides a higher diagnostic performance in high-risk patients than CL. Sawaddisan et al. (13), investigating pregnant women with no history of PTB and with normal CL, reported the optimal AUA cutoff value of 110 degrees.

The value of CCI has been mentioned in some earlier studies. In our study, CCI performed well compared to CL as a screening tool. CCI < 60 % was found to be associated with PTB with a sensitivity of 43% and a specificity of 68%. In the first article that supported this assumption, Parra-Saavedra et al. (16) found that CCI was a better predictor of PTB than CL at any time in pregnancy. Their optimal cutoff was 46–54% at 19–24 weeks. Our cutoff was similar to that reported by BANOS et al (17). Their best cutoff was 64.6 % in the low risk pregnant population.

Considering the use of CCI to identify early stages of cervical remodeling is therefore reasonable, because early diagnosis of high risk pregnancies for PTB would improve pregnancy outcomes.

Importantly, the NPV of all measured markers is more than 90 % in our study population. This suggests that there is a

very low chance of developing PTB with a negative screen test. Therefore, with a high CL, a high CCI, or a low AUA there may be minimal concerns for PTB.

Our data indicate the combination of CCI and CL associated with sensitivity of 39%, specificity of 87%, LR+ of 3 and LR- of 0.7, as well as the combination of AUA and CL measurements with sensitivity of 29%, specificity of 94%, LR+ of 4.8 and LR- of 0.76 have the best performance and can improve prediction of PTB in our population. Assessing the combination model was done in some previous articles. According to Dziadosz et al. (10), when AUA and CL measurements are combined, a stronger prediction of risk for PTB is obtained. The uterocervical angle, cervical length and prior history of spontaneous preterm birth together are reported to have made up the best model for predicting spontaneous preterm birth before 37 weeks of gestation in Farras Lobet's study (14). Banos (17, 18) found no difference in performance between the low risk or high risk pregnancies comparing CCI and CL with CCI alone. Van der Merwe (19) found that in twin gestations, parity, chorionicity, CCI, and AUA together provided the highest level of diagnostic accuracy.

We didn't find any relationship between neither width nor area of CGA and PTB. It is consistent with the findings of Sekiya et al. (9) who detected CGA in 100 % of cases until 27 weeks of gestation, and this rate decreased with the increase in gestational age, suggesting that this marker might be more useful for detection of PTB in symptomatic pregnant women (6). Nevertheless, the absence of CGA at the second trimester was found to be correlated with PTB in a few articles. Most of them had evaluated its absence or presence (6, 20, 21). Only one article assessed glandular cervical score by measuring invasion width and area (22). We assessed and compared its width and area separately.

4-1. Strengths and Limitations

This study has several strengths. To the best of our knowledge, this is the first study to assess multiple cervical parameters, known until today, for PTB prediction in a single prospective cohort of singleton pregnancies. The prospective method of the study decreased selection bias. All of the measurements were performed by one operator so there was no inter-observer variability. The operator had no role in the pregnancy care of the cases. We used Real-time measurements and, therefore, the technical problems for analysis of offline images didn't exist; and measurement bias was minimized as values were evaluated and recorded prior to delivery.

However, due to the low sensitivities of the markers, the prediction accuracy in our cohort is limited. Studies with a larger population can declare the performance of tests better and gain more accurate cutoffs. Since we evaluated the measurements at one point in time in each pregnancy, we can't determine how the serial changes would correlate with risk of PTB. Since refusing to treat women when necessary is unethical, we did not exclude women with progesterone treatment but the aim of the study was to compare the diagnostic accuracy between markers in the same group of women regardless of the treatment done. This study was designed to screen the general population. Performance of these parameters in special populations like pregnant women with or without history of PTB as a main risk factor can decrease confounding variables. Moreover, randomized studies are needed to understand which strategies would be more effective for each one of markers out of normal range, for example evaluating the effect of prophylactic use of progesterone.

5- CONCLUSION

Screening AUA and CCI in the second trimester in addition to CL is predictive of spontaneous PTB in our cohort. A combination of CCI and CL or AUA and CL measurements can lead to a stronger prediction of PTB risk.

6- ETHICAL CONSIDERATIONS

The study protocol was approved by the Institutional Review Board of Tehran University of Medical Sciences, Teheran, Iran (Code: IR.TUMS.MEDICINE.REC.1400.1215). Informed consent was obtained from all participants before performing TVS.

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