Mid-Trimester Cervical Consistency Index and Cervical Length to Predict Spontaneous Preterm Birth in a High-Risk Population

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Abstract

Background Short cervical length (CL) has not been shown to be adequate as a single predictor of spontaneous preterm birth (sPTB) in high-risk pregnancies.

Objective The objective of this study was to evaluate the performance of the mid-trimester cervical consistency index (CCI) to predict sPTB in a cohort of high-risk pregnancies and to compare the results with those obtained with the CL.

Study Design Prospective cohort study including high-risk singleton pregnancies between 19⁺0 and 24⁺6 weeks. The ratio between the anteroposterior diameter of the uterine cervix at maximum compression and at rest was calculated offline to obtain the CCI.

Results Eighty-two high sPTB risk women were included. CCI (%) was significantly reduced in women who delivered <37⁺0 weeks compared with those who delivered at term, while CL was not. The area under the curve (AUC) of the CCI to predict sPTB <37⁺0 weeks was 0.73 (95% confidence interval [CI], 0.61–0.85), being 0.51 (95% CI, 0.35–0.67), p = 0.03 for CL. The AUC of the CCI to predict sPTB <34⁺0 weeks was 0.68 (95% CI, 0.54–0.82), being 0.49 (95% CI, 0.29–0.69), p = 0.06 for CL.

Conclusion CCI performed better than sonographic CL to predict sPTB. Due to the limited predictive capacity of these two measurements, other tools are still needed to better identify women at increased risk.

Risk factors of spontaneous preterm birth (sPTB) such as a history of sPTB <34⁺0 weeks or late miscarriage ≥16 weeks¹,² and Müllerian malformations³,⁴ or cervical surgery⁵ have shown limited utility as predictors of sPTB.⁶–⁹ Neither had short cervical length (CL) shown to be adequate as a single predictor of sPTB in pregnancies with the above-mentioned risk factors.¹⁰ On one hand, the addition of CL surveillance in pregnancies with a history of sPTB does not select all the women who will benefit from treatment.¹⁰ On the other hand, although CL seems to be shorter in women who have undergone cervical surgery or with Müllerian malformations,⁴,¹¹,¹² it has not been demonstrated to be an independent risk factor for sPTB.¹³ Therefore, the use of other or the combination of sPTB prediction tools together with sonographic CL is needed to improve the identification of women at risk who will benefit from the treatments.
Currently available. In this study, we evaluate the cervical consistency index (CCI), an ultrasound measurement that aims to estimate cervical softness by measuring the anteroposterior diameter of the uterine cervix before (AP) and at maximal compression (AP') with the vaginal ultrasound probe and calculating the ratio between the two measurements (AP'/AP × 100). The lower the CCI, the higher the cervical compressibility and cervical softness. Studies based on animal models assessing cervical remodeling along pregnancy suggest an initial phase of cervical softening which starts soon after conception and occurs progressively along pregnancy, followed by a shortening and ripening phase closer to delivery. In addition, slight changes in CL have been associated with increased cervical softening and cervical volume without substantial effacement before term.

Therefore, assessment of the early stage in cervical remodeling such as softening using the CCI would potentially allow early identification of the women at increased risk. In fact, in a previous publication, CCI was found to be a better predictor of sPTB <37+0 weeks and <34+0 weeks than sonographic CL during the second-trimester scan in a low-risk population.

The aim of this study was to evaluate the performance of mid-trimester CCI to predict sPTB in a cohort of high-risk pregnancies and compare the results with those obtained with mid-trimester sonographic CL.

Materials and Methods

Study Population

This was a prospective cohort study including singleton pregnancies between 19+0 and 24+6 weeks of gestational age attending the preterm birth prevention clinic (PBPC) from BCNatal, Barcelona. Women were included if they presented at least, one of the following sPTB risk factors: (1) history of sPTB <34+0 weeks or late miscarriage >16 weeks, (2) Müllerian malformation or cervical conization, (3) CL < 25 mm or preivable premature prelabor rupture of membranes (PPROMs) if detected before the routine second-trimester ultrasound, sPTB was defined as a birth <37+0 weeks related to the spontaneous onset of labor with intact membranes or with PPROMs. PTB for fetal or maternal indications including induction of labor (IOL) for PPROM was excluded from the study.

In our center, high sPTB risk patients are followed in the PBPC every 2 to 3 weeks from week 14 depending on the risk factor and clinical findings. Progesterone is indicated in women with a history of sPTB, late miscarriage, Müllerian malformation, or cervical conization with a CL < 25 mm and in all women with a CL < 20 mm. Prophylactic cerclage is performed in women with ≥3 sPTB or late miscarriages and in women with ≥1 previous sPTB or late miscarriage after conization. Prophylactic cerclage is also indicated with ≥2 sPTB or late miscarriages if they are well documented in the medical records. Ultrasound-indicated cervical cerclage is indicated at up to 24 weeks in women with a history of ≥1 sPTB or late miscarriage with progressive cervical shortening <25 mm despite progesterone treatment. Physical examination-indicated cervical cerclage is indicated in women at up to 24 weeks when there is membrane exposure, after previously ruling out intra-amniotic infection by amniocentesis. Cervical pessary is not yet implemented in our routine clinical practice while awaiting further evidence of its possible benefits.

Information on baseline demographic characteristics and obstetric history were prospectively collected from paper forms filled in by the pregnant women. Perinatal outcomes were retrieved from hospital files. The primary outcome was to compare the diagnostic accuracy of CCI and CL to predict sPTB <37+0 weeks. The secondary outcomes were to compare the diagnostic accuracy of CCI and CL to predict sPTB <34+0 weeks.

Image Acquisition and Cervical Measurements

Image acquisition was performed with a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA) and a Voluson 780 Pro, S6, E6 and E8 (GE Medical Systems, Milwaukee, WI) with a vaginal probe with a frequency between 2 and 10 MHz. Images were acquired in lithotomy position by three trained gynecologists running the PBPC in our center. An image acquisition guide and quality criterion were defined to ensure the optimal acquisition parameters and explained in depth in a previous publication. Briefly, to acquire the basal image, a sagittal view of the cervix was obtained without exerting any pressure with the transducer, identifying the internal and external os as well as the cervical canal (Fig. 1a). To acquire the image at maximal compression, pressure was applied softly and progressively on the cervix until no further compression of the anteroposterior diameter could be observed as described by Parra-Saavedra et al. (Fig. 1b). The images were digitally collected in the original Digital Imaging and Communication in Medicine format, downloaded from the medical imaging software and stored in a research imaging server for the offline analysis. A custom-made program with a graphical user interface (GUI) using MATLAB R2010b (version 7.11.0.584; MATLAB; The Mathworks Inc., Natick, MA) was designed for this purpose also following the procedure described by Parra-Saavedra et al. Quality criteria to consider an image for CCI and CL measurements were (1) visualization of the entire cervix and (2) the cervical canal in the basal image is not inclined more than 45 degrees over the horizontal plane as estimated subjectively or—in doubtful cases—using the angle tool of the GUI. CCI was semiautomatically calculated as the ratio between the anteroposterior diameter of the uterine cervix at maximal compression (AP) and the diameter in the basal image (AP): CCI = AP'/AP × 100 (Fig. 1). CCI and CL measurements were performed offline in a personal computer by N.B. and blinded to the managing physicians and patients.

Statistical Analysis

Data distribution was assessed according to the Shapiro–Wilk’s test of normality. Results were described as absolute and relative frequencies for qualitative variables and median and interquartile range for quantitative variables. Continuous data were compared with Student’s t-test or analysis of variance and with Mann–Whitney’s U-test or Kruskal–Wallis’ test for
In predicting sPTB, AUCs were compared using the DeLong ratios (LR predictive value (PPV), and positive and negative likelihood ratio (LR)) with their 95% confidence intervals (CIs) in predicting sPTB <37<sup>+</sup>0 and <34<sup>+</sup>0 weeks. The resulting AUCs were compared using the DeLong’s method. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and positive and negative likelihood ratios (LR+ and LR−) with their 95% confidence intervals (CIs) in predicting sPTB <37<sup>+</sup>0 and <34<sup>+</sup>0 weeks were calculated for the optimal cutoff based on the ROC curve and for different cutoff points for CCI and CL and for the combined use of CCI and CL (i.e., either or both below the optimal cutoff). The optimal cutoff is that corresponding to the point on the ROC curve situated farthest from the reference line. The McNemar’s test was used to compare the diagnostic accuracy of CCI and CL at certain cutoff points. The relationship between CCI and CL and risk of PTB was analyzed using logistic regression and the estimated probability of PTB by CCI and CL was calculated. A two-sided type I error of 5% was applied in the statistical tests. All the analyses were performed using STATA/IC 13.0 (StataCorp; 4905 Lakeway Drive, College Station, TX).

Results

From November 2014 to November 2015, a total of 96 women at high risk of sPTB were eligible for inclusion. Six women with PPROM were excluded (four because they presented a previable PPROM and subsequently underwent a termination of pregnancy and two women because of a PPROM which required an IOL at 34<sup>+</sup>0 weeks according to the hospital protocol). In addition, eight women were excluded because the images did not fulfill the quality criteria. Finally, 82 high sPTB risk women were included in the analysis. Demographic and pregnancy characteristics of women who delivered <37<sup>+</sup>0 weeks and those who delivered at term are shown in Table 1. The rate of sPTB <37<sup>+</sup>0 weeks was 26.8%, being 17.1% at <34<sup>+</sup>0 weeks. Regarding the demographic characteristics between the sPTB and the term groups, women who delivered preterm were older and the gestational age at scan was significantly greater. A history of preterm delivery was overrepresented in the term group compared with the sPTB group, being 66.7% (40/60) versus 31.8% (7/22), respectively. Of the nine women with a history of sPTB and a CL <25 mm, only three delivered preterm. Of the 17 women with a uterine factor, 4 out of 12 with a Müllerian malformation delivered preterm. The five women with a prior conization delivered at term. The median gestational age of the previous sPTB or late miscarriage was 25<sup>+</sup>0 weeks and did not differ between the groups. Regarding sonographic measurements, the median CL (mm) at mid-pregnancy was not significantly different between the sPTB and the term groups or with the proportion of short CL (CL < 20 or < 25 mm). On the contrary, the CCI (%) was significantly reduced in the women with a preterm delivery compared with the term group. Multivariate logistic regression analysis showed that only CCI was independently associated with sPTB when adjusted for confounders (history of sPTB and cerclage): CCI-adjusted odds ratio of 0.93 (95% CI, 0.88–0.98; p = 0.03). CL was not associated with sPTB.

The AUC of the CCI to predict sPTB <37<sup>+</sup>0 weeks was 0.73 (95% CI, 0.61–0.85), while the AUC of CL was 0.51 (95% CI, 0.35–0.67) (p = 0.03) (Fig. 2). The optimal CCI and CL cutoff points to predict sPTB <37<sup>+</sup>0 weeks were 59.4% (sensitivity 72.7%, specificity 63.3%) and 34.0 mm (sensitivity 54.5%, specificity 56.7%) as shown in Table 2. The discriminative performances of the different CCI and CL cutoffs and of the combined use of CL and CCI (both or either being below the optimal cutoff) are also shown in Table 2. A CL <25 mm, which is the cutoff currently used in clinical practice had a sensitivity of 31.8%, a specificity

Fig. 1 Image of the uterine cervix in the same patient before (a) and at maximal compression (b) with the vaginal probe and the calculation of the cervical consistency index (CCI): AP/AP × 100.
of 81.7%, a PPV of 38.9%, a NPV of 76.6%, and a LR+ of 1.74 and
LR− of 0.84. On comparing certain cutoff points to identify sPTB, the McNemar’s exact test suggested that there was no
statistically significantly difference between optimal cutoff
points of CCI and CL (p = 0.22) and between the 10th centiles
of CCI and CL (CCI of 45% and CL < 20 mm) (p = 0.38).
The AUC of the CCI to predict sPTB < 34 + 0 weeks was 0.68
(95% CI, 0.54–0.82), while the AUC of CL was 0.49 (95% CI,
0.29–0.69) (p = 0.06) (Fig. 3). The optimal cutoff points of
the CCI and CL to predict sPTB < 34 + 0 weeks were 59.4%
sensitivity 78.6%, specificity 58.8%) and 29.7 mm (sensitivity
42.9%, specificity 69.1%) as shown in Table 3. The McNemar’s exact test suggested that to identify sPTB < 34 weeks, there was no statistically significantly difference
between optimal cutoffs of CCI and CL (p = 0.22) and
between the 10th centiles of CCI and CL (45% and CL < 20
mm) (p = 0.57). The discriminative performance of the
different CCI and CL cutoffs and of the combined use of CL.
Table 2 Discriminative performance of the CCI and CL measured with ultrasound and with the combination of the two measurements with regard to predicting spontaneous preterm birth <37\(^{0}\) weeks

<table>
<thead>
<tr>
<th>Cutoff(^{a})</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>LR(^{+}) (95% CI)</th>
<th>LR(^{-}) (95% CI)</th>
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<tbody>
<tr>
<td>CCI</td>
<td>&lt;45%</td>
<td>27.3% (13.1–48.2)</td>
<td>95.0% (86.3–98.3)</td>
<td>66.7% (35.4–87.9)</td>
<td>78.1% (67.3–86.0)</td>
<td>5.5 (1.5–19.6)</td>
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<td>&lt;50%</td>
<td>45.5% (26.9–65.3)</td>
<td>86.7% (75.8–93.1)</td>
<td>55.6% (33.7–75.4)</td>
<td>81.5% (70.0–88.9)</td>
<td>3.4 (1.5–7.5)</td>
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<td></td>
<td>&lt;55%</td>
<td>54.5% (34.7–73.1)</td>
<td>70.0% (57.5–80.1)</td>
<td>40.0% (24.6–57.7)</td>
<td>80.8% (68.1–92.9)</td>
<td>1.8 (1.1–3.1)</td>
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<td></td>
<td>59.4%(^{b})</td>
<td>72.7% (51.8–81.8)</td>
<td>63.7% (49.0–72.9)</td>
<td>41.0% (27.1–56.6)</td>
<td>86.0% (72.3–93.4)</td>
<td>1.9 (1.3–2.9)</td>
</tr>
<tr>
<td>CL</td>
<td>≥ 20 mm</td>
<td>13.6% (4.7–33.3)</td>
<td>88.3% (77.8–94.2)</td>
<td>30.0% (10.5–60.3)</td>
<td>73.6% (62.4–82.4)</td>
<td>1.2 (0.3–4.1)</td>
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<td></td>
<td>&lt; 25 mm</td>
<td>31.8% (16.4–52.7)</td>
<td>81.7% (70.1–89.4)</td>
<td>38.9% (20.3–61.4)</td>
<td>76.6% (64.9–85.3)</td>
<td>1.7 (0.8–3.9)</td>
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<td>&lt; 30 mm</td>
<td>40.9% (23.3–61.3)</td>
<td>70.0% (57.5–80.1)</td>
<td>33.3% (18.6–52.2)</td>
<td>76.4% (63.7–85.6)</td>
<td>1.4 (0.7–2.6)</td>
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<td>34.0 mm(^{b})</td>
<td>54.5% (34.7–73.1)</td>
<td>56.7% (44.1–68.4)</td>
<td>31.6% (19.1–47.5)</td>
<td>77.3% (63.0–87.2)</td>
<td>1.3 (0.8–2.0)</td>
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<tr>
<td>CCI or CL below cutoff</td>
<td>&lt;59.4% and &lt;34.0 mm</td>
<td>50.0% (30.7–69.3)</td>
<td>73.3% (61.0–82.9)</td>
<td>40.7% (24.5–59.3)</td>
<td>80.0% (67.6–88.4)</td>
<td>1.9 (1.0–3.4)</td>
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<td></td>
<td>&lt;59.4% or &lt;34.0 mm</td>
<td>77.3% (56.6–89.9)</td>
<td>46.7% (34.6–59.1)</td>
<td>34.7% (22.9–48.7)</td>
<td>84.8% (69.1–93.3)</td>
<td>1.4 (1.1–2.0)</td>
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Abbreviations: CCI, cervical consistency index; CI, confidence interval; CL, cervical length; LR\(^{–}\), negative likelihood ratio; LR\(^{+}\), positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

\(^{a}\)Values below the cutoff indicate increased risk.

\(^{b}\)Optimal cutoff based on the receiver operating characteristic curve.

Discussion

The main finding of this study is that in a high sPTB risk population assessed during mid-gestation, CCI performs significantly better than sonographic CL to predict sPTB <37\(^{0}\) weeks and is independently associated with sPTB. The combination of CCI with CL does not improve the diagnostic accuracy.

Interestingly, in the high-risk population, the CCI was significantly reduced in the high-risk compared with the low-risk populations. This finding supports the idea that despite use in clinical practice, CL measurement in high-risk singleton pregnancies is not adequate as a stand-alone predictor of sPTB.\(^{10}\) It is important to highlight that when compared with a cohort of singleton low sPTB risk pregnancies published in a previous study, 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.\(^{24}\) This may be due to the fact that up to 32.9% (27/82) of high sPTB risk women in our study received some kind of intervention which could have interfered with the natural course of the condition. To avoid unnecessary interventions, in our center, we treat the patients only when there is an evidence-based indication. However, not to treat high-risk women when it is indicated would not be ethical, and this should be taken into account when evaluating the performance of a predictive tool in a treated population. The main strength is that this is the first study evaluating the predictive

and CCI are also shown in Table 3. The AUC for a model including both CCI and CL (both included to the model) to predict sPTB <37\(^{0}\) weeks was 0.74 (95% CI, 0.63–0.86), which is not significantly different from the AUC of CCI alone (0.73); \(p = 0.57\). The AUC for a model including both CCI and CL to predict sPTB <34\(^{0}\) weeks was 0.68 (95% CI, 0.54–0.82), which is the same as that for CCI alone. The estimated probabilities of sPTB <37\(^{0}\) and <34\(^{0}\) weeks according to the CCI and CL are shown in Figs. 4 and 5.

Reference

Fig. 3 Receiver operating characteristic (ROC) curves for the cervical consistency index (CCI) and cervical length (CL) with regard to predicting spontaneous preterm birth (sPTB) <34 weeks. Abrevations: AUC; Area Under the Curve.
capacity of CCI focused on high sPTB risk pregnancies between 19−0 and 24−6 weeks, at time at which treatment strategies are still useful. 14−17 The main limitation of this study is the number of women included. This can be explained in that about half of women are referred to the PBPC after week 25−0 of pregnancy. Therefore, more efforts should be made to perform a complete risk assessment and refer women with risk factors as early as possible during gestation to maximize the usefulness and efficacy of the therapeutic strategies available. Offline measurements could also be considered a limitation of the study; however, we chose offline analysis to blind CCI measurements to caregivers and the women themselves. As mentioned earlier, we did not exclude women with progesterone treatment or with a cervical cerclage, since treatment is indicated in a considerable number of high-risk patients 25 according to current guidelines 26,27 and the protocol of our institution. Moreover, the main objective of the study was to compare the diagnostic accuracy between CCI and CL in the same high-risk cohort of women regardless of the treatment received. Based on the ROC curve (59.4%), the optimal CCI cutoff in this high-risk population is close to the CCI cutoff of 60% suggested in a previous publication. 28 A CCI of 60%, which corresponded to the 10th centile in a low-risk population, had a sensitivity of 54.4% and a false positive rate of only 7.8%, showing the best performance in a screening scenario. When applied to a high-risk population, in which we aim to optimize

<table>
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<tr>
<th>Cutoff&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>LR&lt;sup&gt;−&lt;/sup&gt; (95% CI)</th>
<th>LR&lt;sup&gt;+&lt;/sup&gt; (95% CI)</th>
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<td>CCI</td>
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<tr>
<td>&lt;45%</td>
<td>21.4% (7.6−47.6)</td>
<td>91.2% (82.1−95.9)</td>
<td>33.3% (12.1−64.6)</td>
<td>84.9% (75.0−91.4)</td>
<td>2.4 (0.7−8.6)</td>
<td>0.8 (0.6−1.1)</td>
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<td>&lt;50%</td>
<td>35.7% (16.3−61.2)</td>
<td>80.9% (67.0−88.0)</td>
<td>27.8% (12.5−50.9)</td>
<td>85.9% (75.4−92.4)</td>
<td>1.9 (0.8−4.4)</td>
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<td>&lt;55%</td>
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<td>66.2% (54.3−76.7)</td>
<td>23.3% (11.8−40.9)</td>
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<td>0.8 (0.4−1.3)</td>
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<td>59.4%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>78.6% (52.4−92.4)</td>
<td>58.8% (47.0−69.2)</td>
<td>28.2% (16.5−43.8)</td>
<td>93.0% (81.4−97.6)</td>
<td>1.9 (1.3−2.8)</td>
<td>0.4 (01−1.0)</td>
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<td>CL</td>
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<td>≤20 mm</td>
<td>14.3% (4.0−39.9)</td>
<td>88.2% (78.5−93.9)</td>
<td>20.0% (5.7−51.0)</td>
<td>83.3% (73.1−90.2)</td>
<td>1.2 (0.3−5.1)</td>
<td>0.9 (0.8−1.2)</td>
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<td>&lt;25 mm</td>
<td>28.6% (11.7−54.6)</td>
<td>79.4% (68.4−87.3)</td>
<td>22.2% (9.0−45.2)</td>
<td>84.4% (73.6−91.3)</td>
<td>1.4 (0.5−3.6)</td>
<td>0.9 (0.6−1.3)</td>
</tr>
<tr>
<td>29.7 mm&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42.9% (21.4−67.4)</td>
<td>69.1% (57.4−78.8)</td>
<td>22.2% (10.6−40.8)</td>
<td>85.5% (73.8−92.4)</td>
<td>1.4 (0.7−2.8)</td>
<td>0.8 (0.5−1.3)</td>
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<td>CCI and CL below cutoff&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40.9% (23.3−61.3)</td>
<td>81.7% (70.1−89.4)</td>
<td>45.0% (25.2−65.4)</td>
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Abbreviations: CCI, cervical consistency index; CI, confidence interval; CL, cervical length; LR −, negative likelihood ratio; LR +, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

<sup>a</sup>Values below the cutoff indicate increased risk.

<sup>b</sup>Optimal cutoff based on the receiver operating characteristic curve.

Fig. 4 Estimated probability of spontaneous preterm birth (sPTB) <37 weeks according to the cervical consistency index (CCI) and cervical length (CL) between 19 and 24 weeks of gestation.

Fig. 5 Estimated probability of spontaneous preterm birth (sPTB) <34 weeks according to the cervical consistency index (CCI) and cervical length (CL) between 19 and 24 weeks of gestation.
the sensitivity, the CCI cutoff of 60% has an improved sensitivity of 72.7% at the expense of increasing the false positive rate to 36.3%, which might be acceptable in a high-risk population already receiving closer follow-up. It was of note that the CL cutoff of 25 mm used in clinical practice had a sensitivity of only 31.8% and a specificity of 81.7%, and the optimal CL cutoff based on the ROC curve also showed poor performance. The technical limitations of the CCI (standardization of the acquisition, horizontal orientation of the cervical canal) are discussed in the previous CCI study and still need to be addressed. However, in a study performed under experimental conditions, when the maximum compressibility of the cervix was achieved, a variation in the force applied did not result in a significant variation in the strain, suggesting reproducibility and robustness among operators in the real clinical setting. Intra- and interobserver agreement and the reliability of the CCI demonstrated to be sufficient for clinical use in a previous study in a low-risk population. Regarding premature cervical remodeling, many efforts have been invested in studying the properties and composition of the cervix. Attempts have been made to evaluate cervical softening with various techniques. The aspiration method aims to assess the stiffness of ectocervical tissue. With this noninvasive tool, the pressure required to displace cervical tissue to a predefined deformation level can be determined. The aspiration technique confirmed that the tissue softens already at the beginning of pregnancy, progresses to a lower consistency in the first two trimesters, and stabilizes at a low level in the third trimester. However, the need for a specific device limits its application in clinical practice. Another method, the shear wave speed, allows objective characterization of stiffness because waves travel more slowly in softer tissue and ultrasound imaging can be used to monitor the propagation of the shear wave and measure its speed. A cross-sectional study of women at 11 to 36 weeks of gestation found a positive correlation between softening and spontaneous preterm delivery although the results were not statistically significant. The results of both techniques confirm that cervical softening starts early in gestation until the second trimester and has a potential association with sPTB. Therefore, CCI aims to easily identify softer cervixes already from weeks 19 to 24 with a technically easy method. Promisingly, other tools aiming to identify premature decidual activation, such as fetal fibronectin alone or in combination with C1 or Cr, are providing encouraging results in high-risk asymptomatic patients. Further studies with a larger number of high sPTB risk women are needed to confirm our results and to externally validate CCI measurement. A larger sample size would also allow stratification by risk factors, minimizing the phenotypic heterogeneity within the sample, and thereby allowing more accurate conclusions about the predictive capacity of the CCI in specific populations. Moreover, the discriminative capacity of the CCI when calculated during the examination should be compared with that of the offline analysis. According to a new paradigm, the three mechanisms which trigger sPTB (premature decidual activation, premature myometrial activation, and premature cervical remodeling) are inextricably intertwined with each other reinforcing the suitability of exploring the combination of cervical assessment with tests assessing other mechanisms. Finally, the limited predictive capacity of both the CL and CCI to evaluate the cervix, particularly in the high-risk population, also supports the need to continue developing other ultrasound tools to improve the identification of women at increased risk of sPTB among those with known risk factors.

Conflict of Interest
The authors declare no conflict of interest.

Presentation
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