Cervical consistency index and quantitative cervical texture analysis by ultrasound to predict spontaneous preterm birth

Núria Baños López


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Mid-trimester sonographic cervical consistency index to predict spontaneous preterm birth in a low-risk population

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KEYWORDS: cervical consistency index; cervical-length measurements; cervix uteri; spontaneous preterm birth; ultrasonography

ABSTRACT

Objectives *To investigate the effectiveness of mid-trimester sonographic cervical consistency index (CCI) for the prediction of spontaneous preterm birth (sPTB) in low-risk pregnancies and to compare its performance with that of mid-trimester sonographic cervical-length (CL) measurement.*

Methods *This was a prospective cohort study of women with a singleton pregnancy examined by ultrasound at 19 + 0 to 24 + 6 weeks' gestation. All women underwent transvaginal ultrasound examination of the cervix, but CCI and CL were measured, offline, only in women without a risk factor for sPTB. Staff and participants were blinded to CL and CCI results. CCI was obtained by calculating the ratio between the anteroposterior diameter of the uterine cervix at maximum compression and at rest. The primary outcome was prediction of sPTB before 37 + 0 weeks. Receiver–operating characteristics (ROC) curves were produced and sensitivity and specificity were calculated for the optimal cut-off based on the ROC curve and for the 1st, 5th and 10th centiles of CCI and CL. Intraclass correlation coefficients (ICC) and Bland–Altman plots were used to estimate intra- and interobserver agreement and reliability for measurement of CCI and CL.*

Results *Of the 749 women who underwent ultrasound examination of the cervix, 532 were included for analysis. The rates of sPTB before 37 + 0 and before 34 + 0 weeks were 4.1% (22/532) and 1.3% (7/532), respectively. The rates of short cervix < 25 mm and ≤ 20 mm were 0.9% (5/532) and 0.4% (2/532), respectively. The area under the ROC curve (AUC) with regard to predicting sPTB before 37 + 0 weeks was 0.84 (95% CI, 0.75–0.93) for CCI compared with 0.68 (95% CI, 0.56–0.81) for CL (P = 0.03). The optimal cut-off based on the ROC curve was 64.6% for CCI (sensitivity, 77.3%; specificity, 82.7%) and that for CL was 37.9 mm (sensitivity, 72.7%; specificity, 61.2%). The AUC with regard to predicting sPTB before 34 + 0 weeks was 0.87 (95% CI, 0.71–1.0) for CCI compared with 0.71 (95% CI, 0.47–0.94) for CL (P = 0.25). The optimal cut-off based on the ROC curve was 63.6% for CCI (sensitivity, 85.7%; specificity, 84.0%) and that for CL was 37.9 mm (sensitivity, 85.7%; specificity, 61.3%). Intraobserver ICC was > 0.90 both for CCI and CL, while interobserver ICC was 0.89 for CCI and 0.90 for CL.*

Conclusions *Second-trimester CCI is a better predictor of sPTB < 37 weeks in low-risk pregnancies than is CL. External validation is needed as well as studies assessing the value of CCI as a screening tool in unselected and high-risk populations. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Finding a good predictor of spontaneous preterm birth (sPTB) remains a challenge. Early and accurate identification of women at increased risk for sPTB is the first and most important step to define a population in which specific interventions may help to improve outcome. Risk assessment based on clinical risk factors (previous sPTB before 34 weeks, miscarriage at or after 16 weeks[1–4], Müllerian malformation and cervical conization[5,6]) has limited value. Cervical length (CL) < 25 mm, as measured on transvaginal ultrasound

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in mid-gestation, is a risk factor for sPTB[7,8]. However, its value for screening a pregnant population consisting mainly of women without a risk factor for sPTB is controversial because of the low sensitivity of a short CL in low-risk women[9–12].

Cervical remodeling in normal pregnancy is explained by microstructural and water-concentration changes that start in the first trimester and progress until term. Softening of the cervix starts early in pregnancy, while shortening occurs at a later stage in the cervical-ripening process[13–15]. Therefore, methods aiming at detecting the early stages of cervical remodeling, such as softening, may identify better women at risk of sPTB than does CL measurement.

The cervical consistency index (CCI), described by Parra-Saavedra *et al.*[16], is an estimate of cervical softness calculated as a percentage based on ultrasound measurement of the anteroposterior diameter of the uterine cervix before (AP) and at (AP′) maximal compression with the vaginal ultrasound probe, using the formula: $(AP'/AP) \times 100$. Therefore, the lower the CCI, the higher the cervical compressibility and cervical softness. In the same study, CCI was measured from 5 to 36 weeks' gestation in women with a singleton pregnancy and no history of Müllerian malformation, conization, cerclage or cervical incompetence. CCI decreased with advancing gestation and was lower in women who delivered preterm than in those who delivered at term. At any time in pregnancy, CCI was found to be a much better predictor of sPTB than was CL.

The aims of this study were to investigate the effectiveness of mid-trimester CCI measurement for the prediction of sPTB in a selected low-risk pregnant population and to compare it with that of sonographic CL measurement.

METHODS

Study population

This was a prospective cohort study in which transvaginal ultrasound examination of the cervix was performed in all women attending BCNatal for a routine second-trimester ultrasound examination between 19 + 0 and 24 + 6 weeks' gestation, provided that one of the four ultrasound examiners trained in measuring CCI was available. Ultrasound images of the cervix were saved for later offline analysis. Only ultrasound images of women without any of the following risk factors were subsequently analyzed: (1) multiple pregnancy; (2) history of sPTB < 34 weeks, miscarriage ≥ 16 weeks, Müllerian malformation or cervical conization; (3) CL < 25 mm, preterm prelabor rupture of membranes (PPROM), or symptom of preterm labor, if detected before the routine second-trimester scan; and (4) treatment to prevent sPTB (progesterone, cervical cerclage or cervical pessary) instituted before the routine second-trimester scan. Gestational age was calculated on the basis of first-trimester crown–rump length measurement.

Information on baseline demographic characteristics and obstetric history were collected prospectively from forms filled in by the women before the routine second-trimester scan. Perinatal outcomes were retrieved from hospital files. sPTB was defined as spontaneous preterm delivery or induction of labor owing to PPROM. Women were excluded from the study if they delivered preterm owing to medical or fetal indications (e.g. Cesarean delivery or induction of labor because of pre-eclampsia), if they were lost to follow-up such that information on gestational age at delivery could not be obtained or if the ultrasound images acquired to calculate CCI did not meet the quality criteria described below.

The study protocol was approved by the local Ethics Committee (ID HCB 2014/0089) and all participants provided written informed consent.

Image acquisition and cervical measurements

For image acquisition, a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) or a Voluson 780 Pro, S6, E6 or E8 (GE Healthcare Ultrasound, Milwaukee, WI, USA) equipped with a 2–10-MHz vaginal probe was used. Images were acquired with the woman in the lithotomy position. Four gynecologists who usually performed the routine second-trimester scans carried out the ultrasound examinations after a supervised training period of 1 month. They had access to an image acquisition guide to ensure optimal acquisition of images. To acquire the image of the cervix before compression, a sagittal view was obtained without exerting any pressure with the transducer, on which the cervical canal and the internal and external cervical ora could be seen clearly (Figure 1a). To acquire the image at maximum compression, the technique described by Parra-Saavedra *et al.*[16] was used as follows: pressure was applied softly and progressively on the cervix until no further compression in the anteroposterior direction could be observed (Figure 1b). The images were saved digitally in the original Digital Imaging and Communication in Medicine (DICOM) format, and then downloaded from the medical imaging software and stored in a research imaging server for offline analysis. Quality criteria to consider an image for CCI and CL measurements were that the entire cervix could be seen and that the cervical canal in the image obtained before compression was not inclined more than 45° over the horizontal plane (Figure 2), as estimated subjectively or, in doubtful cases, using the angle tool of the graphic user interface described below. CCI and CL were measured only if the image obtained without pressure from the probe met the quality criteria.

Custom-made software with a graphic user interface was designed using MATLAB R2010b (version 7.11.0.584; MATLAB; The Mathworks Inc., Natick, MA, USA) in order to calculate CCI semi-automatically (Figure 3). The software was created to replicate the procedure described by Parra-Saavedra *et al.*[16]. CL was measured (in mm) from the internal to the external cervical ora following established guidelines and was rounded to

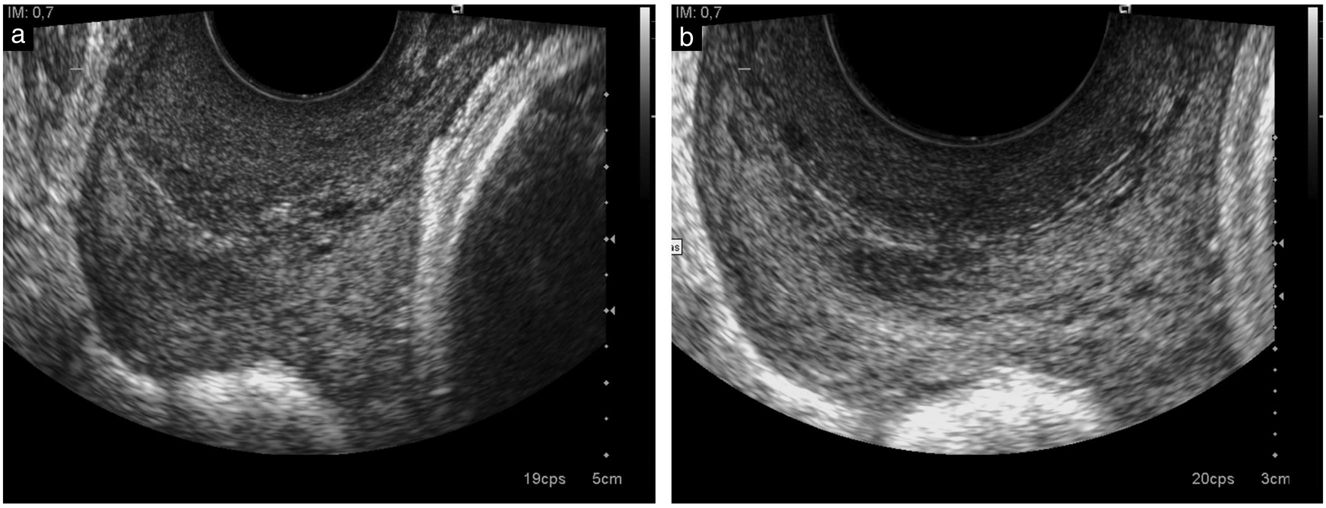

Figure 1 Sagittal view of uterine cervix before (a) and at (b) maximum compression with vaginal probe.

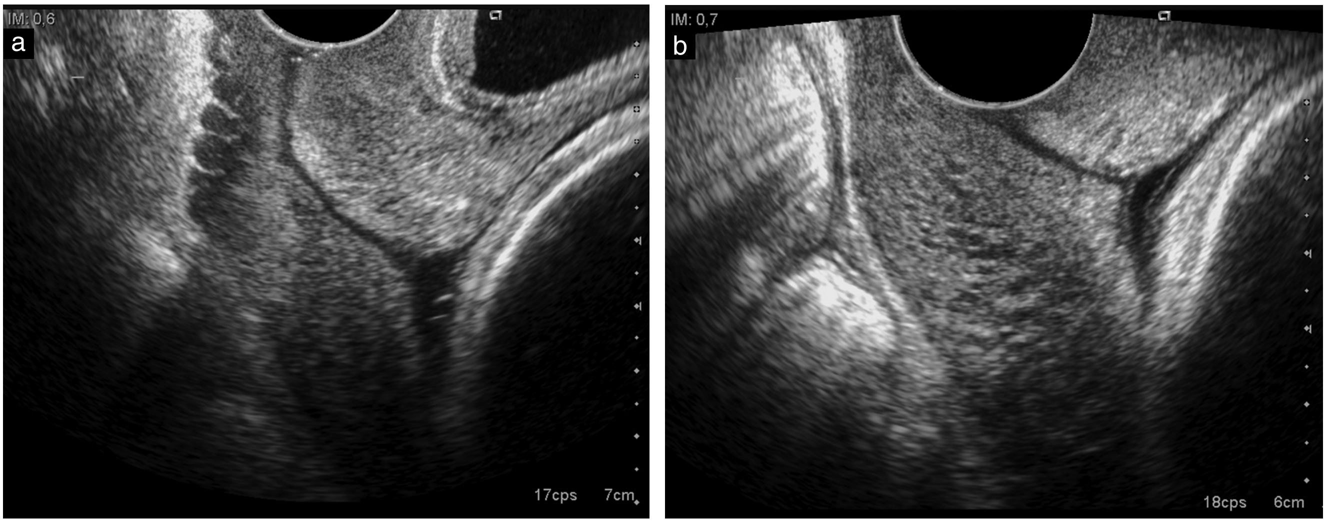

Figure 2 Ultrasound image of non-horizontal cervical canal (inclined $\geq 45^{\circ}$ over horizontal plane and excluded from cervical length or cervical consistency index measurements) before (a) and at (b) maximum compression with vaginal probe.

one decimal place[17]. On the software, a line of the same length as that of the cervix was traced automatically. This line was then adjusted manually to be aligned with the longitudinal axis of the cervix, and a perpendicular line crossing through the midpoint was drawn automatically. This line was adjusted manually to cover the whole anteroposterior diameter of the cervix before (AP) and at (AP′) maximal compression with the probe. CCI was then calculated by the software as the ratio between AP′ and AP, expressed as a percentage. Managing staff and patients were blinded to the CL and CCI results.

To estimate intra- and interobserver agreement and reliability for CL and CCI measurements, 40 images analyzed initially by N.B. were selected by random uniform sampling using MATLAB R2010b by the engineers who had developed the graphic user interface and who had no access to the medical information. Offline CCI and CL measurements were repeated by the same operator (N.B.) to estimate intraobserver agreement and reliability and by a second operator (F.M.) to estimate interobserver agreement and reliability. The repeated analyses were carried out approximately 6 months after the first analyses. The two observers were blinded to the previous results.

Statistical analysis

The primary endpoint was comparison of the effectiveness of CCI and sonographic CL at 19 + 0 to 24 + 6 weeks' gestation for the prediction of sPTB before 37 + 0 weeks. The secondary endpoint was the same comparison for the prediction of sPTB before 34 + 0 weeks.

Data distribution was assessed using the Shapiro–Wilk test of normality. The statistical significance of differences in continuous data was calculated using Student's *t*-test or the Mann–Whitney U-test for normally and non-normally distributed data, respectively, and in categorical data using the chi-square test or Fisher's exact test, as appropriate. Multivariate logistic regression including CCI and CL as predicting variables was performed to assess which

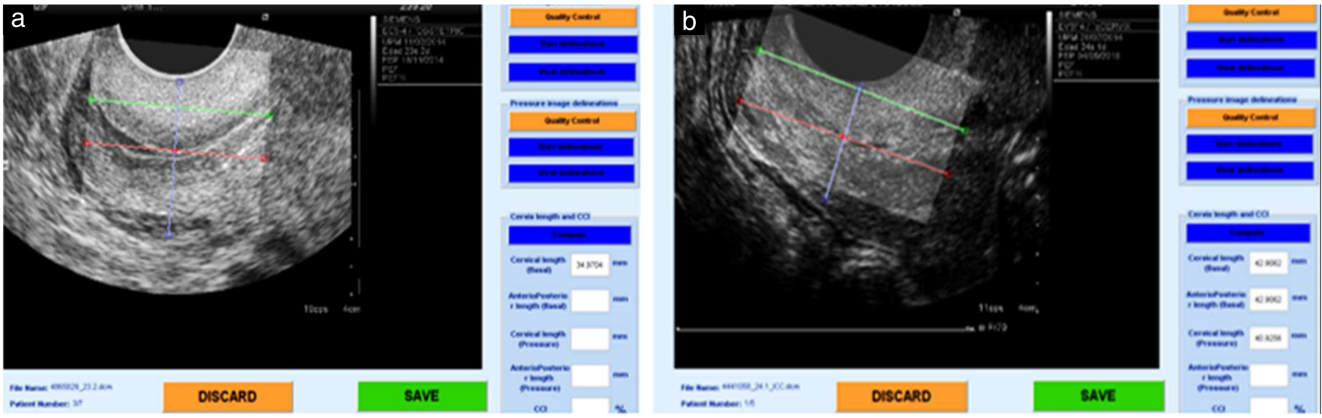

Figure 3 Graphic user interface of software used to calculate cervical consistency index (CCI) from ultrasound measurement of cervical anteroposterior (AP) diameter (blue line) before (a) and at (b) maximum compression. Line with same length as cervical length (green line) was traced automatically by software and aligned manually to longitudinal axis of cervix (red line). Perpendicular line crossing through midpoint was then drawn automatically and adjusted manually to cover whole cervical AP diameter.

variables were associated independently with sPTB. Receiver–operating characteristics (ROC) curves with regard to predicting sPTB < 37 + 0 and < 34 + 0 weeks were drawn for CCI, CL, and for a logistic regression model including both CCI and CL as predicting variables. Areas under the ROC curves (AUCs) and their 95% CIs were calculated. The statistical significance of differences in AUCs was calculated using the DeLong method[18]. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and positive (LR+) and negative (LR−) likelihood ratios and their 95% CIs with regard to predicting sPTB < 37 + 0 and < 34 + 0 weeks' gestation were calculated for the optimal cut-off based on the ROC curve and for the 1st, 5th and 10th centiles of CCI and CL, and for the combined use of CCI and CL (i.e. one or both below the optimal cut-off). The optimal cut-off is the one corresponding to the point on the ROC curve situated furthest from the reference line.

Intraobserver agreement was expressed as the difference between two CL measurements or two CCI values obtained by the same observer, and interobserver agreement as the difference between two results obtained by two different observers. The difference between the measured values was plotted against the mean of the two measurements to assess the relationship between the differences and the magnitude of the measurements. Limits of agreement (mean difference ± 1.96 SD) were calculated as described by Bland and Altman[19]. Systematic bias between two measurements was estimated by calculating the 95% CIs for the mean difference (mean difference ± 2 SE). If zero fell inside this interval, it was assumed that there was no bias. Intra- and interobserver reliability were expressed as intraclass correlation coefficients (ICCs) calculated using a two-way random-effects model (absolute agreement)[20].

Statistical analysis was performed using STATA/IC 13.0 (StataCorp 4905, College Station, TX, USA) or SPSS 20.0 (IBM Corp., Armonk, NY, NY, USA). Two-sided $P \leq 0.05$ was taken to indicate statistical significance.

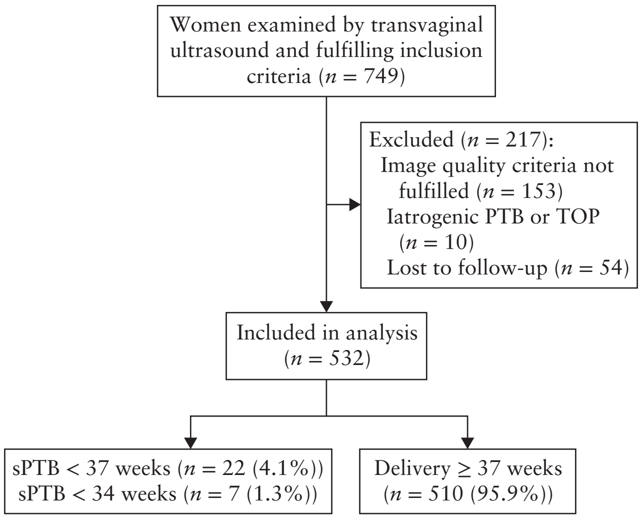

Figure 4 Flowchart summarizing recruitment of women with singleton pregnancy at low risk for spontaneous preterm birth (sPTB) examined with ultrasound at 19–25 weeks' gestation. TOP, termination of pregnancy.

RESULTS

From March 2014 to November 2015, 749 women attending for their routine second-trimester ultrasound examination and fulfilling the inclusion criteria (low risk for sPTB) underwent ultrasound examination of the cervix by one of the doctors trained in the measurement of CCI. Of these, 153 were excluded owing to ultrasound images of the cervix not fulfilling the quality criteria (including 92 cases of a non-horizontal cervical canal), 54 were lost to follow-up such that information on gestational age at delivery could not be obtained, three women were excluded because of termination of pregnancy owing to fetal malformation, and seven women were excluded because of indicated PTB (pre-eclampsia ($n = 3$), placenta previa ($n = 1$), placental abruption ($n = 1$), severe intrauterine growth restriction ($n = 1$) and intrauterine fetal death ($n = 1$)). In total, 532 pregnant women at low risk of sPTB were included (Figure 4).

Table 1 Maternal and pregnancy characteristics, cervical measurements and outcome of women with singleton pregnancy at low risk for spontaneous preterm birth (sPTB) who gave birth at term (≥ 37 + 0 weeks) or had sPTB < 37 + 0 weeks' gestation

Parameter	*Total cohort* (n = *532)*	*Birth ≥ 37 weeks* (n = *510)*	*sPTB < 37 weeks* (n = *22)*	P*
Maternal age (years)	32 (28–36.5)	32 (28–36)	34 (31–39)	0.06
BMI before pregnancy (kg/m^2)	23.2 (20.8–26.1)	23.2 (20.9–26.2)	21.0 (19.8–25.7)	0.35
Caucasian	384 (72.2)	367 (72.0)	17 (77.3)	0.58
Smoker	47 (8.8)	46 (9.0)	1 (4.5)	0.43
Nulliparous	283 (53.2)	273 (53.5)	10 (45.5)	0.46
Fetal malformation†	5 (0.9)	5 (1.0)	0 (0.0)	—
GA at scan (weeks)	20 + 5 (20 + 2 to 21 + 3)	21 + 1 (20 + 2 to 23 + 2)	21 + 1 (20 + 2 to 23 + 2)	0.13
Cervical length				
At scan (mm)	39.6 (35.6–43.3)	39.8 (35.7–43.4)	36.2 (31.4–39.2)	0.004
< 25 mm	5 (0.9)	2 (0.4)	3 (13.6)	< 0.001
≤ 20 mm	2 (0.4)	1 (0.2)	1 (4.5)	0.001
CCI at scan (%)	72.6 (66.2–79.8)	73.0 (66.7–80.1)	58.1 (46.5–64.6)	< 0.001
GA at delivery (weeks)	39 + 6 (38 + 6 to 40 + 4)	40 + 0 (39 + 0 to 40 + 5)	34 + 5 (32 + 0 to 35 + 6)	NA
Birth weight (g)	3300 (2980–3540)	3330 (3000–3550)	2485 (1835–2599)	NA
Onset of labor				0.07
Spontaneous	340 (63.9)	321 (62.9)	19 (86.4)	
Induced	156 (29.3)	153 (30.0)	3 (13.6)‡	
Elective CS	36 (6.8)	36 (7.1)	0 (0.0)	
Mode of delivery				0.10
Vaginal	422 (79.3)	406 (79.6)	16 (72.7)	
Non-elective CS	74 (13.9)	68 (13.3)	6 (27.3)	
Elective CS	36 (6.8)	36 (7.1)	0 (0.0)	

Data are given as median (interquartile range) or *n* (%). *Comparison between birth ≥ 37 weeks and sPTB < 37 weeks. †Interventricular communication, right aortic arch, unilateral multicystic dysplastic kidney, cleft palate, arachnoid cyst. ‡Owing to preterm prelabor rupture of membranes. BMI, body mass index; CCI, cervical consistency index; CS, Cesarean section; GA, gestational age; NA, not applicable.

Table 2 Distribution of cervical consistency index, in %, in 532 women at low risk for spontaneous preterm birth, according to gestational age (GA)

			Centile								
GA (weeks)	n	*Min*	*1st*	*5th*	*10th*	*20th*	*50th*	*80th*	*90th*	*95th*	*Max*
19	40	47	47	60	62	67	80	84	87	89	89
20	282	46	46	57	62	66	73	82	86	89	95
21	112	45	45	55	59	64	72	80	83	85	95
22	49	45	45	54	58	63	71	80	82	84	87
23	40	44	44	48	52	61	71	78	82	82	86
24	9	40	40	44	44	45	59	76	79	82	82
19–24	532	40	45	55	60	64	73	81	84	87	95

Table 3 Distribution of sonographic cervical length measurements, in mm, in 532 women at low risk for spontaneous preterm birth, according to gestational age (GA)

			Centile								
GA (weeks)	n	*Min*	*1st*	*5th*	*10th*	*20th*	*50th*	*80th*	*90th*	*95th*	*Max*
19	40	29	29	30	33	35	41	46	50	53	57
20	282	26	27	31	33	35	40	45	48	50	63
21	112	21	21	30	32	34	40	44	47	49	65
22	49	29	29	30	33	35	40	44	46	50	67
23	40	20	20	25	33	35	39	44	46	51	58
24	9	25	25	25	25	28	35	40	41	41	41
19–24	532	20	25	30	33	35	40	44	47	50	67

Demographic characteristics, cervical measurements and perinatal outcomes for the women included are shown in Table 1. Maternal baseline characteristics did not differ significantly between the women who gave birth at term and those who had sPTB. The rates of sPTB < 37 + 0 and < 34 + 0 weeks were 4.1% (22/532) and 1.3% (7/532), respectively. The prevalence of a short cervix < 25 mm and ≤ 20 mm was 0.9% (5/532) and 0.4% (2/532), respectively. The cervix was significantly shorter (median CL 39.8 mm *vs* 36.2 mm; $P = 0.004$) and the CCI was significantly lower (median 73.0% *vs* 58.1%; $P < 0.001$) in the sPTB group. The distributions (centiles) of CCI and CL according to gestational age are shown in Tables 2 and 3.

ROC curves for CCI and CL are shown in Figure 5. The AUC for CCI with regard to predicting sPTB < 37 + 0 weeks was 0.84 (95% CI, 0.75–0.93) and that for CL was 0.68 (95% CI, 0.56–0.81) ($P = 0.03$). The optimal cut-off based on the ROC curve was 64.6% for CCI (sensitivity, 77.3%; specificity, 82.7%) and 37.9 mm for CL (sensitivity, 72.7%; specificity, 61.2%). The AUC with regard to predicting sPTB < 34 + 0 weeks was 0.87 (95% CI, 0.71–1.00) for CCI and 0.71 (95% CI, 0.47–0.94) for CL ($P = 0.25$). The optimal cut-off for CCI based on the ROC curve was 63.6% (sensitivity, 85.7%; specificity, 84.0%) and that for CL was 37.9 mm (sensitivity, 85.7%; specificity, 61.3%).

Sensitivity, specificity, PPV, NPV, LR+ and LR− for CCI and CL for the prediction of sPTB < 37+0 and < 34+0 weeks, when using the optimal cut-off points based on the ROC curve as well as for other cut-offs, are shown in Tables 4 and S1, respectively. The discriminative performance of the combined use of CL and CCI (both or one being below the optimal cut-off) is also shown.

Multivariate logistic regression analysis showed that only CCI was associated independently with sPTB. The AUC for a model including both CCI and CL for predicting sPTB < 37 weeks was 0.85 (95% CI, 0.76–0.93), which is not significantly different from the AUC of CCI alone (0.84; $P = 0.61$). The AUC for a model including both CCI and CL (both having been forced into the model) for predicting sPTB < 34 week was 0.86 (95% CI, 0.73–0.99), which is not significantly different from the AUC of CCI alone (0.87; $P = 0.92$).

Intra- and interobserver agreement and reliability for CCI and CL are shown in Tables 5 and 6. Bland–Altman plots (Figures S1 and S2) showed that neither intra- nor interobserver differences in measurement results changed with the magnitude of the measurements. There was no systematic bias between the first and second measurement by the same observer, and the intraobserver ICC values for CL and CCI were 0.95 and 0.92, respectively. One of the two observers systematically recorded lower values for CCI and CL. The interobserver ICC values were 0.89 for CCI and 0.90 for CL.

DISCUSSION

This study shows that CCI is superior to sonographically measured CL for predicting sPTB < 37 weeks in a low-risk

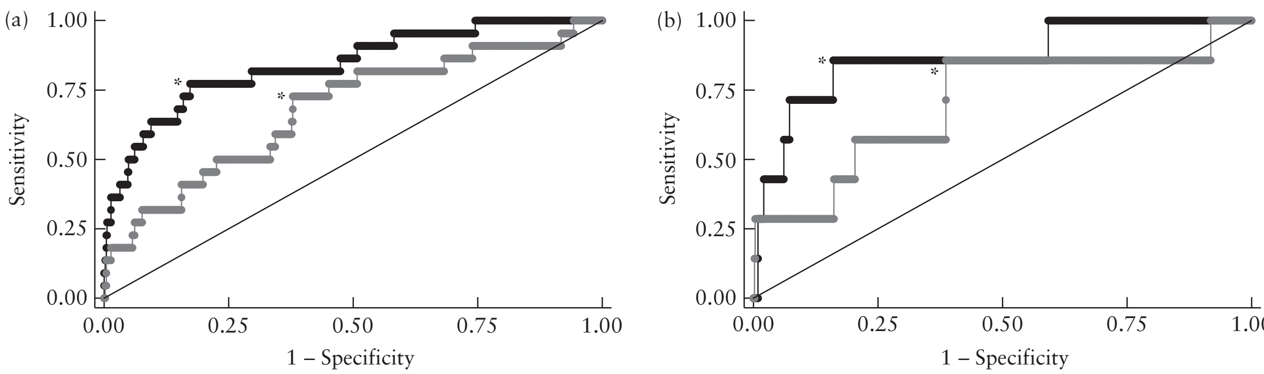

Figure 5 Receiver–operating characteristics (ROC) curves for cervical consistency index (—●—) and cervical length (—●—) for prediction of spontaneous preterm birth < 37 + 0 (a) and < 34 + 0 (b) weeks' gestation in 532 low-risk women with singleton pregnancy. *Optimal cut-off based on ROC curve.

Table 4 Discriminative performance of cervical consistency index (CCI), cervical length (CL) and combination of CCI and CL for prediction of spontaneous preterm birth < 37 + 0 weeks' gestation in 532 low-risk women

*Cut-off**	*Sensitivity (% (n/N))*	*Specificity (% (n/N))*	*PPV (% (n/N))*	*NPV (% (n/N))*	*LR+ (95% CI)*	*LR− (95% CI)*
CCI (%) (centile)						
45.0 (1st)	18.2 (4/22)	99.6 (508/510)	66.7 (4/6)	96.6 (508/526)	46.4 (9.0–239.7)	0.8 (0.7–1.0)
55.0 (5th)	40.9 (9/22)	96.5 (492/510)	33.3 (9/27)	97.4 (492/505)	11.6 (5.9–22.8)	0.6 (0.4–0.9)
60.0 (10th)	54.5 (12/22)	92.2 (470/510)	23.1 (12/52)	97.9 (470/480)	7.0 (4.3–11.3)	0.5 (0.3–0.8)
64.6 (20th)†	77.3 (17/22)	82.7 (422/510)	15.4 (16/104)	98.6 (422/428)	4.5 (2.7–6.2)	0.3 (0.1–0.6)
CL (mm) (centile)						
25.0 (1st)	13.6 (3/22)	99.6 (508/510)	60.0 (3/5)	96.4 (508/527)	34.8 (6.1–197.6)	0.9 (0.7–1.0)
30.0 (5th)	18.2 (4/22)	96.5 (492/510)	18.2 (4/22)	96.5 (492/510)	5.2 (1.9–13.9)	0.8 (0.7–1.0)
33.0 (10th)	31.8 (7/22)	89.6 (457/510)	11.7 (7/60)	96.8 (457/472)	3.1 (1.6–5.9)	0.8 (0.6–1.0)
37.9 (40th)†	72.7 (16/22)	61.2 (312/510)	7.5 (16/214)	98.1 (312/318)	1.9 (1.4–2.5)	0.4 (0.2–0.9)
CCI < 64.6%† and CL < 37.9 mm†	54.5 (12/22)	90.2 (460/510)	19.4 (12/62)	97.9 (460/470)	5.6 (3.5–8.8)	0.5 (0.3–0.8)
CCI < 64.6%† or CL < 37.9 mm†	90.9 (20/22)	53.9 (275/510)	7.8 (20/255)	99.3 (275/277)	2.0 (1.7–2.3)	0.2 (0.05–0.6)

*Values below cut-off indicate increased risk. †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.

Table 5 Intraobserver agreement and reliability for cervical consistency index (CCI) and cervical length (CL) offline measurements in 80 women

		Intraobserver difference		
Parameter	*Value (median (range))*	*Mean (95% CI)*	*Limits of agreement*	*ICC (95% CI)*
CCI (%)	65.1 (45.3–86.2)	−0.538 (−1.773 to 0.696)	−8.104 to 7.027	0.919 (0.852–0.956)
CL (mm)	40.0 (24.7–50.3)	0.322 (−0.250 to 0.894)	−3.184 to 3.828	0.950 (0.908–0.973)

ICC, intraclass correlation coefficient.

Table 6 Interobserver agreement and reliability for cervical consistency index (CCI) and cervical length (CL) offline measurements in 80 women

		Interobserver difference		
Parameter	*Value (median (range))*	*Mean (95% CI)*	*Limits of agreement*	*ICC (95% CI)*
CCI (%)	66.6 (39.9–88.8)	−2.587 (−3.884 to −1.290)	−10.534 to 5.361	0.887 (0.700–0.950)
CL (mm)	40.7 (24.7–52.8)	−1.471 (−2.172 to −0.770)	−5.766 to 2.825	0.904 (0.718–0.959)

ICC, intraclass correlation coefficient.

population examined between 19 + 0 and 24 + 6 weeks' gestation. Combining the two measurements did not improve prediction.

To the best of our knowledge, this is the first study to estimate prospectively the ability of mid-trimester CCI to predict sPTB in low-risk women. It was designed specifically to screen a selected low-risk population in which it remains controversial as to whether sonographic CL screening for sPTB works well[10–12,21–23].

The main limitation of this study is the low number of sPTBs ($n = 22$), which is explained by our population being a selected low-risk population. The rate of sPTB before 37 + 0 weeks (4.1%) is consistent with the rates reported in recently published European series of unselected pregnancies and selected low-risk pregnancies (4.2%[12] and 3.9%[11], respectively).

A second limitation is that CCI was calculated offline using a graphic user interface. This might have resulted in overestimation of the discriminatory ability of CCI, because more time and effort could be spent on analyzing the images than might have been possible if analysis had been done during the examination. Offline analysis was chosen to ensure that all staff and participants were blinded to CCI and CL results so as to avoid results being acted upon. We did not assess the extra time needed to measure and calculate CCI during the examination, but we estimate that it was less than 5 min.

The results for CL were similar to those reported by Parra-Saavedra *et al.*[16]. Moreover, in both studies, CCI was lower in women giving birth preterm than at term, and CCI was superior to CL for predicting sPTB. However, at each gestational week, CCI was on average ten percentage points lower in the study of Parra-Saavedra *et al.*[16]. In their study, the AUC for CCI was larger (0.94 and 0.91 for the prediction of sPTB < 34 and < 37 weeks, respectively, *vs* 0.87 and 0.84 in our study), and the difference in AUC between CCI and CL was larger (AUC for CCI was 0.91 *vs* 0.64 for CL, compared with 0.87 *vs* 0.68 in the current study). These differences may be explained partly by differences in the characteristics of the study populations, measurement techniques and study design. The prevalence of sPTB < 37 and < 34 weeks was higher in the study by Parra-Saavedra *et al.*[16] than in the current study (7.8% *vs* 4.1% for sPTB < 37 weeks and 2.1% *vs* 1.3% for sPTB < 34 weeks). This may be explained by differences in socioeconomic factors (Colombia being a low-income country while Catalonia is not) and by the inclusion in the study of Parra-Saavedra *et al.* of women with a history of sPTB, PPROM or CL < 25 mm detected before the scan. While in the current study the diagnostic performance of CL and CCI was estimated only in the second trimester, CCI was measured in all three trimesters by Parra-Saavedra *et al.*[16]. Moreover, they measured CCI twice and used the lower value, while we measured CCI once. In addition, we excluded images with a non-horizontal cervical canal while no criteria for exclusion of images seem to have been applied by Parra-Saavedra *et al.*[16].

If CCI is to be used for identification of women at high risk for sPTB, one needs to choose a CCI cut-off. In this study, the best cut-off for predicting sPTB < 37 weeks, on the basis of the shape of the ROC curve, was 64.6%. This cut-off detected 77% of sPTB < 37 weeks, with LR+ 4.5, LR− 0.3 and a screen-positive rate of 19.5%. A cut-off of 60% (10th centile) was associated with LR+ 7.0, LR− 0.5 and a screen-positive rate of 9.8%, and at which 54.5% of sPTB < 37 weeks cases were identified. Parra-Saavedra *et al.*[16] found that the optimal CCI cut-off for predicting sPTB < 32, < 34 or < 37 weeks was the 10th centile (corresponding to CCI 46–54% at 19–24 weeks). This cut-off predicted sPTB < 37 weeks with a sensitivity of 79%, specificity of 95%, LR+ of 15.4, LR− of 0.2 and screen-positive rate of 9.8%.

It might be argued that CCI is more difficult to measure than is CL, and that the unknown force exerted by the operator on the cervix is a limitation of the method. However, under experimental conditions, a change in the applied force did not result in a significant change in strain, which led the authors of the experimental study to conclude that the method of measuring CCI should be reproducible and robust in a clinical setting[24]. It is a limitation of the CCI method that 12% of women had to be excluded owing to a non-horizontal cervical canal in the image obtained before compression. We considered that, when the canal was non-horizontal in the image, the force applied by the probe might not be perpendicular to the anteroposterior diameter of the cervix and that the CCI would therefore not reflect the compressibility of the whole cervix. It remains to be established if manipulation of the vaginal transducer could avoid a non-horizontal orientation of the cervical canal.

We judge intra- and interobserver differences in CL and CCI to be acceptable in relation to the magnitude of the measurements, and ICC values were high. Thus, intra- and interobserver agreement and reliability seem sufficient for clinical use of both CL and CCI. This is in agreement with the results of Parra-Saavedra *et al.*[16].

The cut-offs for CCI suggested here with regard to predicting sPTB need to be validated externally, the discriminative ability of CCI when calculated during the examination needs to be compared with that of offline analysis and the time needed to obtain a CCI result during a live examination needs to be estimated. It remains to be seen if CCI is superior to CL measurement for predicting sPTB in high-risk pregnancies, and if strategies to prevent sPTB in women with a short cervix are effective in such women[8,25–30].

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SUPPORTING INFORMATION ON THE INTERNET

Table S1 and **Figures S1** and **S2** may be found in the online version of this article.

