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

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Quantitative analysis of cervical texture by ultrasound in mid-pregnancy and association with spontaneous preterm birth

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KEYWORDS: image biomarker; quantitative ultrasound; spontaneous preterm birth; texture analysis; uterine cervix

ABSTRACT

Objective *New tools are required to improve the identification of women who are at increased risk for spontaneous preterm birth (sPTB). Quantitative analysis of tissue texture on ultrasound has been used to extract robust features from the ultrasound image to detect subtle changes in its microstructure. This may be applied to the cervix. The aim of this study was to determine if there is an association between quantitative analysis of cervical texture (CTx) on mid-trimester ultrasound and sPTB < 37 + 0 weeks' gestation.*

Methods *This was a single-center nested case–control study of a prospective cohort of 677 consecutive women with singleton pregnancy assessed between 19 + 0 and 24 + 6 weeks' gestation. Women at increased risk for sPTB were included unless they received treatment to prevent sPTB. Women who delivered < 37 + 0 weeks (sPTB) were considered as cases and were matched in a 1: 10 ratio with randomly selected contemporary controls who delivered at term. For each woman, one ultrasound image of the cervix was obtained for which quality was assessed, cervical length (CL) measured offline and a region of interest in the midportion of the anterior cervical lip delineated for use in local binary patterns analysis of CTx. A learning algorithm was developed to obtain the combination of CTx features best associated with sPTB based on feature transformation and discriminant analysis regression. The ability of the learning algorithm to predict sPTB was evaluated using a leave-one-out cross-validation technique, which produced a CTx-based score for each participant. Receiver–operating characteristics (ROC) curves were produced and sensitivity, specificity, and positive and negative likelihood ratios were calculated for the optimal cut-off based on the ROC curve. The results were compared with those obtained for CL. Investigators studying the images were blinded to pregnancy outcome at all times.*

Results *Images from 310 women (27 cases and 283 controls) were of sufficient quality and included in the study. Median CTx-based score was significantly lower in cases compared with controls (–1.01* vs *–0.07, P ≤ 0.0001). CTx-based score maintained its significant association with sPTB after adjusting for possible confounders (history of sPTB, conization or Müllerian malformation, and CL < 25 mm). CTx-based score was a better predictor of sPTB (AUC, 0.77; 95% CI, 0.66–0.87) than was CL (AUC, 0.60; 95% CI, 0.47–0.72) (P = 0.03). Median CL was similar for cases and controls (37.7* vs *38.6 mm, P = 0.26), although cases were more likely to have CL < 25 mm (18.5%* vs *0.4%, P < 0.001).*

Conclusion *Quantitative analysis of CTx enables the extraction of information relevant to sPTB from ultrasound images to generate a CTx-based score that is associated independently with sPTB. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Spontaneous preterm birth (sPTB) is an important global health issue[1,2] and the identification of women at risk remains a major challenge in obstetrics. Due to the

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huge health, economic and social impact worldwide[3,4], an effective screening method is needed. Cervical assessment is a key factor in risk evaluation, as sPTB is a multifactorial syndrome that is preceded commonly by premature cervical ripening[5,6]. As implementation of cervical-length (CL) measurement as a screening method in the general population is still controversial[7–9], the development of innovative tools to detect premature cervical remodeling is needed in order to improve the identification of women at increased risk of sPTB. Quantitative texture analysis has been used to extract robust features from the ultrasound image of a particular tissue to detect subtle changes in its microstructure[10–12]. The feasibility of analysis of cervical texture (CTx) for quantifying cervical tissue changes throughout pregnancy has been shown previously[13], confirming the underlying hypothesis that cervical remodeling during a normal pregnancy can be detected on CTx analysis.

The aim of this study was to evaluate the association between quantitative analysis of CTx visualized on mid-trimester ultrasound and sPTB $<37+0$ weeks.

METHODS

This was a single-center, nested case–control study of a prospective cohort of 677 consecutive women with singleton pregnancy assessed between $19+0$ and $24+6$ weeks' gestation. Women with a sPTB risk factor (history of sPTB or miscarriage ≥ 16 weeks, and cervical intervention or Müllerian malformation) were included unless they received treatment, such as progesterone, cervical cerclage or cervical pessary, to prevent sPTB. Also excluded were those with preterm birth for fetal or maternal indication, including induction of labor (IOL) for preterm prelabor rupture of membranes (PPROM). Data on maternal characteristics, obstetric history and perinatal outcome were collected prospectively. Gestational age was calculated based on crown–rump length measured on first-trimester ultrasound. The study protocol was approved by the local Ethics Committee of the Hospital Clínic (ID HCB 2014/0089) and Hospital Sant Joan de Déu (ID PIC-147-15), and all pregnant women provided written informed consent.

One image of the uterine cervix was obtained for each woman. Images were acquired by experienced sonographers who were accustomed to performing screening ultrasound in the study center. An image-acquisition guide[13] was followed by the sonographers in order to ensure that the requirements for further analysis of the images were met.

A sagittal view was obtained of the cervix occupying two-thirds of the screen, without exerting any pressure with the transducer, so that the diameters of the anterior and posterior cervical lips were similar (Figure 1). The internal and external os, as well as the cervical canal, were identified and the entire cervical structure visualized, avoiding zooming and using only the depth function. The focus was placed on the middle of the anterior cervical lip. The cervix was angled horizontally on the image. Shadows and saturations were avoided if possible. Any post-processing functions, such as speckle reduction imaging or smoothing, were inactive. No online measurements were made. Gain and harmonics were at the discretion of the physician. Images were acquired with Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) or Voluson 780 Pro, Voluson S6, Voluson E6 or Voluson E8 (GE Medical Systems, Zipf, Austria) ultrasound machines, with a 2–10-MHz vaginal probe. Data were collected digitally in the original Digital Imaging and Communication in Medicine (DICOM) format and stored for offline analysis in a custom-made program with a graphical user interface using MATLAB R2010b (version 7.11.0.584; The Mathworks Inc., Natick, MA, USA).

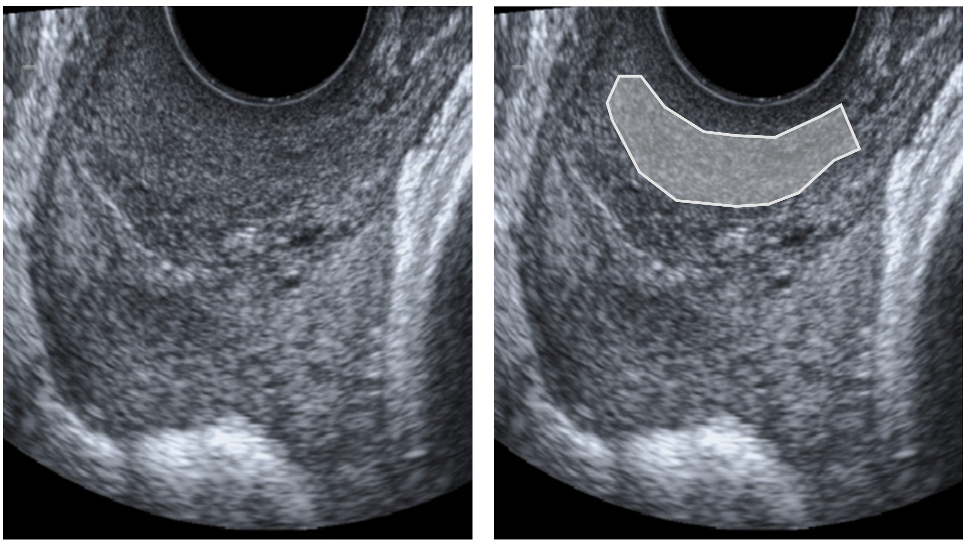

Figure 1 Sagittal view of cervix with region of interest (largest homogeneous region in middle part of anterior cervical lip) for cervical texture analysis delineated.

After reviewing perinatal outcomes, women who delivered after the spontaneous onset of labor at $< 37 + 0$ weeks (sPTB), regardless of membranes rupture, were considered as cases and were matched in a 1:10 ratio with contemporary controls who delivered at term. Controls were selected by random uniform sampling using MATLAB R2010b.

All selected images ($n = 352$) underwent a quality control process (performed by A.P.) before delineation, according to the acquisition criteria to ensure that they were suitable for CTx analysis. To perform quantitative analysis of CTx, a region of interest (ROI) from the ultrasound image was delineated offline manually. The selected ROI was defined as the largest homogeneous region in the middle part of the anterior cervical lip avoiding the cervical canal, the glandular area, and the internal and external cervical or a (Figure 1). The minimum ROI size needed to obtain features using the local binary patterns (LBP) method was 400 pixels. Afterwards, CL was measured offline as the outer to the inner cervical os following established guidelines[14]. CL measurement and ROI delineation were performed by three independent operators (N.B., C.M. and C.J.) who were blinded to pregnancy outcome.

Learning algorithm based on cervical texture

Ultrasound image feature extraction was based on LBP, namely a multiresolution grayscale and rotation-invariant approach. The LBP texture-based method has been used widely for texture classification in the computer vision field[15,16]. The LBP method computes the distribution of binary patterns in the circular neighborhood of each pixel, which is characterized by the radius (r) and number of equally spaced neighboring pixels (p). The purpose of applying the LBP method is to characterize microstructural changes of the uterine cervix by characterizing speckle patterns. In our study, uniform patterns were defined by $p = 16$ and $r = 1$, resulting in 18 specific texture features from each ultrasound scan within the ROI, related to 18 different uniform patterns. In order to obtain the combination of these textural features associated best with sPTB, we computed a learning algorithm based on two modules, including feature transformation and then discriminant analysis-regression. Specifically, a principal component analysis was applied to reduce dimensionality of features into a limited number of linear feature combinations, thus obtaining the most relevant features that explained 95% of the variance within the observed sample. The discriminant analysis regression of the transformed components was estimated using statistical significance of a multivariate analysis of variance (MANOVA) test, thus providing the most discriminant axis (MDA), defined as the most discriminant combination of the transformed features, which maximized distance between the two groups.

Statistical analysis

Data distribution was assessed using the Shapiro–Wilk test of normality. Results are described as absolute and relative frequencies for qualitative variables and as median and interquartile range for quantitative variables. Continuous data were compared using the Mann–Whitney *U*-test and categorical variables using the chi-square or Fisher's exact test. The ability of the CTx algorithm to predict sPTB blindly was evaluated using a leave-one-out cross-validation (LOOCV) technique, and thus a CTx-based score from each woman that combined the transformed CTx features was obtained. Box-and-whiskers plots were used to illustrate the differences between cases and controls for CTx-based score and CL. Stepwise multivariate logistic regression analysis was performed to obtain crude (OR) and adjusted (aOR) odds ratios. A significance level of 0.1 was defined to exclude variables from the saturated model. If the potential confounder changed the estimate of risk by 10% or more, it was considered importantly different and was left in the model. CTx-based score aOR from the model including all candidate confounders is also presented. Classification performances of the CTx-based score and CL were computed by inspection of different thresholds within the sample to estimate ROC curves. The resulting areas under the ROC curves (AUCs) were compared using the DeLong method. Sensitivity, specificity and positive (LR+) and negative (LR−) likelihood ratios and their 95% CIs, with regard to predicting sPTB $< 37 + 0$ gestational weeks, were calculated for the optimal cut-offs based on the ROC curve for CTx-based score and CL, and for CL < 25 mm. The optimal cut-off is the one corresponding to the point on the ROC curve situated farthest from the reference line. A two-sided type-I error rate of 5% was applied throughout statistical testing. All analyses were performed using STATA/IC 13.0 (StataCorp, College Station, TX, USA).

RESULTS

From March 2015 to March 2016, 677 women were included prospectively in the cohort. After reviewing perinatal outcome, 28 women were excluded (15 iatrogenic PTBs due to fetal or maternal indication, and 13 IOL owing to PPROM). Among the 649 patients who fulfilled the inclusion criteria, there were 32 (4.9%) sPTBs $< 37 + 0$ weeks. These were matched with 320 randomly selected term births. Based on image quality, five cases and 37 controls were excluded. This left a total of 310 women (27 cases and 283 controls) in the study (Figure 2). Clinical characteristics and maternal and perinatal outcomes are shown in Table 1. There were no differences between cases and controls in baseline demographic characteristics, except for the prevalence of sPTB risk factors (history of sPTB, conization or Müllerian malformation). Median CL was comparable between the groups, but cases were more likely to have CL < 25 mm than controls (18.5% (5/27) *vs* 0.4% (1/283), $P < 0.001$).

Regarding CTx analysis, three textural features that explained 95% of the variance within the observed sample were selected by principal component analysis. Median CTx-based score was significantly lower in cases.

Box-and-whiskers plots of CTx-based score and CL in cases and controls are provided in Figure 3.

CL, CTx-based score and occurrence of sPTB in the six women with CL < 25 mm are shown in Table 2. CTx-based score in women with CL < 25 mm was significantly lower compared with women with CL ≥ 25 mm (−1.02 *vs* −0.01; $P = 0.01$). CTx-based score was associated independently with sPTB after adjusting for confounders (history of sPTB, conization or Müllerian malformation, and CL < 25 mm): OR 0.31 (95% CI, 0.17–0.56; $P < 0.001$) *vs* aOR 0.37 (95% CI, 0.19–0.64; $P = 0.001$). CL < 25 mm was the only potential confounder that changed the estimate of risk by 10% or more.

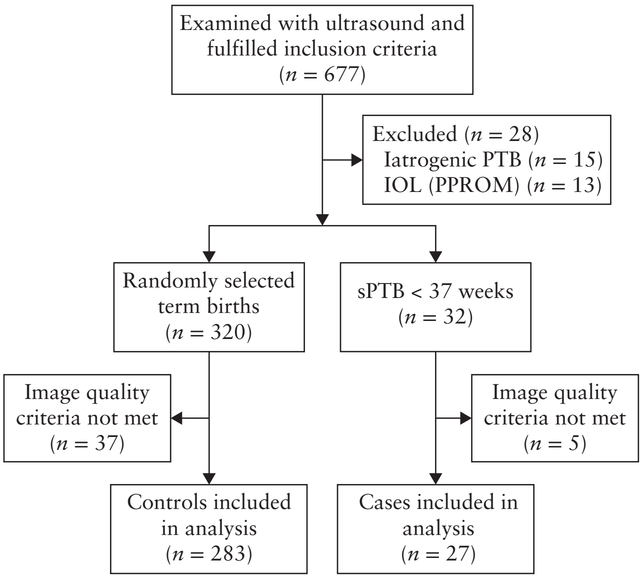

Figure 2 Flowchart of recruited women who had cervical texture assessed on ultrasound at 19 + 0 to 24 + 6 weeks' gestation. IOL, induction of labor; PPROM, preterm prelabor rupture of membranes; PTB, preterm birth; sPTB, spontaneous preterm birth.

The AUC for CTx-based score to predict sPTB < 37 + 0 weeks' gestation (0.77; 95% CI, 0.66–0.87) was higher than for CL (0.60; 95% CI, 0.47–0.72); $P = 0.02$ (Figure 4). The optimal cut-off point for the CTx-based score based on the ROC curve was −0.68, with sensitivity of 70.4%, specificity 77.4%, LR+ 3.1 and

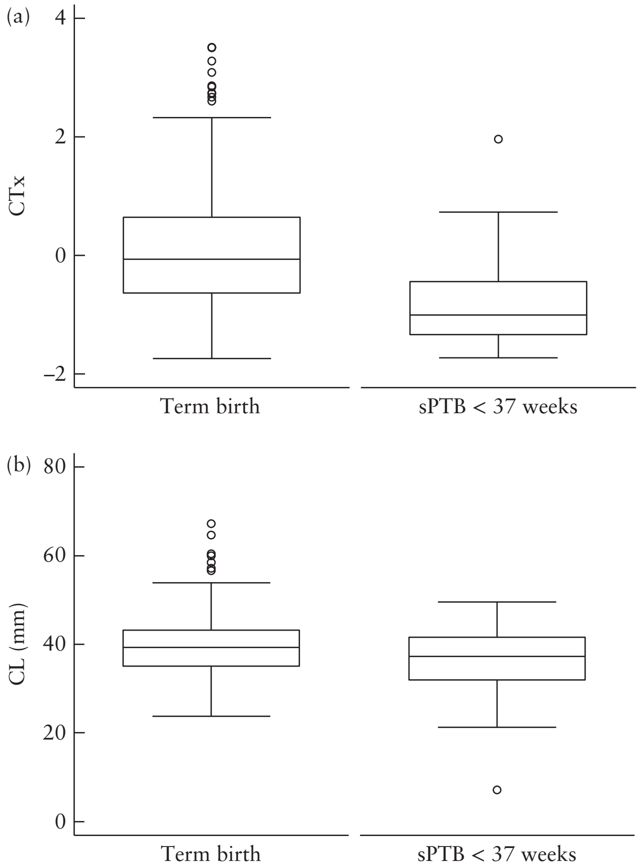

Figure 3 Box-and-whiskers plots of cervical texture (CTx)-based score (a) and cervical length (CL) (b) in 27 women who delivered spontaneously < 37 weeks' gestation (sPTB) and in 283 women selected randomly who delivered at term.

Table 1 Maternal and pregnancy characteristics of women assessed on ultrasound between 19 + 0 and 24 + 6 weeks' gestation for cervical length (CL) and cervical texture (CTx) who had spontaneous preterm birth (sPTB) < 37 weeks or term birth

Characteristic	*Total cohort (n = 310)*	*sPTB (n = 27)*	*Term birth (n = 283)*	P
Maternal age (years)	33 (28–37)	34 (29–38)	33 (28–37)	0.44
Caucasian	223 (71.9)	20 (74.1)	203 (71.3)	0.80
Smoker	46 (14.8)	3 (11.1)	43 (15.2)	0.57
BMI (kg/m^2)	23.0 (21.0–26.1)	25.2 (20.3–26.6)	23.0 (21.0–26.1)	0.69
Nulliparous	159 (51.3)	10 (37.0)	149 (52.7)	0.08
Previous sPTB	35 (11.3)	6 (22.2)	29 (10.2)	0.03
Conization/Müllerian malformation	15 (4.8)	4 (14.8)	11 (3.9)	0.01
GA at scan (weeks)	21 (20.3–22.3)	21.2 (20.3–23.1)	20.6 (20.3–22.2)	0.53
CL at scan (mm)	38.6 (34.3–42.6)	37.7 (32.2–41.5)	38.6 (34.5–42.8)	0.26
CL < 25 mm	6 (1.9)	5 (18.5)	1 (0.4)	< 0.001
CTx-based score	−0.13 (−0.73–0.59)	−1.01 (−1.34 to 0.45)	−0.07 (−0.64 to 0.64)	< 0.001
GA at delivery (weeks)	39.4 (38.4–40.3)	34.6 (32.5–36)	39.6 (38.6–40.3)	NA
Birth weight (g)	3275 (2945–3530)	2300 (1600–2550)	3340 (2990–3560)	NA

Data given as median (interquartile range) or *n* (%). BMI, body mass index; CL, cervical length; CTx, cervical texture; GA, gestational age; NA, not applicable.

LR− 0.4 (Table 3). Conversely, for CL the cut-off was 35.5 mm with sensitivity of 44.4%, specificity 68.2%, LR+ 1.4 and LR− 0.8. Using CL < 25 mm as the cut-off, sensitivity was 14.8%, specificity 98.6%, LR+ 10.5 and LR− 0.9 (Table 3).

DISCUSSION

This study provides evidence that findings on quantitative analysis of mid-trimester CTx are associated with sPTB < 37 + 0 weeks' gestation. The CTx-based score was significantly different between women delivering preterm and those delivering at term ($P < 0.001$), independent of confounders. Although only one woman with short CL delivered at term, her CTx-based score was higher compared with those of women with a short cervix who delivered preterm (−0.07 *vs* − 1.06), supporting the finding that CTx is associated independently with sPTB, regardless of CL measurement. CTx-based score also showed a significantly larger AUC than did CL (0.77 *vs* 0.60, $P = 0.03$).

Table 2 Cervical length (CL), cervical texture (CTx)-based score and occurrence of spontaneous preterm birth (sPTB) < 37 weeks' gestation in six women with CL < 25 mm at 19 + 0 to 24 + 6 weeks' gestation

Case	*CL (mm)*	*CTx-based score*	*sPTB*
1	23.5	−1.06	Yes
2	23.2	−0.85	Yes
3	23.1	−1.34	Yes
4	21.3	−1.46	Yes
5	20.2	−0.07	No
6	7.1	−0.99	Yes

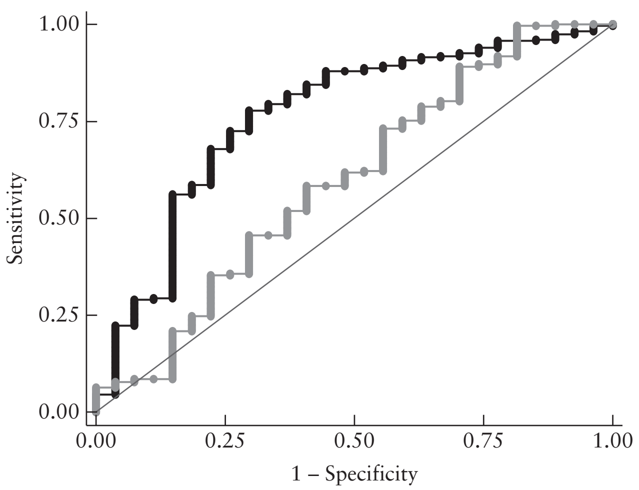

Figure 4 Receiver–operating characteristics curves of CTx-based score (—●—) and cervical length (—●—) for prediction of sPTB < 37 + 0 weeks' gestation in 27 women.

The main strength of this study is that it addresses the association of a technologically innovative ultrasound tool (CTx) with a clinical event (sPTB) in a large cohort of mid-trimester women in the general population. This finding adds to that of a previous longitudinal study that demonstrated the feasibility of CTx for the quantification of cervical changes throughout normal pregnancy in a sample of 700 images obtained between 20 + 0 and 41 + 6 weeks' gestation[13]. Therefore, this method could be applied during the second and third trimesters of pregnancy to evaluate cervical remodeling and identify changes undetectable when using CL or on clinical examination. An additional strength is that the algorithm was tested using a model validation technique (LOOCV) to assess how the results could be generalized to an independent dataset and limit overfitting issues, thereby maximizing robustness.

We acknowledge a number of limitations. Firstly, offline CL measurements were used. In clinical practice, CL is measured online during the examination. We measured it offline intentionally because CL is, at present, not measured routinely in the general population in our center. The offline measurement was made simultaneously with ROI delineation for CTx analysis to ensure that all investigators and patients remained blinded to the results.

Another limitation is the low number of events of sPTB ($n = 27$), allowing us to show only an association between the CTx-based score and sPTB. This low rate (4.9%) of sPTB is akin to that found in other European series[17,18]. The prevalence of history of sPTB (22.2% *vs* 10.2%) and cervical conization or the presence of a Müllerian anomaly (14.8% *vs* 3.9%) was significantly higher in cases than in controls. However, on removal of these candidate confounders from the model, the CTx-based score maintained its statistically significant association with sPTB.

A further limitation is that the robustness, in terms of using different ultrasound equipment, was not tested quantitatively for the cervix images. However, the robustness of the feature extraction method used and the statistical learning procedure has been shown in previous studies[10,11,19]. All ultrasound equipment used in this study has been tested for use in texture analysis and is currently used in clinical practice to assess fetal lung maturity.

Table 3 Discriminative performance of cervical texture (CTx)-based score and cervical length (CL) assessed on ultrasound between 19 + 0 and 24 + 6 weeks' gestation for prediction of spontaneous preterm birth < 37 + 0 weeks' gestation

Predictor	*Cut-off**	*Sensitivity (n (%))*	*Specificity (n (%))*	*LR+ (95% CI)*	*LR− (95% CI)*
CTx-based score	−0.68†	19/27 (70.4)	219/283 (77.4)	3.1 (2.2–4.3)	0.4 (0.2–0.7)
CL	35.5 mm†	12/27 (44.4)	193/283 (68.2)	1.4 (0.9–2.2)	0.8 (0.6–1.2)
CL	< 25 mm	4/27 (14.8)	279/283 (98.6)	10.5 (2.8–39.6)	0.9 (0.7–1.0)

*Values below cut-off indicate increased risk. †Optimal cut-off based on receiver–operating characteristics curve. LR+, positive likelihood ratio; LR−, negative likelihood ratio.

It is worth mentioning that the features selected using the LBP method correspond to specific changes in speckle patterns that might be related to microstructural changes when the cervix is remodeled prematurely. In our work, a homogeneous region of the stroma was evaluated, assuming that acoustic properties of this region might change due to premature remodeling of the cervix. However, to provide insight or interpretation on the structural or histological changes beyond the changes observed in LBP is not possible at this point of the research.

Currently, there is evidence supporting that a mid-trimester short cervix (CL < 25 mm) increases the risk for sPTB[20]. Despite this, universal CL screening in the general population remains controversial. This is in part due to the low prevalence of cervical shortening and the current controversy on the consequences of this observation in terms of treatment[21–24]. However, its limited sensitivity is a major obstacle[7,8,17,18,25]. It is for this reason that there is a lot of ongoing research into evaluation of the cervix using other modalities, such as its distensibility and tissue stiffness[26–31], and composition and optical characteristics[32–39]. These tools may contribute to an improved identification of women at risk for sPTB. To date, cervical elastography, which measures the percentage of tissue deformation when oscillatory compression is applied, has been the most studied method[40–42]. Low strain values in the internal cervical os are associated with a significantly lower risk of sPTB[42]. However, elastography has some important technical limitations[41,43]. The principal one is the inability to standardize the force applied for inducing tissue deformation[44], whereas CTx analysis relies on images 'at rest' in a way that is similar to that for CL measurement. Ultrasonic attenuation has also been investigated for the identification of women at risk of sPTB, and results have suggested that low attenuation may be an additional early marker of sPTB[45]. To sum up, most of the developing ultrasound tools are based on the same hypothesis, i.e. that changes in cervical microstructure, and therefore in cervical properties, can be detected by different methods (e.g. acoustic attenuation[46], shear wave elasticity[39] or texture analysis[13]).

In conclusion, sPTB is associated with mid-trimester CTx changes. We propose that larger validation studies with a new set of images are required to create a predictive model.

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Disclosure

E.G., J.D. and M.P. have served as scientific advisers to Transmural Biotech.

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