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Original Contribution

Predicting Spontaneous Pre-term Birth Risk Is Improved When Quantitative Ultrasound Data Are Included With Historical Clinical Data

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Objective: Predicting women at risk for spontaneous pre-term birth (sPTB) has been medically challenging because of the lack of signs and symptoms of pre-term birth until interventions are too late. We hypothesized that prediction of the sPTB risk level is enhanced when using both historical clinical (HC) data and quantitative ultrasound (QUS) data compared with using only HC data. HC data defined herein included birth history prior to that of the current pregnancy as well as, from the current pregnancy, a clinical cervical length assessment and physical examination data.
Methods: The study population included 248 full-term births (FTBs) and 26 sPTBs. QUS scans (Siemens S2000 and MC9-4) were performed by registered diagnostic medical sonographers using a standard cervical length approach. Two cervical QUS scans were conducted at 20 ± 2 and 24 ± 2 wk of gestation. Multiple QUS features were evaluated from calibrated raw radiofrequency backscattered ultrasonic signals. Two statistical models designed to determine sPTB risk were compared: (i) HC data alone and (ii) combined HC and QUS data. Model comparisons included a likelihood ratio test, cross-validated receiver operating characteristic area under the curve, sensitivity and specificity. The study's birth outcomes were only FTBs and sPTBs; medically induced pre-term births were not included.
Discussion: Combined HC and QUS data identified women at risk of sPTB with better AUC (0.68, 95% confidence interval [CI]: 0.57–0.78) compared with HC data alone (0.53, 95% CI: 0.40–0.66) and HC data + cervical length at 18–20 wk of gestation (average AUC = 0.51, 95% CI: 0.38–0.64). A likelihood ratio test for significance of QUS features in the classification model was highly statistically significant ($p < 0.01$).
Conclusion: Even with only 26 sPTBs among 274 births, value was added in predicting sPTB when QUS data were included with HC data.

Introduction

In 2021, 383,082 (10.49%) of all births in the United States were pre-term, an increase of 4% from 2020 [1]. Pre-term birth (PTB) is defined as birth before 37 completed wk of gestation and refers to any PTB regardless of the reason [1]. Predicting women at risk for spontaneous pre-term birth (sPTB) has been medically challenging because of the lack of signs and symptoms of pre-term labor until intervention, which is too late, and the lack of sufficiently sensitive screening tools to signal sPTB risk.

Herein, a preliminary analysis was conducted of the first 274 women (of a planned 500+ women) who delivered before the 11-mo COVID-19 recruitment shutdown. The study's hypothesis in this study was as follows: predicting the sPTB risk level is enhanced when using both historical clinical (HC) data and quantitative ultrasound (QUS) data compared with using only HC data. HC data defined herein included birth history prior to that of the current pregnancy, as well as, from the current pregnancy, a clinical cervical length assessment and physical examination data. The study's employed methodology was advanced statistical modeling.

The idea underlying the hypothesis was that the cervical microstructure remodels long before women go into labor or cervical length shortening [2–5], leading to the consideration that QUS data could detect early cervical microstructure changes. QUS is a method that uses quantitative ultrasound parameters that reflect tissue microstructure. Because cervical biology and structure change dynamically throughout gestation, QUS has the potential to enable clinicians to make tissue-based decisions about PTB risk in pregnancy rather than waiting for signs and symptoms.

Our group [3] has been testing and refining non-invasive QUS methods that provide information on tissue-based properties of the cervix.

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These include early work related to cervical collagen content and its disorganization and water content of the pregnant rat cervix to gestational age and remodeling [5–7]. Later studies in human pregnancy revealed that QUS's attenuation coefficient (AC) is related to cervical remodeling and sPTB prediction [3,8], and the AC was significantly lower in women who delivered pre-term than those who delivered full term [8]. The objective of this research was to determine whether predicting sPTB risk level is enhanced by using both HC and QUS data compared with using only HC data.

Methods

Study design

Pregnant women were consecutively recruited between April 2018 and March 2020 during their prenatal visits at 18–20 wk of gestation. Because of COVID-19 restrictions, no women were recruited between mid-March 2020 and February 2021. Participation in the study did not change any of the care prescribed by the participants' physician or nurse-midwife. Prenatal care included a routine clinical (non-research) ultrasound cervical length scan by clinic sonographers. Written informed consent approved by the University of Illinois Chicago (UIC) Human Subjects Review Board was obtained prior to enrollment. Women were eligible for the study if they had a singleton pregnancy and could read and speak English. Women were excluded if they had a chronic medical condition (diabetes, hypertension, asthma, autoimmune disorder), cerclage, major fetal anomaly or multiple gestations at the time of consent. The study's birth outcomes were only full-term births (FTBs) and spontaneous pre-term births (sPTBs). Medically induced pre-term births were not included in this analysis. A breakdown of the 274 study population characteristics is outlined in Tables 1 and 2.

The research protocol called for two vaginal quantitative ultrasound (QUS) scans of the cervix at 20 ± 2 and 24 ± 2 wk of gestation for each participant. We chose those time points to determine whether there was a specific time that QUS was predictive of sPTB. Also, in most practices, routine prenatal care includes a fetal anatomy and cervical scan at 18–20 wk of gestation. QUS could be an added measurement to the routine anatomy scan without increasing scanning time. At each research visit, denoted V1 and V2 (the non-research routine clinical visit is denoted V0), 10 cervical and 1 reference phantom QUS acquisitions were performed. Of the 329 participants recruited, this preliminary report includes the 274 participants that completed the study. Reasons for not including 55 participants were (i) missing one of the two QUS visits, (ii) irrecoverable errors from the QUS data or (iii) medical PTB. Thus, the study population included 248 FTBs and 26 sPTBs for which the last deliveries occurred the last week of July 2020.

To predict the sPTB risk when using both HC and QUS (HC + QUS) data compared with using only HC data, advanced statistical modeling techniques were employed. Additionally, the study hypothesis was further explored by stratifying HC data into two groups: (i) those participants with PTB history and (ii) those without PTB history. Area under the receiver operating characteristic (ROC) curve (AUC) and confidence intervals were compared between HC + QUS and HC for each of the two groupings.

QUS data acquisition

Quantitative ultrasound cervical examinations were prospectively performed using the Siemens S2000 (Siemens Healthineers, Munich, Germany) with one of four Siemens MC9-4 transvaginal ultrasonic transducers (frequency range: 3.7–6.8 MHz) by registered diagnostic medical sonographers trained in the research protocol. Cervical length and QUS data were collected and saved at the same time a cervical length scan was conducted. Thus, no extra scanning time was needed to obtain QUS data. QUS cervical scans were performed using a standard cervical length approach as set forth by Iams et al. [9]. During each scan session, 10 QUS data acquisitions in the same cervical location were acquired along with one QUS reference phantom scan. During the first QUS image data acquisition for each participant, scanner settings were adjusted to optimize the cervical B-mode image (Fig. 1); all of the S2000 settings remained unchanged for the subsequent QUS image data acquisitions of that participant session [10]. Each of the 10 acquisitions consisted of selecting a single operator button that recorded a B-mode (jpeg) image and the raw radiofrequency (RF) ultrasonic data. Acquisitions were separated by about 15–20 s. Only the first QUS acquisition (of the 10) was used herein for QUS analysis to match a normal clinical exam situation; 10 acquisitions were acquired for subsequent analyses, such as detailed reproducibility and reliability evaluations.

After completion of the cervical QUS acquisitions, a specially designed calibrated reference phantom (CIRS, Inc., Norfolk, VA, USA) with known attenuation coefficient (AC) and backscatter coefficient (BSC) was scanned without changing the system settings. Twice annually, the reference phantoms underwent ultrasonic characterization at the Bioacoustics Research Laboratory at the University of Illinois Urbana-Champaign to ascertain consistent ultrasonic properties. The purpose of the reference phantom QUS acquisition was to calibrate the S2000's RF values with known and validated AC and BSC values for off-line QUS analyses. The MC9-4 vaginal probe transducer active element lens surface has a 1.1-cm radius of curvature, and the surface of the reference phantom has a specially designed slot approximately 1.5 cm in inside diameter and 1.1 cm deep to fit properly the MC9-4 transducer (Fig. 2). The reference phantom slot allowed for acquisition of the B-mode images (as well as the raw RF data) over much of the 176° array

Table 1
Characteristics of study participants

Characteristic	FTB cohort (n = 248)	sPTB cohort (n = 26)	*p* Value
Maternal age* (y)	28.1 ± 6.3 (15–45)	28.5 ± 6.1 (19–41)	0.75
Maternal age* count ≤ 24 y	85	8	—
Maternal age* count 25–39 y	149	16	—
Maternal age* count ≥ 40 y	14	2	—
Maternal weight* (lb)	169 ± 44 (99–324)	182 ± 45 (88–271)	0.16
Maternal body mass index* (kg/m^2)	29.0 ± 7.2 (17.0–55.5)	30.5 ± 7.1 (14.7–43.8)	0.33
GA* (wk)	19.9 ± 1.5 (16.0–24.7)	19.1 ± 1.4 (16.3–21.0)	0.0088
GA at V1 (wk)	20.3 ± 1.2 (17.7–22.7)	19.9 ± 1.2 (17.7–21.9)	0.14
GA at V2 (wk)	24.9 ± 1.8 (21.7–33.9)	24.1 ± 2.0 (21.0–28.9)	0.038
GA at delivery (wk)	39.2 ± 1.1 (37.0–41.7)	35.1 ± 2.0 (27.7–36.9)	<0.00001
CL* (mm)	36.5 ± 6.0 (20.0–56.7)	36.6 ± 7.9 (19.2–55.0)	0.89
CL* count <25 mm	5	2	—
CL* count ≥25 mm	243	24	—
CL at V1 (mm)	36.1 ± 6.0 (20.0–59.0)	34.4 ± 5.9 (16.3–45.9)	0.17
CL at V2 (mm)	35.3 ± 6.2 (14.7–50.6)	33.5 ± 8.3 (10.6–49.8)	0.19
Infant birth weight (g)	3250 ± 424 (2140 –4430)	2362 ± 387 (1021 –2844)	<0.00001
sPTB (GA in wk) count			
<37		26	—
<36		15	—
<35		7	—
<33		2	—
<31		2	—
<29		1	—
<27		0	—

Quantitative data are listed as mean ± standard deviation (range). In parentheses the corresponding variable's range (minimum value to maximum value) is reported. Count data are listed as indicated counts. *p* Values are derived from two-tailed (0.05 significance level) *t* test.
CL, cervical length; FTB, full-term birth; GA, gestational age; sPTB, spontaneous pre-term birth; QUS, quantitative ultrasound.
* denotes first clinical visit (at V0) at consent. V1 and V2 denote the two QUS acquisition times.

Table 2
Characteristics of study participants[a]

Characteristic	FTB cohort (n = 248)	sPTB cohort (n = 26)
Prior PTB count + prior FTB count		
Nulliparous 0	140	11
Multiparous 1	56	10
Multiparous 2	30	3
Multiparous 3	12	0
Multiparous 4	6	1
Multiparous 5	0	1
Multiparous 6	2	0
Multiparous 7	1	0
Multiparous 10	1	0
Prior pregnancy outcome		
Abortion	34	4
Full-term birth	72	4
Induced pre-term birth	7	1
Miscarriage	36	5
No prior pregnancy	70	5
Spontaneous pre-term birth	28	7
Stillbirth	1	0
Self-identified race		
Asian	5	0
Hispanic	68	8
Native American/Alaskan Native	2	0
Native Hawaiian/other Pacific Islander	1	0
Non-Hispanic Black/African-American	111	15
Non-Hispanic White	51	2
More than one race	7	1
Other/declined to answer	3	0
Birth control with current pregnancy		
No	223	24
Yes	25	2
Progesterone		
No	201	12
Yes	47	14
17-Hydroxyprogesterone	42	12
Vaginal	5	2
Self-identified drinker of any alcohol		
No	245	25
Yes	3	1
Self-identified smoker		
No	239	24
Yes	9	2

FTB, full-term birth; sPTB, spontaneous pre-term birth.
[a] All data are listed as indicated counts.

angle. Before participant recruitment was initiated, a comprehensive QUS repeatability and reproducibility study was conducted among three sonographers using five calibrated phantoms, four MC9-4 transducers and three probe covers (latex cover, non-latex cover and no cover) [10].

Historical clinical features considered

Literature-based historical clinical (HC) data were considered for the prediction HC model. A short cervix (<25 mm) and/or a history of a previous sPTB have been identified as risk factors for sPTB making women eligible for progesterone therapy and/or cerclage: 17-hydroxyprogesterone caproate injection for persons with a history of sPTB or vaginal progesterone suppositories for a short cervix [11,12]. Young women (aged 20–24 y) and older women (>40 y old) are at higher risk of sPTB than women in the age group 25–39 y (odds ratio [OR] = 1.09, 95% CI: 1.02–1.18, and OR = 1.20, 95% CI: 1.06–1.36, respectively) [13]. Women with low body mass index (BMI; <18.5 kg/m^2) have a higher risk of sPTB (OR = 1.26, 95% CI: 0.93–1.7) compared with women with a higher BMI (≥25–29.9 kg/m^2), while women with obesity (BMI ≥30 kg/m^2) have a protective factor against pre-term birth (OR = 0.54, 95% CI: 0.40–0.72) [14]. Nulliparous women and those in their fifth pregnancy are at increased risk for sPTB (OR = 1.95, 95% CI: 1.89–2.00, and OR = 1.26, 95% CI: 1.13–1.41, respectively). Women who have had a FTB have a low risk of having an sPTB [15]. Lastly, the number of prior PTBs (prior PTB count) is a strong risk factor for having another sPTB. Having had a prior PTB increases the risk of having another PTB by 15.4%–85.5% [16] (OR = 5.24, 95% CI: 5.01–5.49) [17]. Progesterone therapy, smoking and alcohol were not included in the HC features (Table 2) because their use by the study participants was low, at 22%, 4% and 2%, respectively.

Therefore, the HC data available to the clinician up to and including the non-research first wellness obstetrical exam consisted of five features: (i) cervical length (CL) at 18–20 wk of gestation (this visit time is denoted V0, that is, CLV0); (ii) maternal age at V0; (iii) BMI at V0; (iv) prior birth count, the sum of the numbers of prior FTBs and prior PTBs; and (v) prior PTB count, the number of prior PTBs (Table 2).

QUS features considered

Seven of the eight individual QUS features, namely, AC, BSC, Lizzi–Feleppa (LF) slope, intercept, midband fit and envelope statistics parameters k and μ, were computed from the acquired and calibrated raw RF ultrasonic data by using previously described procedures [18]. The eighth individual QUS feature was shear wave speed (SWS), which the S2000 provided directly. Briefly, the AC is an objective measure of the spatial rate of ultrasonic energy loss in tissue. The BSC is an objective measure of the fraction of ultrasonic energy returned from tissue; logarithmic transformed BSC, denoted BSCdB, is defined herein as 10 log (BSC). Both AC and BSC are intrinsic chemical and structural properties of tissue that are not dependent on either the ultrasonic system or the operator [19,20]. LF slope (denoted slope), intercept (denoted int) and midband fit (denoted mid) are computed through linear regression of BSCdB versus frequency [19,20]. LF slope, int and mid are the linear regression slope, intercept and regression values at the center frequency, respectively. LF mid is directly related to BSCdB; LF slope is related to the size of the tissue's ultrasonic scatterers, and LF int is a linear combination of LF slope and LF mid (*i.e.,* LF int = LF mid − LF slope × center frequency), providing an exaggerated measure of the LF slope (scatterer size) because the LF int is well outside of the bandwidth of the BSCdB–frequency linear regression line [21]. QUS features k and μ are estimated by fitting a homodyned K distribution to the distribution of envelope amplitude of the RF data; k is an estimate of the ratio of the coherent to diffuse signal and represents the level of the tissue's structure or periodicity in scatterer locations, and μ is an estimate of the effective number of scatterers per resolution cell [22]. SWS represents a tissue elastic property estimate. There are 16 individual QUS features (8 from V1 and 8 from V2) (Table 3).

Derived QUS features (rate of change, absolute rate change) were selected from each of the eight individual QUS features to leverage the two visits (V1 and V2) that occurred chronologically and were identified by weeks of gestation age (denoted GAV1 and GAV2). The two time-based derived features provided the capability to compare individual QUS features relative to the acquired time difference between V1 and V2 with time in weeks represented by gestational age (GA), expressed in weeks/(40 weeks) = fraction of full term. The two time-based QUS features of "rate of change QUS data at V1 and V2" and "absolute rate change QUS data at V1 and V2" are, respectively, for example:

Rate of change "QUSrate": krate = (kV1 − kV2)/|GAV1 − GAV2|
Absolute rate "QUSabsrate": ACabsrate = |ACV1 − ACV2|/|GAV1 − GAV2|

Two more derived QUS features were time-normalized individual features selected with respect to time at either V1 or V2, namely, GAV1 or GAV2. The following two normalized features of "product of QUS data with GA" are, respectively, for example:

Product of intV1 and GAV1 = intV1*GAV1

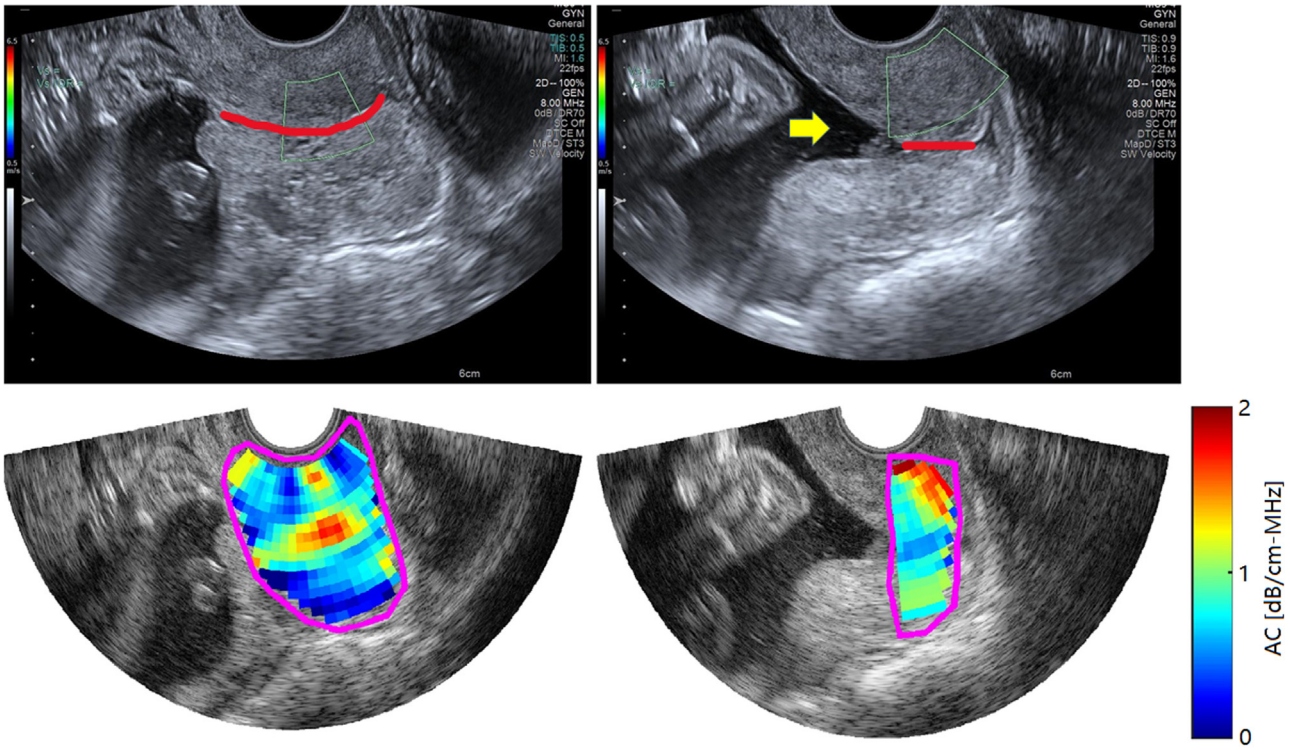

Figure 1. Cervical quantitative ultrasound (QUS) scan for a participant at V1 at 19 5/7 wk (upper left image) and 22 wk (upper right image) of gestational age. Cervical length was 30.2 mm at V1 and 10.6 mm at V2. The *red line* indicates the cervical canal where cervical length is measured. The *yellow arrow* indicates the opening of the internal os of the cervix that is called funneling. The cervix shortens from the internal os to the external os. The *green box* identifies the region of the cervix where shear wave speed was estimated. The *pink line* traces the field of interest (FOI) of the cervix that identifies the region of the cervix that was processed for QUS for V1 (lower left) and V2 lower right images, which also illustrate voxels of attenuation coefficient (AC). The AC was calculated for the cervix at V1 (0.80 dB/cm-MHz) and V2 (0.98 dB/cm-MHz). VO denotes first clinical visit at consent. V1 and V2 denote the two QUS acquisition times.

Product of SWSV2 and GAV2 = SWSV2*GAV2

The unit for "QUSrate" and "QUSabsrate" is QUS unit/GA in weeks. The unit for "product of QUS feature and GAV1 or GAV2" is QUS unit * GA in weeks.

In total, there were 16 individual QUS features and 32 derived QUS features for a total of 48 candidate QUS features (Table 3).

Feature screening

The primary response outcome was the binary indicator for sPTB versus FTB. With the sPTB indicator used as the response variable, the scaled HC + QUS features were evaluated using nested fivefold cross-validation [23] of L1 penalized logistic regression using the SciKit-Learn Python package Logistic RegressionCV. L1 penalized logistic variables by imposing an overall bound on the size of regression coefficients determined by a hyperparameter [24,25]. The L1 penalty hyperparameter was chosen to maximize the cross-validation estimate of the AUC. The AUC optimization was nested within another 5-fold cross-validation loop to reduce bias [26]. To reduce variation in the results, the nested cross-validated L1 penalized logistic regression was repeated 1000 times using (i) HC features only and (ii) both HC and QUS (HC + QUS) features. On the basis of these results, feature selection frequencies were computed for the two model classes. Features with the highest two selection frequencies above a 20% threshold for each model class were identified for potential inclusion in the final predictive models using HC features only and using HC + QUS features.

Final model development

Features selected as potential predictors in the nested cross-validation process were considered for ordinary logistic regression analysis of sPTB risk. The HC model considered only clinical history features identified as potential predictors. The HC + QUS model considered both the HC features and the additional QUS features identified by nested cross-validation of the L1 penalized logistic regression. Statistical significance of the difference between the models with and without QUS features was assessed using the likelihood ratio test (LRT).

For both Model HC and Model HC + QUS, descriptive metrics were computed including the ROC curve from 10-fold cross-validation, repeated 1000 times, the AUC of the average ROC curve, and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for several types of classification threshold. The ROC curve was used to calculate optimal classification thresholds according to Youden's J statistic, J = sensitivity + specificity − 1 [27,28]. In addition, for comparison, rule-in thresholds were computed to equalize sensitivities at 0.80, so that specificities could be compared, while rule-out classification thresholds were computed to equalize specificities at 0.80, so that sensitivities could be compared. Confidence intervals of ROC curves from 10-fold cross-validated logistic regression were constructed using the Delong method [29] and averaged across 1000 repetitions to construct the AUC confidence interval for the average ROC curve.

Results

The cross-validated feature screening process identified prior PTB as a stratification (subgroup) factor related to differential risk of sPTB, consistent with the existing literature [12,16,30,31]. Within the subgroup of participants who had a prior PTB, the only HC feature selected with a frequency >20% was prior PTB count. Among QUS features, ACabsrate was selected most frequently as a risk predictor for the subgroup of patients having a history of PTB. Within the subgroup without prior PTB, the HC features selected most frequently were BMIV0 and CLV0, whereas different QUS features were selected, that is, intV1*GAV1 and

Figure 2. Reference phantom surface revealing the slot in which the transvaginal transducer probe was positioned to obtain a full-field B-mode image (as well as the raw radiofrequency data). Scale: U.S. coin (dime) has a diameter of 1.8 cm.

slopeV1*GAV1. Table 4 summarizes the feature selection results from 1000 repetitions of 5-fold cross-validated L1 logistic regression.

Among the selected HC features, CLV0 is part of current clinical practice [11], and history of PTB has long been considered a risk factor [12,16,31]. In the present study, none of the three selected HC features (BMIV0, CLV0, prior PTB count) was found to have statistically significant coefficients in the logistic regression (see Supplementary Material, Fig. S1, Table S1, Appendix S1 online only). Therefore, the final logistic regression model using HC features only had the form

$$\log(\text{odds sPTB}) = \beta_0 + \beta_1 \text{PriorPTB} \quad (1)$$

where β_0 and β_1 are model coefficients estimated from the data by maximum likelihood. PriorPTB = 1 if the prior PTB count is positive, and PriorPTB = 0 if the participant had no prior PTB. The estimated model coefficients and standard errors were computed using the R function glm [32]. The results of fitting Model HC are outlined in Table 5.

There is support from previous studies for the selected QUS features. AC was identified during the second trimester as having an association with sPTB [3,4] as well as in the third trimester [8]. The LF Intercept (intV1) is representative of the correlated LF measurements (Intercept, Slope, Midband) for non-invasive detection of fatty liver disease [18]. Multiplying by gestational age fraction of full term provides an adjustment for variation in gestational ages at the times of the visits. SlopeV1*GAV1 was not found to be a statistically significant feature in logistic regression modeling. Logistic regression analysis indicated that although the binary indicator for prior PTB was statistically significant, the prior birth count was not statistically significant if the binary indicator for non-zero count was included (see Supplementary Material, online only). Therefore, the final logistic regression model included the binary indicator for prior PTB and the two QUS features identified for the two subgroups (with prior PTB and without prior PTB). The resulting predictive model HC + QUS had the form

Table 3
Four or five initial HC features and 32 initial QUS features for which there are either 52 or 53 initial features

HC feature (4/5[a])	QUS feature (48)		
	Individual (16)		Derived (32)
Prior PTB count[a]	At V1 and V2		Rate change (8)
Prior birth count	AC	Mid	Absolute rate change (8)
CL at V0 (CLV0)[b]	BSC (dB)	*k*	Product with GAV1 (8)
Maternal age at V0	Slope	μ	Product with GAV2 (8)
Body mass index at V0	Intercept	SWS	

Numbers in parentheses denote the number of initial features by "with" or "without" a prior PTB count.
AC, attenuation coefficient; BSC, backscatter coefficient; CL, cervical length; GA, gestational age; PTB, pre-term birth; QUS, quantitative ultrasound; SWS, shear wave speed.
[a] Used "with prior PTB count"; not used "without prior PTB count." The study hypothesis is further explored by stratifying these two feature categories (either with or without PTB history).
[b] VO denotes first clinical visit at consent. V1 and V2 denote the two QUS acquisition times.

Table 4
Top two selected features with selection frequency >20% for participants either with or without a PTB history

With prior PTB		Without prior PTB	
HC	QUS + HC	HC	QUS + HC
Features (1)	Features (2)	Features (2)	Features (2)
Prior PTB count	ACabsrate	BMIV0[a]	intV1*GAV1
	Prior PTB count		
		CLV0	slopeV1*GAV1

Numbers in parentheses denote the number of selected features for that category.
AC, attenuation coefficient; BMI, body mass index; CL, cervical length; HC, historical clinical data; int, intercept; PTB, pre-term birth; QUS, quantitative ultrasound data.
[a] VO denotes first clinical visit at consent.

Table 5
HC and HC + QUS model coefficient estimates, standard errors and coefficient *Z*-test results based on maximum likelihood estimation of the coefficients in eqns (1) and (2) using the full data set (n = 274)

Model	Feature	Coefficient	SE	*Z* value	*p* Value
HC	(Intercept)	−2.8	0.31	−8.9	<2*e*-16[a]
	Prior PTB	1.2	0.42	2.8	0.0049[a]
HC + QUS	(Intercept)	2.6	2.5	1.0	0.30
	PriorPTB	−4.9	2.5	−1.9	0.054[b]
	PriorPTB*ACabsrate	0.36	0.18	2.0	0.041[a]
	(1 − PriorPTB)*intV1*GAV1[c]	0.34	0.16	2.1	0.037[a]

AC, attenuation coefficient; CL, cervical length; GA, gestational age; HC, historical clinical data; int, intercept; PTB, pre-term birth; QUS, quantitative ultrasound data; SE, standard error; VO, first clinical visit at consent.
[a] Statistically significant at $p < 0.05$.
[b] Statistically significant at $p < 0.1$.
[c] VO denotes first clinical visit at consent. V1 and V2 denote the two QUS acquisition times.

Table 6
Likelihood ratio test results

Model	Residual degree of freedom	Deviance	LRT degree of freedom	LRT deviance difference	LRT *p* value
HC	272	163.91	—	—	—
HC + QUS	270	155.09	2	8.82	0.012[a]
HC	272	163.91	—	—	—
HC + CLV0	271	163.90	1	0.01	0.91
HC + QUS	270	155.06	—	—	—
HC + QUS + CLV0[b]	269	155.08	1	0.01	0.91

The top two rows are results for the LRT for null hypothesis model HC (in which the QUS features have zero coefficients) versus full model HC + QUS; the LRT test statistic is the difference between the deviance for model HC and the deviance for model HC + QUS and has an approximate χ^2 distribution with 2 degrees under the null hypothesis. The last two rows indicate the result for the LRT for null hypothesis model HC (in which the CLV0 feature has a zero coefficient) versus the HC + CLV0 model.
CL, cervical length; HC, historical clinical data; LRT, likelihood ratio test; QUS, quantitative ultrasound.
[a] Statistically significant at $p < 0.05$.
[b] VO denotes first clinical visit at consent. V1 and V2 denote the two QUS acquisition times.

$$\log(\text{odds sPTB}) = \beta_0 + \beta_1 \text{PriorPTB} + \beta_2 \text{PriorPTB} * \text{ACabsrate} + \beta_3(1 - \text{PriorPTB}) * \text{intV1} * \text{GAV1} \quad (2)$$

where β_0, β_1, …, β_3 are model coefficients estimated from the data by maximum likelihood, PriorPTB = 1 if the Prior PTB count is positive, and PriorPTB = 0 if the participant had no prior PTB; GAV1 and GAV2 are gestational ages for visits 1 and 2 expressed as fractions of 40 wk (fraction of full term); and ACabsrate is the absolute rate of change in AC between visits 1 and 2. With history of PTB, the model in eqn (1) estimates risk of sPTB-based PriorPTB binary variable only, adjusting for the baseline risk for this subpopulation. Without history of PTB, the model in eqn (1) estimates risk of sPTB using CLV0 and intV1*GAV1 measurements and coefficients to adjust the baseline risk for this subpopulation. The coefficients were estimated by maximum likelihood using the generalized linear model function (glm) in R [32]. The results of fitting Model HC + QUS are outlined in Table 5.

Results of an LRT of the null hypothesis that Model HC is sufficient versus the alternative that Model HC + QUS is required are summarized in Table 6. The LRT test statistic is the difference between deviances for the reduced Model HC and the full Model HC + QUS, where deviance = −2*log(likelihood). The LRT was highly significant, at $p < 0.01$, so we reject the HC model in favor of the full HC + QUS model, which indicates the added value of the QUS features for sPTB risk estimation versus HC features alone.

To assess the predictive effectiveness of obstetrical cervical length (CLV0), likelihood ratio tests of Models HC and QUS + HC versus the same models with CLV0 added were performed. The CLV0 feature was not a statistically significant predictive feature when included in either Model HC or Model HC + QUS ($p = 0.91$ in each case; Table 6).

Model HC + QUS indicates that for the subpopulation with a prior PTB, ACabsrate was a statistically significant risk predictor, whereas for the subpopulation without a history of PTB, intV1*GAV1 was a statistically significant risk predictor. The model provides estimated effects based on the log-odds-ratio interpretation of the logistic regression [33]. Table 7 provides odds ratios for increased estimated risk and confidence intervals associated with a 1-unit increase in either of the QUS features holding other variables fixed. The resulting risk multiplier is the odds ratio.

Receiver operating characteristic curves were computed for the models using 10-fold cross-validation logistic regression with 1000 repetitions using the pROC package in R [34] and visualized using the R package ROCR [35]. The resulting ROC curves from the individual cross-validated logistic regression repetitions and the average ROC curve using threshold averaging method are illustrated in Figure 3. Average AUCs and AUC confidence intervals were computed by averaging AUC values and 95% confidence interval endpoints using the Delong method for the individual repetitions [29,34]. For Model HC, average AUC was 0.53 with a CI of 0.40−0.66. For Model HC + QUS, the average AUC was 0.68 with a CI of 0.57−0.78. For Model HC + CLV0, the average AUC was 0.51 with a CI of 0.38−0.64.

In Model HC, only the binary indicator PriorPTB was statistically significant, and viewed as a classifier, this model relied primarily on the binary indicator for classification. This feature results in the unusual shape of the ROC curve where it improves on the no-skill classifier only for a threshold with a false-positive rate of approximately 0.35 and otherwise performs poorly. The 95% confidence interval for Model HC's AUC fails to rule out the no-skill value of 0.50. In contrast, Model HC + QUS has a higher average AUC, and its 95% confidence interval is significantly above the no-skill level of 0.50. The mean value of the Delong paired *Z*-test statistic for comparing the two average ROC curves for Model HC and Model HC + QUS from 10-fold cross-validation logistic regression runs was 3.48, corresponding to $p < 0.001$ (two-sided). The same Delong test for the difference between the average ROC curves of Model HC and Model HC + CLV0 does not detect any significant difference between the two average ROC curves with mean value *Z* statistic of −1.13, corresponding to a *p* value of 0.32.

The overall prevalence of PTB in the study sample was 0.091, with a prevalence of 0.054 among participants with no history of PTB and a prevalence of 0.169 among participants who had at least one prior PTB. Using the Youden, rule-in and rule-out classification thresholds described earlier, Table 8 compares sensitivity, specificity, PPV, NPV and accuracy for classification for the HC and HC + QUS models. The 95% confidence intervals were computed using the normal approximation applied to the corresponding proportions and binomial standard deviations from the repeat cross-validation samples.

Because of the low prevalence of 0.091 of sPTB in the study, PPV is low as well, although for Model HC + QUS they are higher than the overall prevalence rates. Similarly, NPVs are relatively high because of the low prevalence, and accuracy is a poor measure of relative performance because of the low prevalence. Therefore, direct comparison of sensitivity and specificity provides the most reliable comparisons

Table 7
Risk odds ratio estimates and 95% profile likelihood confidence intervals for QUS features in Model HC + QUS associated with a one-unit increase in the feature

Subpopulation	Predictive feature	Odds ratio for risk (confidence interval)
With prior PTB	ACabsrate	1.4 (1.0−2.1)
Without prior PTB	intV1*GAV1[a]	1.468 (1.03−1.9)

AC, attenuation coefficient; GA, gestational age; int, intercept; PTB, pre-term birth.
[a] V1 denotes quantitative ultrasound acquisition time.

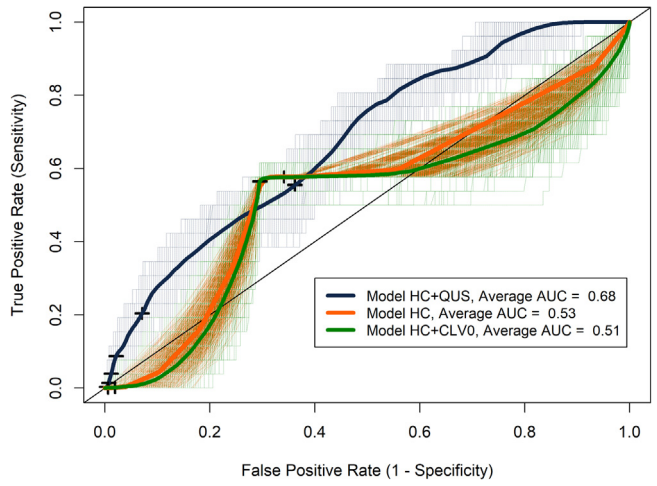

Figure 3. Threshold averaged receiver operating characteristic curves based on 1000 repetitions of 10-fold cross-validation logistic regression. The *solid orange curve* is for logistic regression classification using HC features only; the *solid navy blue curve* is for logistic regression classification using both HC and QUS features, and the solid green curve is for logistic regression classification using HC + CLV0 features. The dashed curves represent individual results from the 1000 repetitions of cross-validation logistic regression for Models HC, HC + QUS and HC + CLV0 models, respectively. For Model HC + QUS, average AUC = 0.68, and 95% CI = 0.57–0.78. For Model HC, average AUC = 0.53, and 95% CI = 0.40–0.66. For Model HC + CLV0, average AUC = 0.51, and 95% CI = 0.38–0.64. AUC, area under the receiver operating characteristic curve; CI, confidence interval; HC, historical clinical data; QUS, quantitative ultrasound data; VO denotes first clinical visit at consent.

because of the independence of these parameters from the overall population prevalence of sPTB.

The results in Table 8 indicate that when specificity was equalized at 0.80 (rule-in), the HC + QUS classifier improved on the sensitivity of the HC classifier from 0.19 to 0.40. Similarly, when sensitivity was equalized at 0.80 (rule-out), the HC + QUS classifier improved on the specificity of the HC classifier from 0.10 to 0.44. The other metrics for Model HC + QUS were uniformly and substantially better than for Model HC for both the rule-in and rule-out thresholds.

Discussion

Pre-term birth is defined as birth before 37 completed weeks of gestation [1]. More than 330,000 infants were born pre-term in 2021 [1]. Consequences of PTB for survivors are severe, can be lifelong and cost society $30 billion annually, a cost that far exceeds that of any major adult diagnosis. Novel QUS technology has been developed by our multidisciplinary investigative team and shows promise for becoming a widely available and useful method for the early detection of sPTB. QUS is a methodology that can readily be added to current clinical ultrasound systems. Cervical QUS data acquisition can be obtained at the same time and anatomical plane as cervical length measurements without adding more scanning time to the examination workflow.

Additionally, as commercial diagnostic ultrasound companies increase the diagnostic capabilities of their ultrasonic imaging systems, there are at least two ultrasonic companies that have done so by incorporating QUS capabilities into their scanners to yield on-screen quantitative QUS outcomes as participants are scanned, one being Siemens (ACUSON Sequoia) [36] using an integrated phantom approach and the other being GE (LOGIC E10) [37] using their ultrasound-guided attenuation parameter (UGAP), both approaches currently being liver specific.

Of most clinical importance, a short cervix is one of the few risk factors that is assessed in women who have not had a sPTB to assess PTB risk [12,15,16,31]. In the United States, CL measurements are commonly used to assess sPTB risk [38]. Thus, for nulliparous women and multiparous women with only a prior full-term birth, predictors for sPTB are simply not available [12,15,16,31]. In fact, cervical length screening has poor prediction in low-risk women without a history of sPTB or short cervix [12,39]. Specific detailed best practice guidelines have been developed for the recommended use of CL measurements to identify pre-term birth risk in pregnancy [40]. Our results suggest that QUS may be an important indicator of sPTB risk in this population.

Importantly, QUS provides early information on the microstructure of the cervix rather than waiting for cervical shortening or symptoms of pre-term labor. Of note, the cervical length measurements in our study at visits 1 and 2 were very similar between participants that delivered sPTBs and FTBs. Our previous work on the pregnant rat [5,6,] provided evidence of the relationship of ultrasonic attenuation and backscatter coefficients with cervical remodeling, collagen concentration and collagen disorganization, as well as gestational age, in the rat cervix. In women admitted for cervical ripening with prostaglandins followed by oxytocin for induction of labor, QUS detected cervical remodeling changes after 12 h of prostaglandin therapy [8]. The potential impact of QUS in the clinical care of pregnant women is great. For example, clinicians could determine whether treatments, such as progesterone or prostaglandins, had an impact on cervical tissue remodeling, rather than basing clinical care on symptoms or watching and waiting, especially with induction of labor; if the cervix is not remodeled or ready for labor, it may be wise to wait [4,8]. In 2011, the Food and Drug Administration (FDA) approved 17-hydroxyprogesterone caproate weekly injections to prevent recurrent pre-term birth in women with a singleton pregnancy and a previous spontaneous singleton pre-term birth [41]. The withdrawal of U.S. Food and Drug Administration (FDA) approval of 17-hydroxyprogesterone caproate is being considered due to suggesting lack of evidence to prevent risk of PTB [41]. Basing clinical decision-making and care on cervical microstructure has the potential to improve the care of pregnant women and provide a basis for developing and objectively evaluating present and new treatments to prevent PTB.

A caveat in the preliminary analysis presented here is that the initial screening of features introduces a potential bias compared with testing of a fixed set of features by design. In support of the final models,

Table 8
Comparison of classification sensitivity, specificity, PPV, NPV and accuracy between HC and HC + QUS models using three types of classification threshold

Threshold type	Model	Classification threshold	Sensitivity	Specificity	PPV	NPV	Accuracy
Youden's *J*	HC	0.080 (0.05, 0.11)	0.57 (0.51, 0.63)	0.703 (0.65, 0.76)	0.17 (0.123, 0.21)	0.94 (0.91, 0.97)	0.69 (0.64, 0.74)
	HC + QUS	0.070 (0.04, 0.10)	0.69 (0.64, 0.75)	0.52 (0.46, 0.57)	0.13 (0.09, 0.17)	0.94 (0.91, 0.95)	0.53 (0.47, 0.59)
Rule-in	HC	0.17 (0.12, 0.21)	0.17 (0.12, 0.21)	0.80 (0.75, 0.85)	0.08 (0.05, 0.11)	0.90 (0.867, 0.94)	0.74 (0.69, 0.79)
	HC + QUS	0.13 (0.09, 0.17)	0.36 (0.30, 0.42)	0.80 (0.75, 0.85)	0.16 (0.16, 0.20)	0.92 (0.89, 0.95)	0.79 (0.70, 0.80)
Rule-Out	HC	0.050 (0.03, 0.08)	0.80 (0.75, 0.85)	0.09 (0.06, 0.31)	0.08 (0.05, 0.11)	0.82 (0.78, 0.87)	0.16 (0.12, 0.20)
	HC + QUS	0.050 (0.03, 0.08)	0.80 (0.75, 0.85)	0.39 (0.336, 0.45)	0.12 (0.08, 0.16)	0.95 (0.92, 0.97)	0.43 (0.37, 0.49)

The three classification threshold types are (i) maximum Youden's *J*, (ii) rule-in threshold with specificity = 0.80 and (iii) rule-out threshold with sensitivity = 0.80. Estimates are based on 1000 repetitions of 10-fold cross-validation; 95% confidence intervals are shown in parentheses.
HC, historical clinical data; NPV, negative predictive value; PPV, positive predictive value; QUS, quantitative ultrasound data.

however, it has been noted that AC [4,5,8] and LF int [18] were previously identified as relevant tissue-based QUS features.

Cervical length measurements [11,12] and HC have been the mainstay of risk assessment for sPTB for years because no other credible biomarkers were available. Our work shows promise of QUS being an added ultrasound feature available to clinicians to assess sPTB risk based on tissue microstructure and without adding scanning time for data acquisition. Notably, the traditional risk factors for sPTB (age, parity, history of PTB, cervical length <25 mm, smoking, BMI and alcohol use) were not predictive of sPTB in our sample of participants. Even with only 26 sPTBs, our data suggest value is added for predicting sPTB when QUS data are included with historical clinical data.

Conflict of interest

The authors declare no competing interests.

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Data availability statement

Data sharing will be available once all articles are published.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2022.12.018.

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