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Cervical consistency index is a valid predictor of preterm birth in low-risk pregnant women

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ABSTRACT

BACKGROUND

Preterm birth (PTB) remains a global problem associated with perinatal morbidity, including low birth weight, growth retardation and irreversible damage to the nervous system. The objective of this study was to determine the predictive value of cervical consistency index (CCI) to indicate the occurrence of PTB in mid trimester screening of low risk pregnant women.

METHODS

This was a prospective study conducted on low-risk pregnant women at 14-28 weeks of pregnancy. The cervical length (CL) and AP cervical diameter were measured and the CCI determined according to the formula AP2/AP1*100. The ROC curves were drawn according to gestational age and the sensitivity and the specificity were calculated for optimal cut-off for 1st, 5th, 10th, 21th, and 24th centiles of CCI. The inter-observer agreement was validated by interclass correlation coefficients (ICC).

RESULTS

A total of 149 participants were enrolled in this study. Among them, 12.08% had PTB (<37weeks) and 87.92% had normal birth. Mean CCI for all subjects was 68.60%, but was lower in PTB (48.9%). The best cutoff for predicting PTB based on CCI was 59.46% with 99.18% sensitivity and 85% specificity. The AUC for CCI for prediction of PTB <37weeks was 0.936. There was no inter-observer difference in measurement of CCI and CL (ICC values for CCI and CL were 0.997 and 0.990 respectively).

CONCLUSION

In women with normal CL the CCI could predict PTB in the second trimester in low risk women. So, CCI is a valid predictor of PTB in low risk women.

Keywords: Pre term birth, cervical consistency index, low risk pregnancy

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INTRODUCTION

Preterm birth (PTB) is defined as a delivery of an infant before 37 weeks of pregnancy.(1) According to the WHO, each year about 15 million infants are born preterm and this number is rising every year, despite some progression in the medical field.(2) The overall incidence of PTB ranges from 5 to18% of infants born annually.(2) So this complication becomes a major concern in gynecology and obstetrics. Preterm birth has been divided into three categories: extremely preterm (less than 28 weeks), very preterm (28-32 weeks) and moderate preterm (32-37 weeks).(2,3) Preterm birth is responsible for neonatal morbidity and complications. These complications are due to the immature development of organs like the lungs, which is associated with respiratory distress syndrome (RDS), hence, the neonates may have cerebral palsy, vision problems, gastrointestinal complications, etc.(4,5) The neonatal mortality rate has been decreasing in recent years, but PTB contributes to the death of 1.5 million infants annually.(6) The mortality rate increases with decreasing gestational age.(7) More than 75% of preterm births occurs during the 32th to 36th weeks of pregnancy.(8) Some risk factors including; the maternal age at delivery, weight, the introduction of assisted reproductive technology (ART), have increased the incidence of PTB recently.(9) Risk assessment like; history of previous abortion or PTB, Müllerian malformation, and cervical conization, multiple gestation, bleeding in the second trimester, and low pregnancy weight, are some of the predispositional factors for the occurrence of PTB in the current pregnancy, although their sensitivity is not reliable.(10)

In normal term, the cervix becomes soft but the uterus is closed until term, but in preterm birth the cervix shortens.(11) Cervical length (CL), which is measured via transvaginal ultrasound (TVU), is a good predictor for PTB, especially in symptomatic women,(12) although the accuracy of this technique is limited in asymptomatic women.(13) It should be noted that about 50% of PTB occurs in asymptomatic women.(14) Hence, despite determination of the CL index for the screening of PTB the rate has not decreased yet, especially in low-risk women.(15)

In the study of Parra-Saavedra et al.(16) an ultrasonographic marker was investigated to measure cervix consistency throughout pregnancy quantitatively by transvaginal ultrasonography. Recently, a new technique based on measurement of the anteroposterior diameter of the cervix before and after cervical compression and calculating the cervical consistency index (CCI), has been administered for prediction of PTB.(16) It is shown that CCI is lower in women with preterm delivery and is also decreased in the third trimester of pregnancy. So, it could be a good indicator for PTB in low-risk women.(16) Previous studies conducted on low risk women demonstrated that CCI was the better indicator of PTB in the second trimester, although women with CL under 25 mm were enrolled in previous studies where CL<25mm is the predictor of PTB. In the current research, women with CL<25 mm were excluded, because medical intervention is needed in order to prevent complications such as PTB. So for the first time we evaluated normal pregnant women who were referred for routine screening and the association of CCI with the occurrence of PTB in this group was evaluated, and compared with the cervical length.(17)

Although CCI performed better than sonographic CL in predicting PTB, due to the still limited predictive capacity of these two measurements, other tools are needed to better identify women at increased risk of preterm delivery.(17)

Both CCI and CL measurements were significantly reduced in the high-risk compared with the low risk pregnancies. However, the diagnostic accuracy of both measurements was better in the low-risk population than in the high-risk population.(18)

The novelty of the study is that in the previous studies, in addition to healthy pregnant women with normal cervical length, pregnant women with reduced cervical length were studied. The present study did not include women with cervical length lower than 25, who are at risk for early delivery. In addition, the cervical congestion index in healthy pregnant women with normal cervical length was studied. Because of the inclusion of normal cervical length and early delivery in the healthy pregnant women group, the present study is better for confirming the greater efficiency of CCI as compared to cervical length in predicting early delivery. The objective of this study was to determine the predictive value of cervical consistency index (CCI) to indicate the occurrence of PTB in mid trimester screening of low risk pregnant women.

METHODS

Research design

This was a prospective study conducted in Shohadye Tajrish Hospital, Tehran, Iran from April 2017 to March 2018.

Research subjects

The sample size was determined according to Cazanas et al.[19] (effect size^2=0.082) and the gestational age and CCI in linear multiple regression model for prediction of PTB were considered. The optimum sample size was 140. Singleton pregnant women with low risk of preterm labor in the 14-28 weeks of pregnancy, including women who do not have the risk factors for preterm labor. The exclusion criteria were multiple pregnancies and use of drugs for the prevention of preterm labor (such as non-steroidal anti-inflammatory drugs, progesterones, magnesium sulfate, and calcium channel blockers), use of c*erclage* pessary, cervical length lower than 20mm that requires the intervention to prevent preterm labor. Women with one of the preterm labor risk factors (previous preterm labor, loss of pregnancy due to cervical incompetency), cervical cone biopsy, and presence of molar anomalies in the reproductive system, were excluded from the study.

Measurements

Women with gestational ages in the range of 14-28 weeks underwent transvaginal sonography examination. The cervical length and anterioposterior diameter were measured twice during pregnancy and the CCI index was calculated. Gestational age was calculated according to reliable last menstrual period recall data or first trimester sonographic examination.

Ultrasound examination

The sonographic examination was carried out twice for each participant using GE VOLUSON E8 (GE Healthcare Ultrasound, Milwaukee, WI, USA) ultrasound machine which is equipped with a transvaginal probe. Cervical length, anterioposterior cervical diameter , gestational age, maternal weight, body mass index (BMI), age and parity were determined during the examination.

Determination of cervical consistency index (CCI)

In order to determine the CCI, the following steps were performed. Cervical length was measured according to the standard technique described in a previous study.[17]

The measurement of anterioposterior cervical diameter was carried out with an empty bladder and the cervical length was measured without any pressure. Then the midpoint of the line running along the longitudinal cervical axis was marked as (C/2), then a line perpendicular to the longitudinal cervical axis through the point C/2 was drawn from the anterior lip to the posterior lip of the cervix. This length was designated the AP1 diameter. Then pressure was applied with the vaginal probe progressively until it reached the highest pressure at which there was no further shortening of the anterioposterior cervical diameter. Then the AP2 diameter was measured in a same way as described for AP1

(Figure 1). To calculate the CCI the AP2 was divided by AP1 then multiplied by 100:
CCI= (AP2 D AP1) ×100

The measurement were performed twice and the lowest number was used for statistical analysis and inter-observer agreement.(16) The patients were followed up to end of pregnancy and the outcome and date of delivery were recorded.

Statistical analysis

All data were analyzed with SPSS v.22 (IBM Copr, Armonk, NY). The gestational age in the second trimester (14-28 weeks) was evaluated to determine the ability of CCI to predict the PTB (<37weeks). A multivariate logistic regression model for CCI and CL was constructed to assess the independent relation of each variable with PTB.

The relationship between quantitative variables was assessed with Pearson's correlation coefficient test. Distribution of CCI and CL were analyzed in different percentiles according to gestational age at scan time.

Receiver operating characteristic (ROC) curves were drawn for CCI as predicting variable. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), as well as positive and negative likelihood ratios (LR+ and LR-) were analyzed at 95% confidence interval to predict the PTB <37 weeks and the optimal cut-off point based on the ROC curves was calculated. All data obtained from the ROC curves demonstrate the diagnostic ability of CCI and CL to predict preterm birth. The area under the ROC curves (AUS) also was calculated.(18)

Reliability of measurement

The agreement between two measurements determined by different observers is called inter-observer agreement. So, each participant was examined twice at one-hour interval by two observers. The differences were calculated using a Bland and Altman plot and intraclass correlation coefficient (ICC) (20) Limits of agreement (mean differences ± 1.96) (Standard Deviation*1.96) ± mean) were calculated with the one-sample t-test and the systematic bias between two measurements was calculated at 95% CI for mean difference.

Ethical clearance

Each participant signed an informed consent letter and the study was approved by the Ethics Committee of Shohadye Tajrish Infertility Research Center (under no. IR.SBMU.RETECH.REC.1397.306).

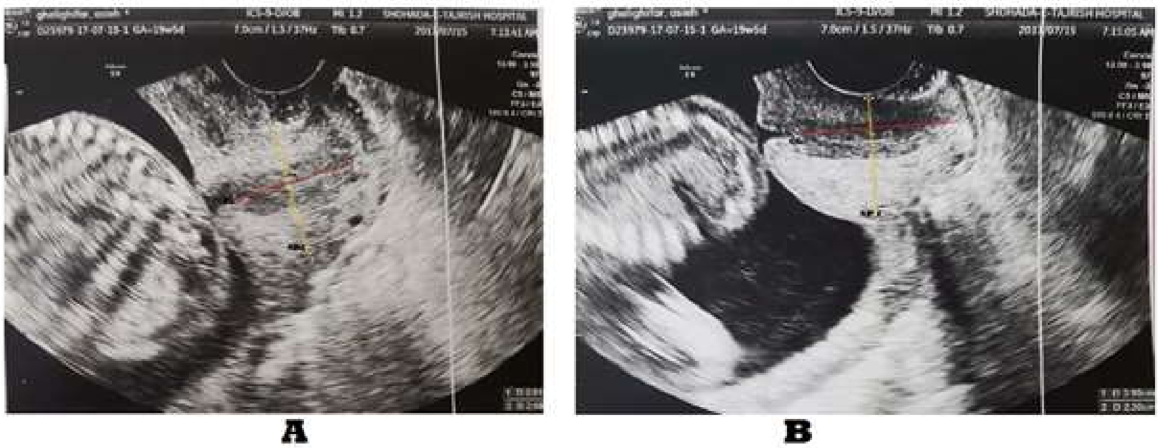

Figure 1. Ultrasound image of cervix before (A) and after maximal compression with probe (B). The anterioposterior diameters (AP1, AP2) and cervical length (CL1, CL2) were measured in each position. The CCI index was determined from AP2/AP1*100 for each participant

Table 1. Distribution of characteristics of patients enrolled in the study (n=149)

Characteristic	n = 149	Normal birth (n=131)	Preterm birth (n=18)	p
Maternal age (years)	28.93 (16-44)	29.4(17-44)	25.2 (16-36)	>0.05
BMI before pregnancy	25.06 (20.2-35.56)	25.1 (20.2-35.56)	24.17 (20.3-29.62)	>0.05
Weight gain (kg)	14.49 (4-30)	14.70 (4-30)	12.94 (6-22)	>0.05
Gestational age at scan (weeks)	19.42 (14-27)	19.29 (14-27)	20.3 (17-28)	>0.05
Gestational age at delivery (weeks)	38 (31-41)	38.47 (36-41)	34.9 (31-36)	0.000
Infant weight (g)	3139 (1870-4100)	3218 (2500-4100)	2563 (1870-3640)	0.031
Mode of delivery				
Noninvasive delivery	79 (53.7%)	67 (51.1%)	12 (66%)	NS
CS	69 (46.3%)	63 (48.1%)	6 (33%)	NS
CCI (%)	68.60 (34.86-93.02)	71.32 (50-93.02)	48.9 (34.8-64.61)	0.000
CL (mm)	32.89 (20.05-44.8)	33.28 (24.1-44.8)	30.63 (20.05-36.50)	>0.05

BMI: body mass index; CS: cesarean; CCI; cervical consistency index; Cl: cervical length; *one case was excluded due to abortion in 17th week of gestation

RESULTS

About 200 pregnant women, who were referred to Shohadye Tajrish Hospital, Tehran, Iran for routine examination, were enrolled in this study. A total of 51 women were excluded from the study due to several factors as follows. About 12 women were excluded due a maternal indication or a iatrogenic disorder before the 37th week of pregnancy, such as fetal growth retardation, preeclampsia, non reassuring fetal assessment, 3 women with a history of multiple pregnancy, 8 women with a history of abortion (≤20 weeks), and 28 women receiving progesterone for prevention of PTB. Participants with cervical length under 25mm and having a non-horizontal cervix were also excluded from the study. All participants were followed up to delivery. About 149 pregnant women who were referred for a routine check-up in the second trimester were enrolled in this study. Among 149 pregnancies, 18 cases had PTB before 37 weeks (12.08%) and 131 cases had a normal birth (87.92%). The prevalence of normal delivery was relatively higher than that of cesarean section (53.7% vs. 46.3%).The characteristics of participants in the normal and preterm birth groups are summarized in Table 1.

There was no statistical difference in maternal age among women who had a normal birth and those with PTB(p>0.05). Sonography assessment results demonstrated that the mean cervical consistency index was 68.60% (71.32 to 48.9%) in which the percentage of CCI was lower in PTB (48.9% vs. 71.32%) (p=0.00) (Table 1).

In order to determine the best cut-off value of CCI, the ROC curves were used and the specificity, sensitivity, positive and negative predictive values and positive and negative likelihood ratio for best cut-off values to predict the PTB before 37 weeks were calculated. The best cut-off for predicting the PTB based on CCI was 59.46% (sensitivity 99.18%, specificity

Table 2. Cervical consistency index cutoff based on ROC curve to predict PTB before 37 weeks

Cut-off*	Sensitivity	Specificity	LR+	LR-	PPV	NPV
47.75 p(1)	1 (100%)	50%	2	0.5	21.56	100
54.6 p(5)	0.969 (99.04%)	65%	2.768571	0.361197	27.99	99.79
57.32 p(10)	0.868 (99.131%)	70%	5.526667	0.180941	31.22	99.82
59.46 p(21)**	0.829 (99.18%)	85%	5.526667	0.180941	47.61	99.87
62.675 p(24)	0.775 (99.23%)	95%	15.5	0.064516	73.6	99.88

*Value lower than cutoff indicates high risk;**optimal cutoff based on ROC curve corresponds to 21th centile LR+, positive likelihood ratio, LR-, negative likelihood ration, PPV, positive predictive value, NPV, negative predictive value, P1, 1st centile; p5, 5th centile; p10, 10th centile; p21, 21th centile; p24, 24th centile

85%), which according to the distribution of CCI in gestational ages at scan was located in percentile 21 (Table 2). The ROC curves for CCI are shown in Figure 2. AUC for CCI in relation to predicting the PTB before 37 weeks was 0.936 (95%CI 0.891-0.982;p=0.000). The specificity, sensitivity, positive and negative predictive values and positive and negative likelihood ratio for CCI and cut-offs of CCI in regard to predicting the.

To ensure the reliability of the CCI and CL measurements by one specialist, the ICC test was performed. The Bland-Altman plots (Figure 2) illustrate that there are no inter-observer differences in the measurement of CCI and CL. The inter-observer ICC values for CCI and CL were 0.997 (95%CI, 0.996-0.998) and 0.990 (95%CI, 0.993-0.997) respectively. The inter-observer agreement reliability of the CCI and CL (data was not shown).

DISCUSSION

The purpose of this study was to determine the diagnostic value of the cervical consistency index (CCI) in the prediction of preterm birth (PTB) (under 37 weeks) in low-risk pregnant women. Our results indicated that the CCI could be a reliable value for predicting PTB in a low-risk population in the second trimester.

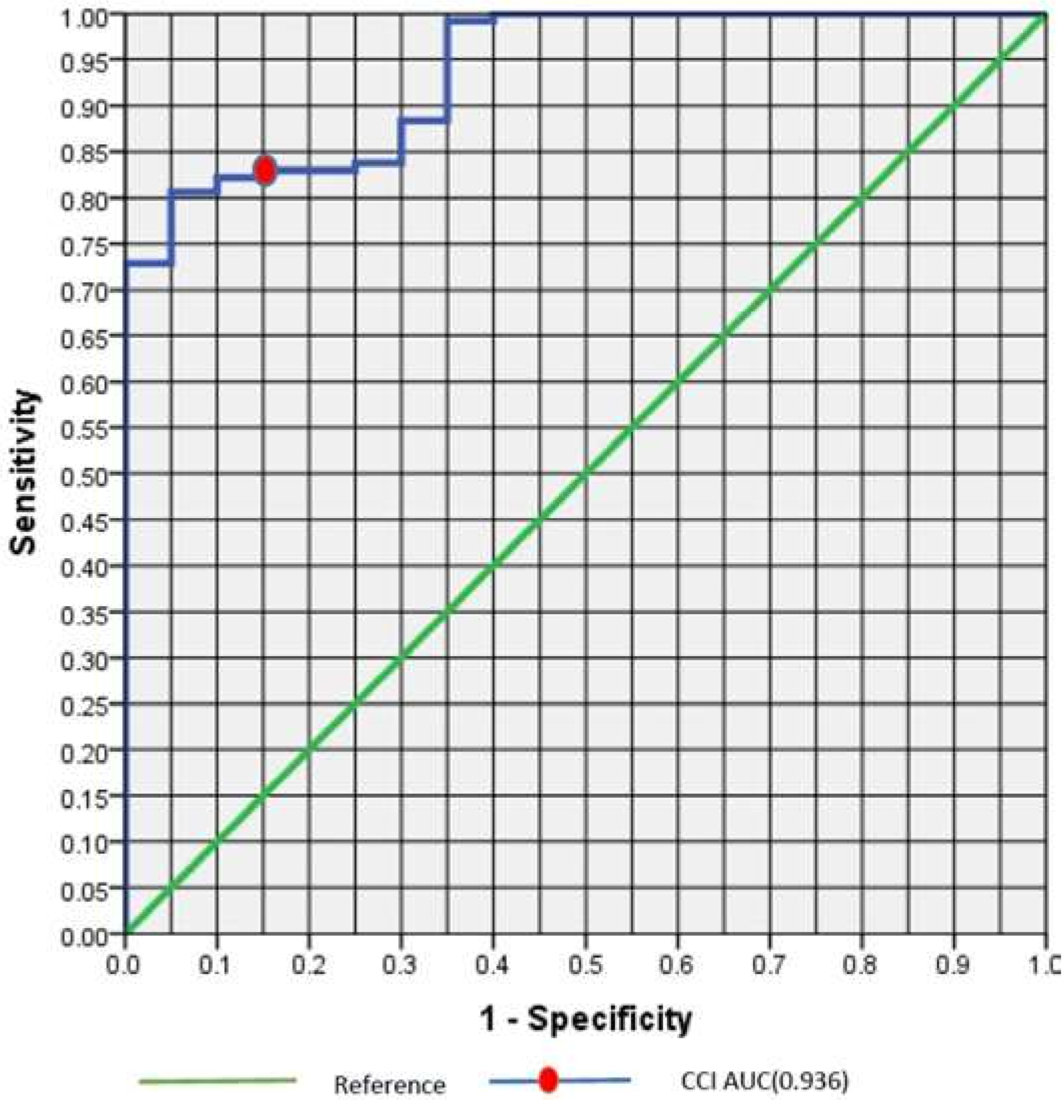

Figure 2. Receiver operating characteristics (ROC) curve for Cervical Consistency Index(CCI) for prediction of PTB before 37 weeks AUC: Area under ROC curve. ⬬Optimal cut-off based on ROC curve

This was a first study in Iran to assess the CCI in low-risk pregnant women using transvaginal sonography. Evaluating the percentage of CCI in the second trimester (14-28 weeks), demonstrated that low CCI in this period of pregnancy may lead to preterm labor (delivery before 37 weeks).(16)

In the current study, the PTB rate was 12.8% which was higher than that of a previous report from Iran,i.e. 5.6 %.(21) The PTB rate in the United States is about 12%, which is similar to the current study.(22) Preterm birth (PTB) is one of the major causes of neonatal mortality in the population.(23) According to the WHO the PTB rate ranges from 5 to 18% and about 5-7% of infants die due to PTB in developed countries.(2) This indicates that the PTB rate is higher in developing countries and because the current study was just about one hospital in Tehran, some socio-economic differences may also have an effect on the prevalence of PTB.(24)

In our study, in order to predict the PTB risk, the cervical length was determined.(18) However, a CL of less than 25mm indicates the need for medical intervention in order to prevent the complications of PTB.(10) In low-risk women with a CL higher than 25mm no medical intervention is necessary, but as demonstrated in this study the rate of PTB in pregnant women with CL above 25mm was noticeably high (12%). So it is clear that CL could not be a reliable factor for predicting PTB. According to a previous study, changes in cervical length may be a late outcome and softness of the cervix occurs before shortening, and water concentration during the ripening process may not cause any clear symptoms and could not be detected in the first trimester.(25)

The assessment of cervical consistency by pelvic examination did not have any clinical value for predicting PTB. For the first time, cervical consistency was measured by transvaginal sonography. The CCI index in our study was lower in women with preterm delivery than in those with term delivery, as was also demonstrated in other studies. The low cervical consistency index indicates weakness of the cervix and is directly related to preterm birth.(26)

In order to determine the predictive value of CCI for detection of PTB, the cutoff value is needed. According to our study, the best cutoff for predicting PTB before 37 weeks was 59.46% with 85% specificity, 99.18% sensitivity, LR+ 5.52, and LR- 0.18, which is connected with percentile 21 of the gestational week. The study by Baños et al.(18) found the best cutoff to predict the PTB before 37 weeks in percentile 20 (corresponding to CCI 64.6 %, sensitivity 72%, specificity 61.2% LR+1.9 and LR- 0.4).

In order to confirm the inter-observer differences in the measurement of CCI and CL, the ICC value was calculated and was 0.99 in both measurements. So the measures obtained were reliable and sufficient for clinical use in both CCI and CL.

The main limitation of our study is the limited number of PTB (n=18) cases, due to the low risk population selection of the study. However, in the current study, in which only low risk people were selected and women with CL under 25mm were excluded from the study, a good relation between CCI and PTB in the low risk population has been obtained, so indicating the validity of the current study.

This study was conducted in one hospital, but in order to confirm the reliability of our results, it is better to repeat it in other centers with large populations. Finally, due to lack of persons with expertise for measuring the anterioposterior diameter of cervix and determining the CCI, we did not have inter-observer agreement. With regard to the increase of the expert people in the measurement of the cervical compression index, it is better that the present study be performed in a larger and multi-centre study by a number of people, allowing conclusions to be made on inter-observer reliability.

CONCLUSION

Determination of CCI in asymptomatic pregnant women could prevent occurrence of

PTB and medical implication following complications in the newborn, hence CCI should be calculated in routine sonography examination.

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CONFLICT OF INTEREST

All authors declare that they do not have any conflict of interest.

CONTRIBUTORS

PP contributed to the basic concept and design of the study. FS and MA contributed to writing the manuscript and performing the experiment. MM and SSG contributed to sample preparation and data collection. OGS contributed to the statistical analysis. All authors read and approved the final manuscript.

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