Cervical elastography at 18 to 23 weeks to predict spontaneous preterm birth in individuals with a history of preterm birth

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BACKGROUND: Individuals with a history of spontaneous preterm birth are at increased risk for recurrence in a subsequent pregnancy. Current methods used to predict those at highest risk are not precise. Cervical elastography is an investigational ultrasonographic technique that measures cervical tissue stiffness and may aid in identifying individuals at highest risk.

OBJECTIVE: This study aimed to assess the association between previously described cervical elastography measures—obtained using a semiautomatic application (E-cervix)—and preterm birth <37 weeks' gestation in a high-risk cohort with a history of spontaneous preterm birth.

STUDY DESIGN: Individuals with a singleton pregnancy between 18+0 and 23+6 weeks of gestation with a history of spontaneous preterm birth <37 weeks were prospectively enrolled. Exclusion criteria included the presence of a current cerclage or any uterine anomaly. The primary exposures were the E-cervix quantitative parameters (internal os stiffness, external os stiffness, internal−to−external os stiffness ratio, hardness ratio, and elasticity contrast index), which were measured at the time of enrollment. Transvaginal cervical length was also measured as an exposure to compare the current standard of care and accepted cutpoint of 25 mm alongside the E-cervix parameters. The primary outcome was preterm birth <37 weeks. The intra- and interrater reliability intraclass correlation coefficient for each parameter was calculated using a mixed-effects model. The area under the curve was derived from receiver operating characteristic curves to evaluate the association of each parameter with the primary outcome, and the optimal cutpoints for each continuous parameter were identified. Multivariable logistic regression was performed for the parameters that were either significant on univariate analysis or had an area under the curve of ≥0.6, using the calculated cutpoint to create a binary exposure and adjusting for gestational age at the earliest prior preterm birth, number of prior preterm births, and progesterone use. A sensitivity analysis was performed excluding medically indicated preterm birth.

RESULTS: Of the enrolled 245 individuals with a history of spontaneous preterm birth, 69 (28%) had preterm birth <37 weeks. Intrarater and interrater reliability were good for all parameters (intrarater: 0.60−0.74; interrater: 0.62−0.71). In univariate analysis, only the internal−to−external os stiffness ratio was significantly associated with increased risk of preterm birth compared with no preterm birth (0.97±0.23 vs 0.90±0.20; P=.01). Cervical length, internal os stiffness, external os stiffness, hardness ratio, and elasticity contrast index did not show significant associations. The area under the curve for external os stiffness was 0.6, indicating a good association, whereas the values for the remaining parameters were satisfactory (0.51−0.59). In multivariable logistic regression analysis, an internal−to−external os stiffness ratio ≥1.0 was associated with 2-fold higher odds of preterm birth <37 weeks (adjusted odds ratio, 2.48; confidence interval, 1.34−4.58), and an external os stiffness ≥30 (indicating lower tissue stiffness) was associated with 46% reduced odds of preterm birth <37 weeks (adjusted odds ratio, 0.54; confidence interval, 0.30−0.97). Cervical length <25 mm was not associated with preterm birth.

CONCLUSION: Elastography with E-cervix technology can be reliably assessed in a cohort of women with prior preterm birth. The parameter most useful for predicting preterm birth was an internal−to−external os stiffness ratio ≥1.0, whereas cervical length <25 mm was not predictive in our cohort.

Key words: cervical length, elastography, preterm birth, spontaneous preterm birth, transvaginal ultrasound

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Introduction

Preterm birth (PTB) complicates 10% of pregnancies in the United States[1] and is a leading cause of perinatal morbidity and mortality.[2] Although a history of spontaneous PTB is the strongest predictor of recurrence,[3−5] this risk is further increased among those with a higher number of prior PTBs and prior PTBs at an earlier gestational age.[6,7] Accurate identification of those at high risk for PTB is important because it can aid in more efficacious application of interventions aimed at decreasing PTB and its sequelae. The association

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Why was this study conducted?
Current methods used to predict preterm birth are not precise. Cervical elastography may aid in identifying individuals at risk for preterm birth.

Key findings
E-cervix parameters measured during mid-second trimester anatomic assessment were reliable and were associated with recurrent preterm birth.

What does this add to what is known?
There are limited data on the use of cervical elastography as a screening tool for predicting preterm birth risk. Prior studies have either used shear elastography focusing on external forces during imaging, which may not be reproducible, or have been conducted in cohorts with already shortened cervices at the time of evaluation.

between decreased cervical length (CL) measurements obtained using transvaginal ultrasound and increased risk of PTB has been recognized since the 1990s.[8−10] Currently, interventions such as progesterone administration and cerclage placement are heavily reliant on midtrimester CL measurements, even among those with a history of PTB. However, CL measurement may fail to identify up to two-thirds of individuals who will experience PTB, and is even less reliable in an unselected population.[9,11−15]

The current methods for identifying individuals who would benefit from PTB prevention interventions are limited. This is evidenced by recent changes in long-standing obstetrical society recommendations for use of progesterone in individuals with a history of PTB, which is now most consistently recommended for only those who also have a CL <25 mm.[16,17] Additional objective parameters need to be assessed to aid in improved identification of this at-risk cohort. Cervical elastography is a promising investigational ultrasonographic technique that measures cervical tissue strain (or stiffness) and has an established association with PTB in the literature, although the data are varied.[18−22] Specifically, the novel E-cervix application (Samsung Medison, Seoul, Republic of Korea), which assesses tissue strain using an individual's internal forces, such as blood vessel pulsations, shows potential for reliably predicting PTB.[23−27] We sought to assess the association between previously described E-cervix parameters[22] and PTB <37 weeks in a high-risk cohort with a history of PTB.

Materials and methods

Participants

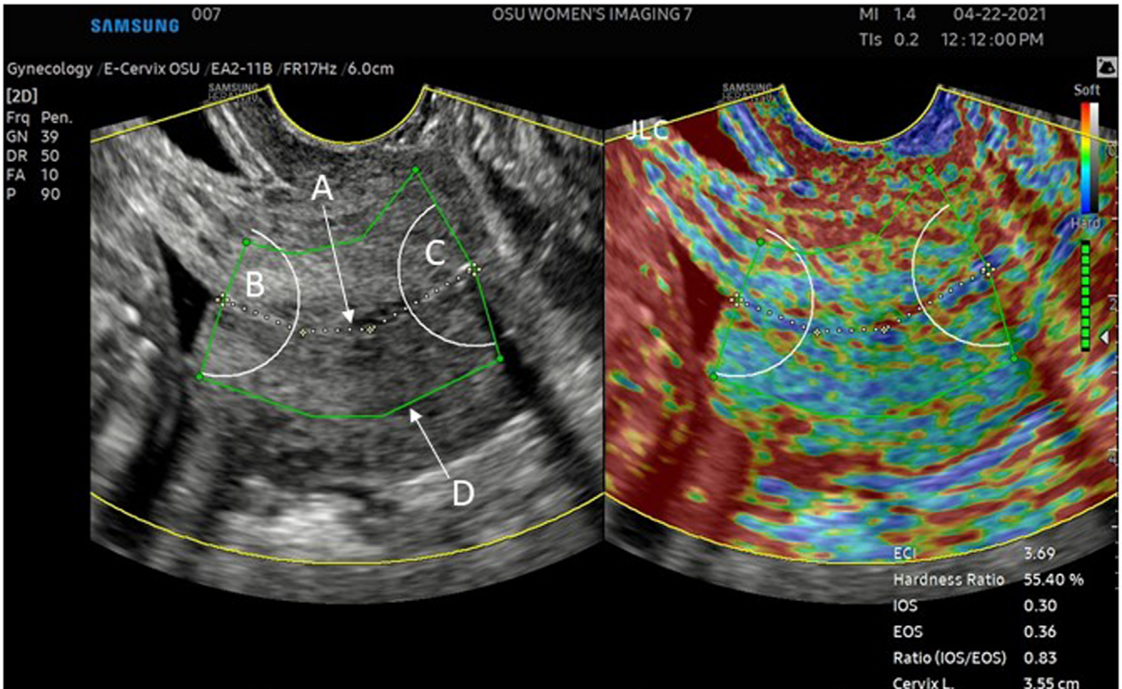
This was a prospective cohort study of individuals with a singleton pregnancy and a history of spontaneous PTB <37 weeks of gestation who underwent transvaginal ultrasonographic assessment with E-cervix application between 18 weeks 0 days and 23 weeks 6 days of gestation. Enrollment occurred at 2 outpatient centers associated with 1 academic hospital from April 2021 through February 2023. Individuals aged 18 to 50 years without an in situ cervical cerclage at the time of enrollment or uterine anomaly were eligible. Individuals were included regardless of progesterone use. Those with prior PTB in which delivery was initiated because of a maternal or obstetrical indication rather than spontaneous onset were excluded. Clinical research staff screened daily ultrasound schedules to identify potentially eligible participants. All patients with a history of spontaneous PTB without a cerclage in situ routinely undergo transvaginal CL screening within the gestational age window of the study as part of clinical care in our practice. Individuals scheduled for a clinical transvaginal ultrasound who met other eligibility criteria were approached before their transvaginal ultrasound to discuss the study. Written informed consent was obtained before enrollment. This study was approved by The Ohio State University Biomedical Sciences Institutional Review Board (IRB# 2019H0482). The design and conduct of the study and data analysis and interpretation were performed by the study team independent of the funder.

Data collection, exposures, and outcomes

After enrollment, basic participant demographic information was entered into the REDCap (Vanderbilt University, Nashville, TN) study database. Among those enrolled, 20% (n=50) were randomly selected to undergo elastography measurements by 2 sonographers to assess interobserver variability. Randomization was performed within the REDCap application using a computer-generated simple randomization scheme developed by a member of the bioinformatics department who was not otherwise involved in the study. Once it was determined whether the participant would have elastography assessment by 1 or 2 sonographers, the ultrasound examination was performed using a transvaginal transducer (3−10 MHz) and the Samsung HERA W10 ultrasound system with accessible E-cervix software.[23] The assessment included CL measurements performed in accordance with the standards of the Perinatal Quality Foundation.[28] We used a 4-point measurement of the cervical canal to account for curved measurements. Three CL measurements were collected, and the shortest acceptable measurement was used for analysis.

Cervical elastography was then performed following a previously published standardized E-cervix protocol.[22,23] The E-cervix system was developed to generate semiautomated measurements of tissue strain, which is a measure of tissue motion or deformation in response to a compressional force. Briefly, the transvaginal transducer is placed in the anterior fornix of the vagina to visualize the cervix in the sagittal orientation with both the internal and external os visible. No additional pressure is placed on the cervix by the sonographer, and motion artifacts introduced by

FIGURE 1
E-cervix parameter definitions and image diagram



Parameter	Definition	Diagram label	Interpretation
Cervical length	Continuous line in cervical canal extending from external os to internal os	Label A- dotted line	CL < 2.5 cm is considered shortened
Internal os stiffness (IOS)	Average strain within the machine-defined 1 cm radius semicircle at the internal os	Label B- area within white semicircle	Ranges from 0 (harder tissue) to 1.0 (softer tissue)
External os stiffness (EOS)	Average strain within the machine-defined 1 cm radius semicircle at the external os	Label C- area within white semicircle	Ranges from 0 (harder tissue) to 1.0 (softer tissue)
Internal-to-external os stiffness ratio (I-E ratio)	Average strain at the internal os divided by the average strain at the external os	B/C	>1: IOS is softer <1: EOS is softer
Hardness ratio (HR)	Percentage of total cervix area characterized as hard (strain value <0.3)	Label D- area within green outline	Ranges from 0% (all areas soft) to 100% (all areas hard)
Elasticity contrast index (ECI)	Strain heterogeneity within the entire cervix	Label D- area within green outline	Ranges from 0 (homogenous) to 81 (heterogenous)

[1]Region of interest (ROI): defined by green box
[2]Deidentified image taken from study sample

CL, cervical length.

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movement of the probe are minimized by the sonographer using feedback provided by the E-cervix application. The endocervical canal is measured with the placement of calipers by the sonographer at the internal and external cervical os. The system then automatically generates 1-cm semicircle radii that define the internal and external os regions of interest (ROI). This is modified by the sonographer once they place the ROI box that includes the entire cervix within the imaging plane. The E-cervix software then analyzes the tissue strain in the ROI on the basis of internal stresses such as gravitational force from the maternal body habitus, maternal respiration, and blood vessel pulsations to calculate measurements from 5 parameters. These parameters are (1) internal os stiffness (IOS), defined as the strain within 1 cm of the internal os; (2) external os stiffness (EOS), defined as the strain within 1 cm of the external os; (3) internal—to—external os stiffness ratio (I-E ratio), defined as IOS divided by the EOS; (4) hardness ratio, defined as the percentage of the total cervix that was hard (strain value <0.3); and (5) elasticity contrast index (ECI), which is a measure of strain heterogeneity within the entire cervix. The measures of tissue strain range between 0 and 1, with lower values indicating harder tissue (Figure 1).

This process using the E-cervix application was repeated 3 times by the same sonographer to generate 3 sets of measurements for each elastography parameter. Once the study was completed by the first sonographer, it was repeated with 3 additional measurements collected by a second sonographer in the subset of participants randomly selected to assess the interrater reliability. These assessments were completed independently, and each sonographer did not have knowledge of the results of the other's study. Average values of the E-cervix parameters from the 3 images obtained from only the first sonographer were used in the overall analysis. All sonographers participating in this study were credentialed by ARDMS (American Registry for Diagnostic Medical Sonography) in the specialty of obstetrics and gynecology, with additional CLEAR certification and at least 3 years of experience in perinatal care. Each study sonographer also underwent E-cervix−specific training. This training consisted of a presentation of the application, a concurrent hands-on review of the technology, and approval of practice imaging by an onsite specialist before study initiation.

Maternal demographic and clinical data were manually abstracted from the medical record by study team members following enrollment. These data included maternal age, self-reported race and ethnicity, body mass index, tobacco use, prior uterine or cervical procedures, and pregnancy history. Information about the management of the current pregnancy was obtained, including progesterone use, cerclage placement, and delivery information following enrollment. Given that the presence of a cerclage at the time of enrollment was an exclusion criterion, women in this cohort were only eligible for ultrasound- or examination-indicated cerclages. In patients with a history of spontaneous PTB, standard practice within our institution is to discuss cerclage placement if CL is <25 mm or if the cervix is dilated at <24 weeks of gestation. Pessary placement for PTB prevention was not routinely practiced at our institution during the collection period and was not available to any of the participants. Delivery information included gestational age at time of delivery, indication for preterm deliveries, and mode of delivery.

The primary exposure was transvaginal ultrasonographic CL measurement and the 5 elastography measurements from the E-cervix application. The primary outcome was any PTB <37 weeks.

Statistical analysis

Baseline characteristics were compared between participants who delivered <37 weeks of gestation (preterm) and those who delivered at ≥37 weeks of gestation (term). Categorical variables were compared using the chi-squared test. The distribution of the continuous data was assessed using the Kolmogorov−Smirnov test, and comparisons between groups were made using the Student *t* test or Mann−Whitney U test, as appropriate. The mean value for each parameter was compared between participants who delivered preterm and those who delivered at ≥37 weeks. The ability of each parameter to predict the primary outcome of PTB was assessed by generating receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC). To further assess the clinical utility of the sonographic parameters measured in this study in the prediction of PTB, we identified the optimal cutpoint on the ROC curve for each parameter by calculating the Youden index, which maximizes the sensitivity and specificity of a measure.[29] For the parameters that were either significant in univariate analysis or had an AUC ≥0.6, we performed multivariable logistic regression using the calculated cutpoint to create a binary exposure, adjusting for gestational age at earliest prior PTB, cerclage placement in the current pregnancy, number of prior PTBs, and progesterone use in the current pregnancy. A sensitivity analysis was performed by excluding medically indicated PTB from the outcome. The intra- and interrater reliability intraclass correlation coefficient for each elastography parameter was calculated using a mixed-effects model. Data analysis was performed using Stata 15.1 (StataCorp, College Station, TX). Statistical significance was set at a *P* value <.05.

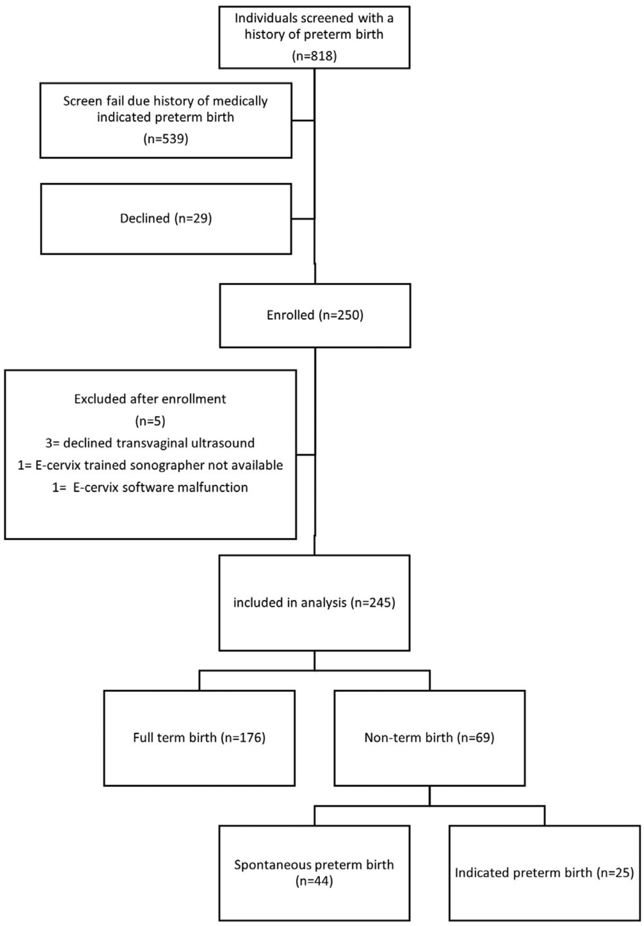
We aimed to enroll 250 participants on the basis of an a priori sample size calculation. At the time of our sample size calculation, E-cervix was a new technology with very little information about each of the elastography parameters and their association with PTB to guide our estimate. On the basis of published data from our own center,[30] we anticipated a rate of PTB <37 weeks of 39.6% among individuals with a history of PTB. With 250 women, we could estimate 2-sided 95% confidence intervals (CIs) for proportions, with a maximum width of 12.5 percentage points by group.

Results

We screened 818 individuals with a history of PTB and identified 279 individuals who met the inclusion criteria during the study period. Among those approached to discuss enrollment, 250 (89.6%) individuals provided consent. Five participants dropped out after enrollment before the examination because they declined a vaginal ultrasound (3), an E-cervix−trained sonographer was not available (1), or there was an E-cervix software malfunction (1). Of the 245 individuals enrolled, 69 (28%) had any PTB <37 weeks, and 44 (18%) had spontaneous PTB <37 weeks (Figure 2).

Patients who had PTB (<37 weeks) in the current pregnancy were more likely to have delivered at an earlier gestational age in their prior pregnancy (median, 33 [interquartile range (IQR), 28−35] vs 34 [IQR, 32−36] weeks; *P*=.02), had a higher number of prior PTBs (1 [IQR, 1−2] vs 1 [IQR, 1−1]; *P*=.04), and were more likely to have a cerclage placed following enrollment (13% vs 4%; *P*=.01). Cerclage placement occurred at a mean gestational age of 20.5 (SD, 1.5) weeks for a short CL measuring a mean length of 21.8 mm (SD, 3.3 mm). All other characteristics were similar, including age, race/ethnicity, body mass index, parity, tobacco exposure, history of cervical procedure for

FIGURE 2
Flow diagram of enrollment and preterm birth outcome



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dysplasia, history of dilation and curettage, and progesterone use (Table 1).

In univariate analysis, CL, IOS, EOS, hardness ratio, and ECI measurements were similar between individuals who delivered preterm and those who delivered at term. However, a higher I-E ratio was significantly associated with an increased risk of PTB (0.97± 0.23 vs 0.90±0.20; *P*=.01). When plotting ROC curves, the AUC for the EOS was found to predict PTB (AUC, 0.60) better than the other measures, but none provided adequate discrimination (Table 2).

Multivariable logistic regression was performed using values determined in our cutpoint analysis only for parameters that had an AUC ≥0.6 (ie, EOS) or that were significantly associated with PTB on univariate analysis (ie, I-E ratio). We also evaluated CL <25 mm as the current standard metric.

In multivariable logistic regression analysis, an I-E ratio >1.0 was associated with >2-fold higher odds of PTB <37 weeks (adjusted odds ratio [aOR], 2.48; CI, 1.34−4.58), whereas EOS >0.30 (indicating softer tissue) was associated with 46% reduced odds of PTB <37 weeks (aOR, 0.54; CI, 0.30−0.97). Similar findings were observed in the sensitivity analysis excluding indicated PTB (I-E ratio: aOR, 2.36; CI, 1.11−5.0; EOS: aOR, 0.48; CI, 0.23−0.97). A standard CL threshold <25 mm was not significantly associated with PTB <37 weeks or spontaneous PTB <37 weeks (Table 3). Finally, both intrarater reliability (n=245) and interrater reliability (n=45) for all 5 E-cervix parameters were good (Table 4).

Discussion

Principal findings

We found that all 5 E-cervix parameters can be reliably measured at 18 through 23 weeks of gestation in individuals with a history of PTB. We identified 2 E-cervix parameters, EOS and the I-E ratio, that were significantly associated with PTB <37 weeks. The EOS measurement reflects average strain within a 1-cm radius of the external os, with values closer to 0 indicating harder tissue, and those closer to 1 indicating softer tissue. In our study, softer tissue (EOS >0.30) was inversely proportional to PTB, with values above this threshold being associated with almost half the odds of PTB compared with those below the threshold. The I-E ratio measurement reflects IOS strain divided by EOS strain, with a ratio >1.0 indicating that the internal os is softer than the external os. A ratio >1.0 increased the odds of PTB over 2-fold in our study.

Results in the context of what is known

Although the relationship of cervical elastography and PTB has been assessed in both high-risk and low-risk populations, most of the reported literature has investigated applications of shear-wave elastography or strain elastography with external compressive forces.[19−21,31−36] Standardizing the amount of force applied by the transvaginal ultrasound probe and variation in the pressure applied across the different regions of the cervix are central challenges related to cervical elastography.[37] The E-cervix technology is designed to overcome these limitations by using strain elastography with internal compressive forces such as gravitational forces from maternal body habitus, maternal respiration, and blood vessel pulsations. This allows for the technology to be less sonographer-dependent and more reproducible. Several studies have investigated the reliability of the E-cervix application parameters and found a similar moderate to high degree of intra- and interrater reliability; however, these studies were conducted either in unselected populations or patients with an already shortened cervix.[24,38,39]

TABLE 1
Demographic information by preterm birth outcome

Characteristics	Preterm birth <37 wk (n=69)	No preterm birth <37 wk (n=176)	*P* value
Age, y	29.7 (5.6)	30.9 (5.2)	.11
Race/ethnicity			
Non-Hispanic White	34 (49.3)	109 (61.9)	.28
Non-Hispanic Black	27 (39.1)	48 (27.3)	
Hispanic	4 (5.8)	9 (5.1)	
None of the above[a]	4 (5.8)	10 (5.7)	
Parity Median (IQR 25%—75%)	3 (2—4)	3 (2—4)	.61
Number of prior PTBs Median (IQR 25%—75%)	1 (1—2)	1 (1—1)	.04
Any tobacco history	12 (17.4)	39 (22.2)	.68
BMI	31.5 (8.2)	30.6 (6.9)	.38
Earliest GA of prior PTB, wk Median (IQR 25%—75%)	33 (28—35)	34 (32—36)	.02
Prior LEEP or cervical conization	8 (11.6)	15 (8.5)	.46
Prior dilation and curettage	18 (26.1)	28 (15.9)	.07
Progesterone during pregnancy	58 (84.1)	128 (72.7)	.06
Cerclage placed during current pregnancy[b]	9 (13.0)	7 (4.0)	.01
GA at examination, wk Median (IQR 25%—75%)	19.0 (18.4—20.0)	19.0 (18.6—20.1)	.62

All data are presented as number (percentage) or mean±SD unless otherwise stated.

GA, gestational age; *IQR*, interquartile range; *LEEP*, loop electrosurgical excision procedure; *PTB*, preterm birth.

[a] None of the above inclusive of Asian, Native Hawaiian, Pacific Islander, Native American, and >1 race; [b] In all cases, cerclage was placed following cervical elastography evaluation.

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Patberg et al[22] assessed an unselected population, and established normative E-cervix measurement data in the mid-second trimester in this low-risk population. Consistent with their findings, average values for the E-cervix parameters in our study also were within the 10th to 90th percentile of their published data, thus providing external validation of their findings.

One of the most valuable potential applications of cervical elastography is the prediction of PTB by detecting early cervical remodeling as measured by a change in tissue strain. Studies evaluating specifically the use of the E-cervix application and prediction of PTB have assessed patient populations that differ from our study sample, including individuals with a history of loop electrosurgical excision procedure,[40] individuals in the third trimester,[38] low-risk unselected populations,[22] or individuals with an already shortened cervix.[27,41] Similar to our study, Patberg et al[22] found that the individual parameters were not predictive of PTB. However, increasing ECI was associated with an increased risk of spontaneous PTB after adjusting for confounders in their study. ECI was not associated with PTB in our study, but low EOS strain and increased I-E ratio were factors associated with higher risk. The association between CL and PTB is well-established,[8–10] and thus the absence of a statistically significant association between CL <25 mm and PTB in our study may simply reflect the small number of individuals in the cohort with a short cervix (n=11; 4.4%).

Clinical implications

Although our study's finding of a significant association between both the EOS and I-E ratio parameters and PTB is promising, further research using the E-cervix application is needed to better understand this association. Our finding that more patients with low strain at the external os (ie, harder tissue) delivered preterm compared with those with a softer external cervical os is counterintuitive. However, the small difference in average EOS between participants who delivered preterm and those who delivered at ≥37 weeks (0.30 [SD, 0.1] vs

TABLE 2
E-cervix parameters and the association with preterm birth <37 weeks of gestation

Parameter	Parameter definition[a]	Preterm birth <37 wk (n=69) Mean (SD)	No preterm birth <37 wk (n=176) Mean (SD)	*P* value	ROC/AUC[b]	Optimal cutpoint
Cervical length (mm)	—	36.41 (7.61)	37.90 (7.01)	.14	0.56	40.2
Internal os stiffness	Average strain within the system-defined 1-cm radius semicircle at the internal os	0.28 (0.07)	0.28 (0.06)	.96	0.52	0.28
External os stiffness	Average strain within the system-defined 1-cm radius semicircle at the external os	0.30 (0.10)	0.32 (0.08)	.06	0.60	0.30
Internal—to—external os stiffness ratio	Average strain at the internal os divided by the average strain at the external os	0.97 (0.23)	0.90 (0.20)	.01	0.59	1.0
Hardness ratio	Percentage of total cervix area characterized as hard (strain value <0.3)	65.02 (14.26)	63.54 (13.29)	.44	0.55	63.8
Elasticity contrast index	Strain heterogeneity within the entire cervix	3.69 (1.11)	3.63 (1.13)	.71	0.51	3.54

AUC, area under the curve; *ROC*, receiver operating characteristic; *SD*, standard deviation.

[a] Definitions modified from Patberg et al,[22] 2021; the measures of tissue strain range between 0 and 1, with lower values indicating harder tissue; [b] AUC values: 0.9 to 1.0: excellent; 0.8 to 0.9: very good; 0.7 to 0.8: good; 0.6 to 0.7: satisfactory; 0.5 to 0.6: unsatisfactory.

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TABLE 3
Cervical length, external os stiffness, and internal—to—external os stiffness ratio cutpoints and their association with all preterm birth <37 weeks of gestation and spontaneous preterm birth <37 weeks of gestation

PTB <37 wk	<37 wk (n=69)	≥37 wk (n=176)	OR (95% CI)	aOR (95% CI)[a]
Cervical length, mm				
<25	5 (45.5)	6 (54.6)	2.21 (0.65—7.51)	1.88 (0.54—6.55)
≥25	64 (27.4)	170 (72.7)	Ref	Ref
External os stiffness				
>0.30 (softer)	31 (23.0)	104 (77.0)	0.56 (0.32—0.99)	0.55 (0.31—0.97)
≤0.30 (harder)	38 (34.6)	72 (65.5)	Ref	Ref
Internal—to—external os stiffness ratio				
>1.0	30 (38.5)	48 (61.5)	2.05 (1.15—3.66)	2.48 (1.35—4.58)
≤1.0	39 (23.4)	128 (76.7)	Ref	Ref
Spontaneous PTB <37 wk (n=220)	**<37 wk (n=44)**	**≥37 wk (n=176)**		
Cervical length, mm				
<25	4 (40.0)	6 (60.0)	2.77 (0.77—9.92)	2.00 (0.52—7.65)
≥25	40 (19.0)	170 (81.0)		
External os stiffness				
>0.30 (softer)	19 (15.5)	104 (84.6)	0.53 (0.27—1.03)	0.50 (0.25—1.00)
≤0.30 (harder)	25 (25.8)	72 (74.2)		
Internal—to—external os stiffness ratio				
>1.0	18 (27.3)	48 (72.7)	1.85 (0.93—3.67)	2.37 (1.13—4.96)
≤1.0	26 (16.9)	128 (83.1)		

aOR, adjusted odds ratio; *CI*, confidence interval; *PTB*, preterm birth; *OR*, odds ratio.

[a] aOR: adjusted for gestational age of earliest prior PTB, number of prior PTBs, and progesterone use in current pregnancy.

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TABLE 4
Intra- and interrater reliability of the E-cervix parameters

Parameter	Intrarater reliability[a] (95% CI) (n=245)	Interrater reliability[a] (95% CI) (n=48)
Internal os stiffness	0.60 (0.53—0.65)	0.62 (0.40—0.78)
External os stiffness	0.70 (0.65—0.75)	0.71 (0.55—0.85)
Internal—to—external os stiffness ratio	0.62 (0.55—0.67)	0.69 (0.52—0.82)
Hardness ratio	0.66 (0.60—0.71)	0.64 (0.45—0.82)
Elasticity contrast index	0.74 (0.69—0.79)	0.69 (0.48—0.84)

CI, confidence interval.

[a] Intraclass correlation coefficient values: <0.4: poor; 0.4 to 0.59: fair; 0.6 to 0.74: good; 0.75 to 1.00: excellent.

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0.32 [SD, 0.08]) might indicate that EOS is of less clinical relevance. The finding that a softer internal cervical os relative to the external os (ie, a higher I-E ratio) is associated with higher rates of PTB is consistent with our understanding of cervical changes associated with PTB, including the well-established sonographic observation of cervical funneling among individuals at risk for PTB.[42,43] These findings may improve the detection of those at risk for PTB. In our cohort, CL was not a significant predictor, and historically, a shortened CL has failed to identify up to two-thirds of individuals who ultimately experience PTB.[9,11−15]

Strengths and limitations

Our data contribute to the growing literature on the use of cervical elastography for predicting PTB. Strengths of our study include using the E-cervix application to assess a novel cohort of high-risk women with a history of spontaneous PTB, as well as assessing both the intra- and interrater reliability within this population. This study involved a large, prospectively enrolled cohort, allowing for accurate and thorough covariate assessment. Finally, assessing the cervix during the standard time frame of anatomic survey in the midtrimester allows for easy clinical application.

Limitations of our study include the widespread use of progesterone within our cohort. Progesterone use may affect early cervical remodeling and potentially alter early changes that could be detected on the E-cervix application. However, given the widespread adoption of progesterone supplementation in obstetrics, particularly for those with a history of PTB, our results are generalizable to clinical practice. Although the inclusion of those with a history of cervical excision and those who underwent cerclage placement following enrollment may have biased the results, these participants constituted only a small proportion of the overall sample. Furthermore, their inclusion increased the study's generalizability given that such cases are common among individuals with a history of PTB.

In addition, although our cohort was considered high-risk, we observed a PTB rate of only 28%, whereas we anticipated a PTB rate of 39.6% on the basis of our historical cohort.[30] Similarly, the rate of CL <25 mm was 4.5%, whereas prior studies estimated that approximately 10% of individuals with a history of PTB exhibit a CL <25 mm.[13] This suggests that our study may have been underpowered to detect a clinical difference among all E-cervix parameters. One explanation for the lower-than-expected PTB rate and short CL rate is the transition from intramuscular progesterone to vaginal progesterone during the collection period. Most patients in our cohort who were administered progesterone took the vaginal form (60.8%), in contrast to the historical cohort used for power analysis, wherein intramuscular progesterone was the standard of care. Furthermore, because the primary outcome was found to be underpowered and the rates of PTB <32 weeks (6.4%) and <35 weeks (9.6%) were low, additional PTB gestational age cutoffs were not included in the analysis to minimize the risk of type II error. Finally, because this was an exploratory analysis of the use of the novel E-cervix technology, multiple comparisons were performed for the multiple E-cervix parameters, increasing the risk for a type I error. Thus, significant findings will need to be confirmed with additional studies.

Conclusion

Elastography with E-cervix technology can be reliably assessed in a cohort of women with prior PTB. The finding that a softer internal cervical os relative to the external cervical os (I-E ratio >1.0), as detected by elastography, may be associated with higher risk of PTB has potential clinical implications; however, further investigation is required.

CRediT authorship contribution statement

Miranda K. Kiefer: Writing − review & editing, Writing − original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Jessica R. Russo:** Writing − review & editing, Visualization, Software, Project administration, Methodology, Investigation, Data curation. **Pamela M. Foy:** Writing − review & editing, Visualization, Validation, Supervision, Software, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Jiqiang Wu:** Writing − review & editing, Validation, Methodology, Formal analysis. **Mark B. Landon:** Writing − review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Heather A. Frey:** Writing − review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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