OBSTETRICS

Personalized assessment of cervical length improves prediction of spontaneous preterm birth: a standard and a percentile calculator

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BACKGROUND: A sonographic short cervix (length <25 mm during midgestation) is the most powerful predictor of preterm birth. Current clinical practice assumes that the same cervical length cutoff value should apply to all women when screening for spontaneous preterm birth, yet this approach may be suboptimal.

OBJECTIVE: This study aimed to (1) create a customized cervical length standard that considers relevant maternal characteristics and gestational age at sonographic examination and (2) assess whether the customization of cervical length evaluation improves the prediction of spontaneous preterm birth.

STUDY DESIGN: This retrospective analysis comprises a cohort of 7826 pregnant women enrolled in a longitudinal protocol between January 2006 and April 2017 at the Detroit Medical Center. Study participants met the following inclusion criteria: singleton pregnancy, ≥1 transvaginal sonographic measurements of the cervix, delivery after 20 weeks of gestation, and available relevant demographics and obstetrical history information. Data from women without a history of preterm birth or cervical surgery who delivered at term without progesterone treatment (N=5188) were used to create a customized standard of cervical length. The prediction of the primary outcome, spontaneous preterm birth at <37 weeks of gestation, was assessed in a subset of pregnancies (N=7336) that excluded cases with induced labor before 37 weeks of gestation. Area under the receiver operating characteristic curve and sensitivity at a fixed false-positive rate were calculated for screening at 20 to 23 6/7, 24 to 27 6/7, 28 to 31 6/7, and 32 to 35 6/7 weeks of gestation in asymptomatic patients. Survival analysis was used to determine which method is better at predicting imminent delivery among symptomatic women.

RESULTS: The median cervical length remained fundamentally unchanged until 20 weeks of gestation and subsequently decreased nonlinearly with advancing gestational age among women who delivered at term. The effects of parity and maternal weight and height on the cervical length were dependent on the gestational age at ultrasound examination (interaction, *P*<.05 for all). Parous women had a longer cervix than nulliparous women, and the difference increased with advancing gestation after adjusting for maternal weight and height. Similarly, maternal weight was nonlinearly associated with a longer cervix, and the effect was greater later in gestation. The sensitivity at a 10% false-positive rate for prediction of spontaneous preterm birth at <37 weeks of gestation by a short cervix ranged from 29% to 40% throughout pregnancy, yet it increased to 50%, 50%, 53%, and 54% at 20 to 23 6/7, 24 to 27 6/7, 28 to 31 6/7, and 32 to 35 6/7 weeks of gestation, respectively, for a low, customized percentile (McNemar test, *P*<.001 for all). When a cervical length <25 mm was compared to the customized screening at 20 to 23 6/7 weeks of gestation by using a customized percentile cutoff value that ensured the same negative likelihood ratio for both screening methods, the customized approach had a significantly higher (about double) positive likelihood ratio in predicting spontaneous preterm birth at <33, <34, <35, <36, and <37 weeks of gestation. Among symptomatic women, the difference in survival between women with a customized cervical length percentile of ≥10th and those with a customized cervical length percentile of <10th was greater than the difference in survival between women with a cervical length ≥25 mm and those with a cervical length <25 mm.

CONCLUSION: Compared to the use of a cervical length <25 mm, a customized cervical length assessment (1) identifies more women at risk of spontaneous preterm birth and (2) improves the distinction between patients at risk for impending preterm birth in those who have an episode of preterm labor.

Key words: biomarkers, cerclage, customization, parity, personalized medicine, pessary, prematurity, short cervix, sonographic cervical length, spontaneous preterm labor and delivery, ultrasound, vaginal progesterone

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Introduction

Preterm birth is the leading cause of perinatal morbidity and mortality,[1–4] and it accounts for 35% of deaths among neonates globally.[5] Preterm birth has both short- and long-term health consequences, such as increased risk of neurodevelopmental impairment, respiratory and gastrointestinal complications, vision and hearing losses, cognitive and behavioral deficits, and chronic disease in adulthood.[6–8] Despite the extensive efforts to improve maternal and infant health outcomes in the United States, the rate of preterm birth has not improved during recent years,[9,10] and it remains higher relative to other developed countries.[11]

Spontaneous preterm birth (sPTB) is a syndrome caused by multiple etiologies, such as intraamniotic infection, cervical disease, decline in progesterone action, disruption of maternal-fetal tolerance, decidual senescence, uterine

AJOG at a Glance

Why was this study conducted?

This study aimed to determine whether the customization of cervical length (CL) assessment, including maternal parity, weight, height, and gestational age, improves the prediction of spontaneous preterm birth (sPTB).

Key findings

A customized standard for CL that considers adjustment for gestational age, maternal parity, weight, and height improves the prediction of sPTB.

What does this add to what is known?

Customization of sonographic CL assessment improves the prediction of sPTB.

overdistension, maternal stress, decidual hemorrhage, and vascular disease.[12,13] Known risk factors for sPTB include a history of preterm birth,[14,15] a previous late miscarriage,[16] previous cervical excisional surgery,[17,18] genetic factors,[19–24] and a transvaginal sonographic short cervix, the most powerful predictor of sPTB.[25–31]

A sonographic short cervix develops as a result of multiple processes that may include primary cervical disease, intraamniotic infection and intraamniotic inflammation, progesterone deficiency, structural damage from previous surgeries (eg, conization or loop electrosurgical excision procedure [LEEP]), or in utero exposure to diethylstilbestrol.[29,32,33] Effective screening tools, necessary to identify women at risk of sPTB, would allow improved implementation of interventions to minimize the potential impact of this adverse outcome.[34–36] Women with a sonographic short cervix benefit from treatment with vaginal progesterone, which reduces the rate of preterm birth by about 35% in this subset of patients.[37–39]

There are several limitations to the implementation of universal cervical length (CL) assessment to predict sPTB. For example, maternal characteristics, such as parity, weight, and height, have been shown to be correlated with CL[25,40–42]; however, the current definition of a short cervix uses a fixed cutoff value (CL <25 mm during the midtrimester of pregnancy) for all women.[29,39,43–45] Given that CL changes with advancing gestational age in normal pregnancy[46–49] and with previous uterine evacuation[50] and that cervical shortening is strongly associated with preterm birth,[31,51] the use of a fixed cutoff value approach may not be the optimal way to assess risk. Of note, the earlier the diagnosis with a short cervix, the shorter the interval to delivery[52] even in women who receive progesterone treatment.[53] The customization of a sonographic CL screening according to gestational age and maternal factors could improve the performance of this biomarker. Such an approach was reported for the evaluation of fetal growth[54–56] resulting in improvements over the one-size-fits-all standards.[57–59] Although it is known that the combination of CL and obstetrical history improves the prediction of sPTB,[60] there are no studies aimed at personalizing the assessment of cervical length. Therefore, this study aimed to (1) establish a customized CL standard by incorporating maternal characteristics and gestational age at screening and (2) evaluate whether the customization of CL improves the prediction of sPTB compared to the current standard of care.

Materials and Methods

This retrospective longitudinal study involved data from transvaginal sonographic assessments of the cervix in women enrolled between January 2006 and April 2017 at the Center for Advanced Obstetrical Care and Research of the Perinatology Research Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, US Department of Health and Human Services; the Department of Obstetrics and Gynecology of Wayne State University School of Medicine; and Hutzel Women's Hospital, Detroit, MI. All study participants provided written informed consent before the collection of demographic or clinical information, images, and samples. The use of demographic or clinical information, images, and samples obtained from patients for research was approved by the Human Investigation Committee of Wayne State University.

From a set of 8226 pregnancies with available CL measurements obtained during research or clinical ultrasound evaluations, 7826 pregnancies were selected on the basis of the following criteria: a singleton pregnancy, at least 1 CL measurement performed between 8 and 40 weeks of gestation, delivery after 20 weeks of gestation, and availability of relevant demographics and clinical characteristics (weight, height, age, parity) (Figure 1). The resulting longitudinal dataset included 38,293 CL measurements with a median of 4 (interquartile range [IQR], 2–8) per pregnancy. Gestational age was determined by the last menstrual period and confirmed by ultrasound examination.

Sonographic assessment of the cervix

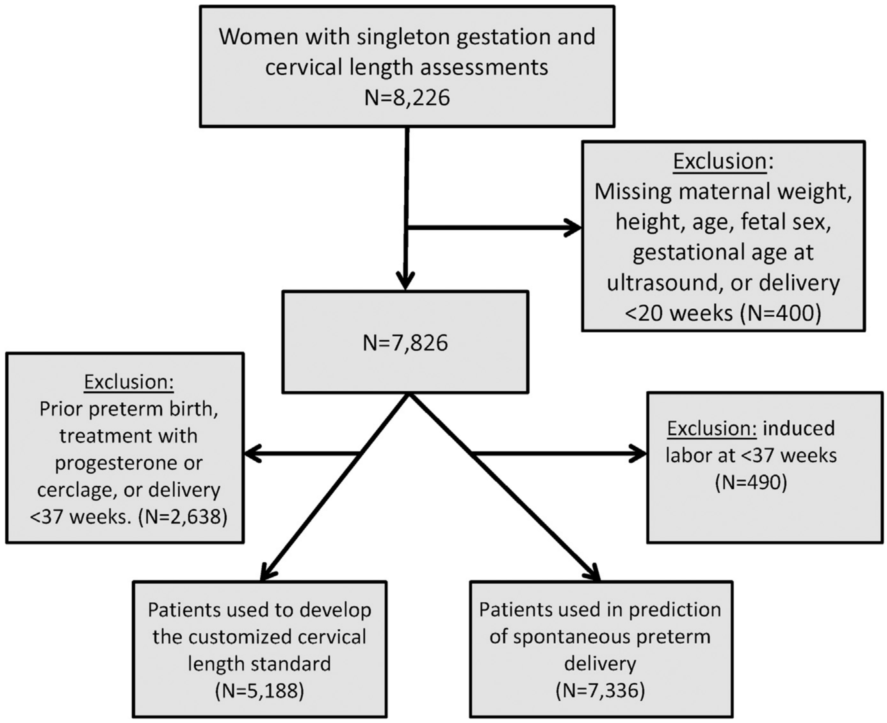
Transvaginal ultrasound examinations were performed using commercially available ultrasound systems (Acuson Sequoia, Siemens Medical Systems, Mountain View, CA; Voluson 730 Expert or Voluson E8, GE Healthcare, Milwaukee, WI) equipped with endovaginal transducers with frequency ranges of 5 to 7.5 MHz and 5 to 9 MHz, respectively. The CL was measured according to the following sonographic criteria: (1) a midsagittal plane with a clear view of the endocervical canal and of the internal and external cervical os, (2) equal size of the anterior and posterior cervical lips, and (3) an equal density of the anterior and posterior cervical lips.[29,45,61,62] Three measurements of the CL were obtained, and the shortest was recorded. All operators underwent training prior to data collection.

Statistical analysis

Building a customized cervical length standard

This analysis was performed using CL data from women who delivered at term, had no history of preterm birth, did not receive progestogen treatment (17-α-hydroxyprogesterone caproate or vaginal progesterone) or cerclage, and had no history of cervical surgery (cervical cerclage, conization [cone biopsy], or a loop electrosurgical excision procedure; N=5188) (Figure 1). Linear mixed-effects models[63] were used to fit CL measurements as a polynomial function of gestational age, and they included maternal characteristics with a significant effect on CL among these covariates: parity, weight, height, age, and race and ethnicity. Of note, these models account for eventual differences in the number of observations among subjects and for the within-subject correlation of measurements via subject-specific random effects.[63] A combination of forward selection and backward elimination was applied for model selection starting with a baseline model that allowed for interaction terms between parity and quadratic terms of weight and height with cubic polynomial terms of gestational age. To improve normality of the CL data distribution, before model fitting, data were transformed using a Box-Cox transformation specifically designed for longitudinal data analysis.[64] Maternal weight, height, and age were standardized by subtracting the mean and dividing by the standard deviation for the purpose of comparing their relative effects on CL.

FIGURE 1
Study design



The figure illustrates the patient population used to define the cervical length standard and to assess the prediction of spontaneous preterm delivery.

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Assessment of customized and noncustomized cervical length screening for the prediction of spontaneous preterm birth

From the cohort of 7826 pregnancies (Figure 1), cases with induced labor before 37 weeks of gestation were excluded from the analysis, yielding a set of 7336 pregnancies. Receiver operating characteristic (ROC) curves were constructed by using CL (noncustomized approach) or CL percentiles (customized approach) to predict sPTB on the basis of data collected in predefined windows of gestation: 20 to 23 6/7, 24 to 27 6/7, 28 to 31 6/7, and 32 to 35 6/7 weeks. Only research or clinical scans obtained before eventual diagnosis with spontaneous preterm labor or spontaneous rupture of membranes were included in this analysis. Differences in the area under the ROC curve (AUC) were assessed with a DeLong test for correlated ROC curves.[65] In addition, sensitivity at a 10% false-positive rate (FPR) was compared between methods by applying McNemar tests. Furthermore, to predict sPTB at <37 weeks of gestation, we compared the customized percentile approach (positive if <10th percentile) in terms of sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (−LR) to the CL of <25 mm or <15 mm. Moreover, we compared the +LR between a CL of <25 mm and a percentile cutoff value for the customized approach that resulted in the same −LR to predict sPTB at <33, <34, <35, <36, and <37 weeks of gestation. To assess the generalization of the findings, the customized model development and prediction performance evaluation were also conducted via 10-fold cross-validation, in which patients were randomly assigned to 10 folds with similar rates of sPTB. Subsequently, by rotation, data from 90% of the patients were used to develop the customized model, which was then applied to calculate CL percentiles and AUC for the prediction of sPTB on the remaining 10% of patients. AUC statistics were averaged over the 10 test sets.

Comparison of customized and noncustomized assessments in symptomatic patients

Survival analysis was utilized to compare the interval from scan to delivery in symptomatic women who had a negative test result to those with a positive test result on the basis of either the customized or noncustomized CL screening methods at 28 to 31 6/7 or 32

TABLE 1
Maternal and clinical characteristics of the study population

Characteristics	Study population (N=7826)	Subset included to develop the cervical length standard (N=5188)	Subset included for prediction of sPTB (N=7336)
Age, y	23 (20–28)	23 (20–27)	23 (20–28)
Weight, kg	72.6 (59.0–88.5)	72.6 (59.0–88.5)	72.6 (59.0–88.5)
Height, cm	162.6 (157.5–167.6)	162.6 (157.5–167.6)	162.6 (157.5–167.6)
BMI, kg/m^2	27.4 (22.7–33.3)	27.2 (22.6–33.1)	27.3 (22.6–33.2)
Race			
African American	7077 (90.4)	4701 (90.6)	6627 (90.3)
White	324 (4.1)	199 (3.8)	303 (4.1)
Asian	46 (0.6)	29 (0.6)	42 (0.6)
Hispanic	45 (0.6)	30 (0.6)	44 (0.6)
Other	334 (4.3)	229 (4.4)	320 (4.4)
Parity			
0	2800 (35.8)	2195 (42.3)	2591 (35.3)
1	2207 (28.2)	1518 (29.3)	2105 (28.7)
≥2	2819 (36.0)	1475 (28.4)	2640 (36.0)
History of preterm birth	1457 (18.6)	—	1327 (18.1)
Smoking	1577 (20.2)	969 (18.7)	1471 (20.1)
Drugs	2111 (27.0)	1420 (27.4)	1980 (27.0)
Alcohol	276 (3.5)	160 (3.1)	254 (3.5)
Superimposed preeclampsia	295 (3.8)	118 (2.3)	221 (3.0)
Chronic hypertension	482 (6.2)	278 (5.4)	448 (6.1)
Preeclampsia	538 (6.9)	271 (5.2)	422 (5.8)
Asthma	1455 (18.6)	931 (17.9)	1364 (18.6)
Anemia	1303 (16.6)	876 (16.9)	1214 (16.5)
Preterm birth at <37 wk	1637 (20.9)	—	1147 (15.6)
PPROM	455 (5.8)	5 (0.1)	276 (3.8)
Cervical surgeries	197 (2.5)	—	178 (2.4)
Progestogen treatment	478 (6.1)	—	432 (5.9)

Data are presented as median (interquartile range) for continuous variable and number (percentage) for categorical variables. The significance of differences between cohorts in terms of demographics is not reported because they are different by design and the 3 sets overlap.

BMI, body mass index; *sPTB*, spontaneous preterm birth; *PPROM*, preterm prelabor rupture of the membranes.

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to 35 6/7 weeks of gestation. All analyses were conducted using the R language and environment for statistical computing,[66] and a *P* value of <.05 was considered statistically significant.

Results

Patient characteristics

Among the 8226 pregnancies with available CL assessments, 7826 (95.1%) met the inclusion criteria and were considered for analysis (Figure 1). The summary of demographic characteristics is presented in Table 1 for the study cohort (n=7826), the subset of term delivery controls used to develop the customized standard (n=5188), and those included in evaluating the prediction of sPTB (n=7336). Among the study population (n=7826), women self-reported as African American (90.4%, n=7077), White (4.1%, n=324), Asian (0.6%, n=46), Hispanic (0.6%, n=45), and Other (4.3%, n=334). The rate of preterm birth at <37 weeks of gestation, spontaneous or induced, was 20.9% (n=1637), whereas the rates of sPTB at <33 and <37 weeks of gestation were 6.3% (n=498) and 14.6% (n=1147), respectively. History of preterm birth was documented in 18.6% (n=1457) of patients; 2.5% (n=197) had a previous cervical surgery; and

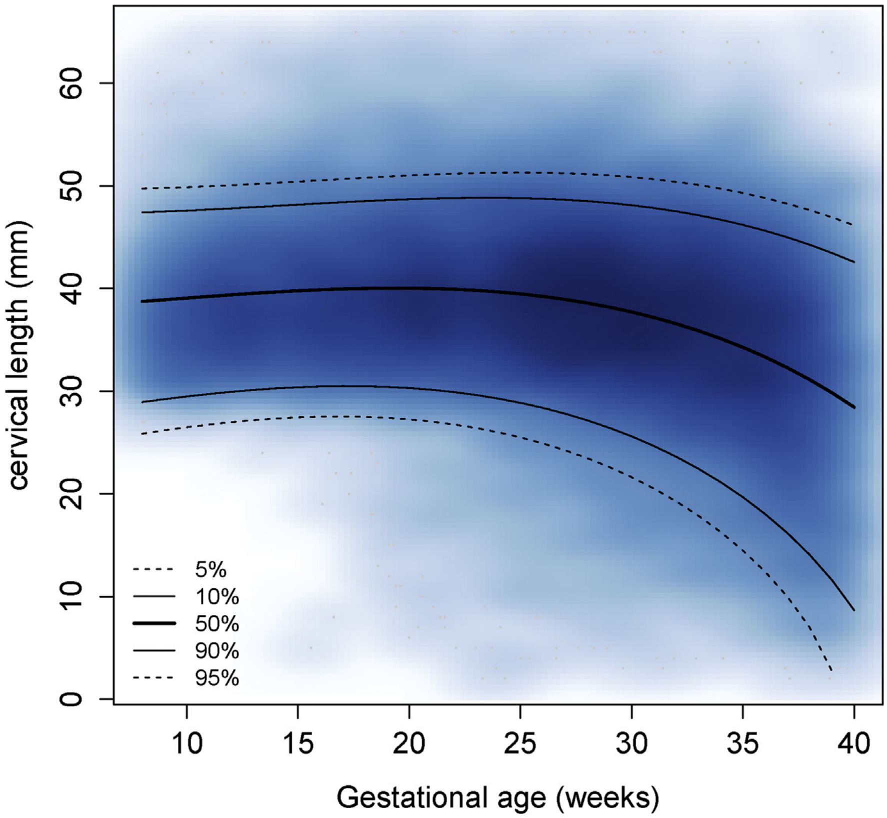
6.1% (n=478) received progesterone treatment during the current pregnancy.

A customized standard for cervical length evaluation

The interobserver correlation of the transvaginal CL was estimated on the basis of 182 instances when a clinical evaluation and a research ultrasound evaluation were conducted in the same day for the same patients. The interobserver correlation was 77%, similar to 76% reported elsewhere.[67]

Figure 2 presents the CL measurements derived from the 5188 pregnancies used to create the customized CL standard. Superimposed on these data are the 5th, 10th, 50th, 90th, and 95th percentiles as a cubic function of gestational age derived from the linear mixed-effects model (Table 2). Spline-based transformations of gestational age were also explored in the mixed-effects model fitting, as we have previously described,[68,69] and found a similar model fit with the cubic polynomials (data not shown). Of note, the 10th percentile of cervical length measurements of term delivery controls reached 25 mm at about 30 weeks of gestation. The median CL (about 39 mm) was almost unchanged between 8 and 20 weeks of gestation, yet thereafter, it decreased nonlinearly with gestational age, demonstrating a higher rate of cervical shortening when approaching term gestation. The effects of parity, maternal weight, and maternal height on the CL were dependent on the gestational age at ultrasound examination, as indicated by the significance of the interaction terms between gestational age and these covariates (interactions, $P<.05$ for all) (Figure 3; Supplemental Table). Parous women had a longer cervix, and the differences, relative to nulliparous women, increased with advancing gestation after adjusting for maternal weight and height. Similarly, maternal weight was associated with an increase in CL, and this increase was higher later in pregnancy. The nonlinear effect of maternal weight on CL suggests that the increase in CL with weight diminishes at the higher end of the maternal weight range. Finally, for the same maternal weight and parity, taller mothers had a slightly shorter cervix after 22 weeks of gestation (Figure 3, G).

FIGURE 2
Cervical length as a function of gestational age



The intensity of the *blue color* shows the density of the longitudinal measurements available for model fitting. *Lines* represent the different percentiles obtained using linear mixed-effects models.

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The estimates for the effect of maternal characteristics and gestational age on CL measurements in the population of women used to create the customized CL standard are shown in the Supplemental Table. Calculators of the customized percentiles (for 1 scan or batch analysis) were also implemented and are available from the authors' website at http://bioinformaticsprb.med.wayne.edu/software/.

Prediction of spontaneous preterm birth in asymptomatic women

Figure 4 displays a comparison of ROC curves constructed from CL or customized CL percentile data for the prediction of sPTB (<37 weeks of gestation) based on observations at 20 to 23 6/7, 24 to 27 6/7, 28 to 31 6/7, and 32 to 35 6/7 weeks of gestation in asymptomatic women. The AUC of the customized CL screening was significantly higher than that of the CL (noncustomized method) for all 4 gestational-age intervals (DeLong test, $P<.001$) (Table 3). The improvement in AUC statistics (2%−4%) was more accentuated when screening occurred later in gestation, which was expected given that the effects of covariates were higher later in gestation and that the cervix shortens at a higher rate when approaching term delivery (Table 3). AUC statistics obtained via cross-validation for the prediction of sPTB by customized CL percentiles (AUC of 0.71 at 20−23 6/7, 24−27 6/7, and 28−31 6/7 weeks of gestation and AUC of 0.69 at 32−35 6/7 weeks of gestation) were very similar to those presented in the main analysis in Table 3,

TABLE 2
Cervical length percentiles as a function of gestational age for the subset of women included in the analysis to establish the customized standard (N=5188)

Gestational age (wk)	5th percentile	10th percentile	25th percentile	50th percentile	75th percentile	90th percentile	95th percentile
8	25.9	28.9	33.8	38.7	43.4	47.4	49.7
9	26.2	29.2	34.0	38.9	43.5	47.5	49.8
10	26.5	29.5	34.2	39.1	43.7	47.6	49.9
11	26.7	29.7	34.4	39.2	43.8	47.7	50.0
12	27.0	29.9	34.6	39.4	43.9	47.8	50.1
13	27.2	30.1	34.7	39.5	44.0	47.9	50.2
14	27.3	30.3	34.9	39.7	44.2	48.0	50.3
15	27.5	30.4	35.0	39.8	44.3	48.2	50.4
16	27.5	30.5	35.1	39.9	44.4	48.3	50.5
17	27.5	30.5	35.1	40.0	44.5	48.4	50.7
18	27.5	30.5	35.2	40.0	44.6	48.5	50.8
19	27.4	30.4	35.1	40.0	44.6	48.6	50.9
20	27.3	30.3	35.1	40.0	44.7	48.7	51.0
21	27.0	30.1	35.0	40.0	44.7	48.8	51.1
22	26.8	29.9	34.8	39.9	44.7	48.8	51.2
23	26.4	29.6	34.6	39.8	44.7	48.8	51.2
24	26.0	29.3	34.4	39.7	44.6	48.8	51.3
25	25.5	28.9	34.1	39.5	44.5	48.8	51.3
26	24.9	28.4	33.7	39.2	44.4	48.7	51.3
27	24.2	27.8	33.3	38.9	44.2	48.6	51.2
28	23.5	27.2	32.8	38.6	44.0	48.5	51.1
29	22.6	26.4	32.3	38.2	43.7	48.3	51.0
30	21.6	25.6	31.6	37.7	43.3	48.1	50.9
31	20.5	24.7	30.9	37.2	43.0	47.8	50.6
32	19.3	23.6	30.1	36.6	42.5	47.5	50.4
33	17.9	22.4	29.2	35.9	42.0	47.1	50.1
34	16.3	21.1	28.2	35.1	41.4	46.7	49.7
35	14.5	19.7	27.1	34.3	40.8	46.2	49.3
36	12.4	18.0	25.8	33.3	40.0	45.6	48.8
37	10.0	16.2	24.5	32.3	39.2	45.0	48.3
38	7.0	14.1	23.0	31.1	38.3	44.3	47.6
39	2.7	11.6	21.3	29.8	37.3	43.5	46.9
40	0.0	8.7	19.4	28.4	36.2	42.6	46.2

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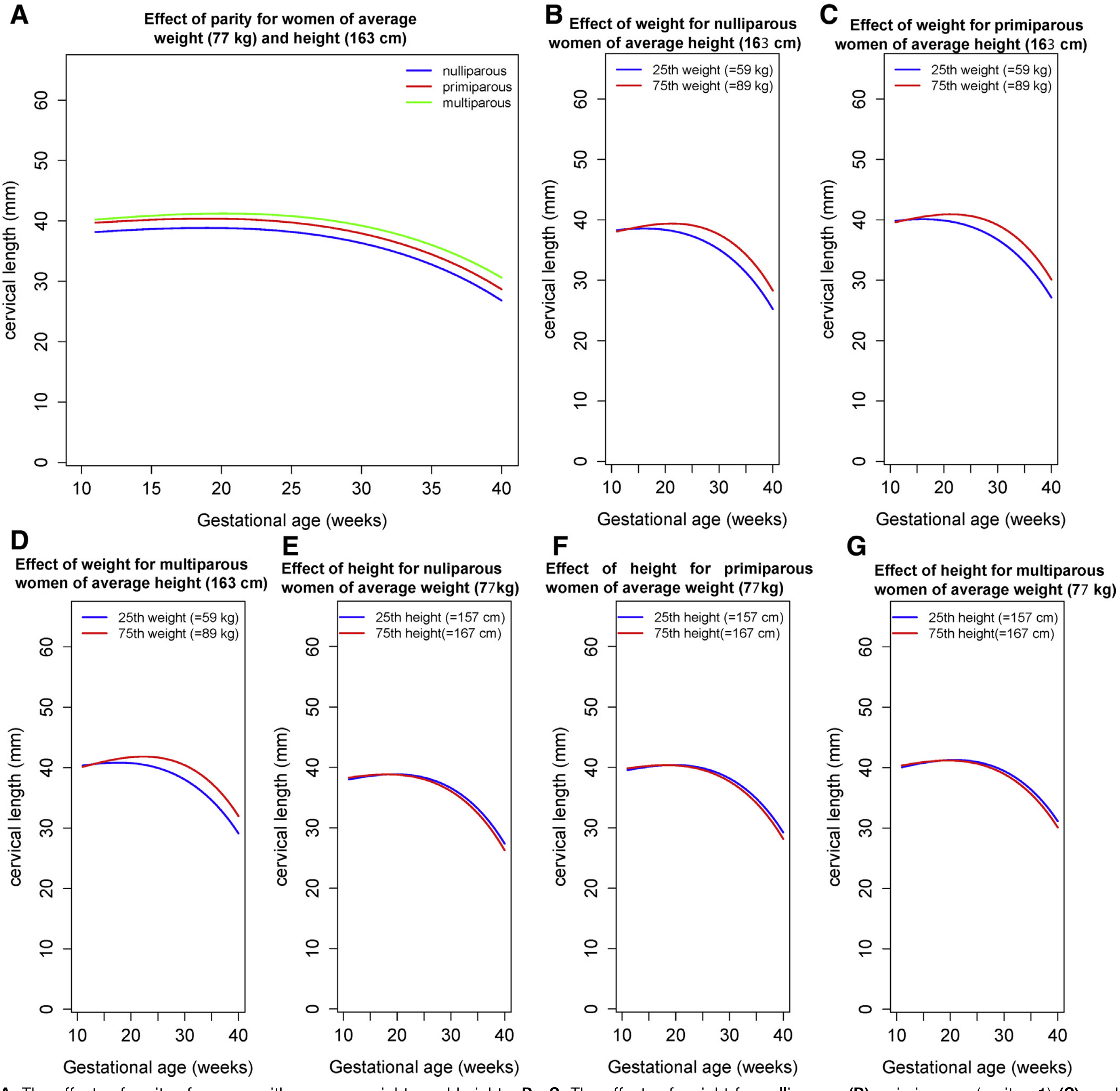
indicating that there was very limited overfitting to the current cohort.

More importantly, the sensitivity at a 10% FPR for each gestational-age interval at screening was higher for the customized approach than the noncustomized approach. Although the sensitivity (10% FPR) for the prediction of sPTB by a short cervix ranged from 29% to 40% throughout gestation, it reached 50%, 50%, 53%, and 54% at 20 to 23 6/7, 24 to 27 6/7, 28 to 31 6/7, and 32 to 35 6/7 weeks of gestation, respectively, for a low customized CL percentile (McNemar

FIGURE 3
Effects of maternal covariates on cervical length across gestation



A, The effects of parity of women with average weights and heights. **B—C,** The effects of weight for nulliparous **(B)**, primiparous (parity=1) **(C)**, and multiparous (parity≥2) **(D)** women with average heights. **E—G,** The effects of height for nulliparous **(E)**, primiparous (parity=1) **(F),** and multiparous (parity=2) **(G)** women with average weights. *Lines* represent the average (50th percentile) obtained with linear mixed-effects models.

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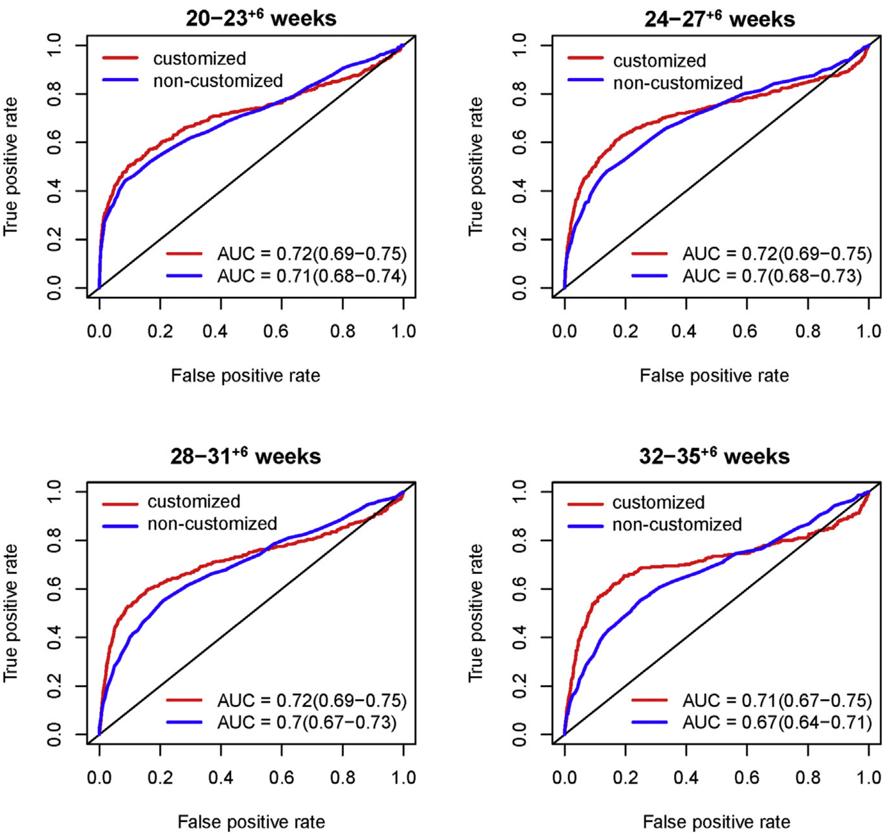
test, *P*<.001) (Table 3). Of note, to achieve the same FPR (10%), the CL cutoff varied from 18 to 28 mm, whereas the customized CL percentile cutoffs varied from the 14th percentile to the 21st percentile, depending on the gestational age at screening (Table 3).

The current CL screening practice involves a fixed CL cutoff (<15 mm or <25 mm), regardless of gestational age at screening, to predict sPTB. Table 4 presents a comparison of sensitivity and specificity of a customized percentile <10th percentile against a fixed 15 mm or 25 mm cutoff value for CL, and it reveals that the FPR of the clinical standard substantially differs among

FIGURE 4
Prediction of spontaneous preterm birth by CL (noncustomized) and customized CL percentiles



Each panel shows results for screening at a different gestational age at scan, as shown in the title of each figure. AUC statistics and sensitivity at 10% false positive rate at all gestational age intervals are significantly higher for the customized approach than the noncustomized approach (*P*<.05).

AUC, area under the ROC curve; *CI*, confidence interval; *CL*, cervical length; *ROC*, receiver operating characteristic.

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gestational-age intervals at screening. The FPR (1-specificity) of a CL of <25 mm increased from 5% at 20 to 23 6/7 weeks of gestation to 16% at 32 to 35 6/7 weeks of gestation; hence, such an approach is either too conservative or too liberal depending on the gestational age at screening. The number needed to evaluate (NNE=1/positive predicted value) also increased from 2.0 at 20 to 23 6/7 weeks of gestation to 5.6 at 32 to 35 6/7 weeks of gestation. However, screening by the customized CL percentile <10th percentile ensures a more stable FPR (about 5%−7%) and NNE (2.0−2.4) throughout the gestational-age span. Moreover, the +LR of the customized approach to predict sPTB increased from 6.9 (95% confidence interval [CI], 5.9−8.1) at 20 to 23 6/7 weeks of gestation to 8.5 (95% CI, 6.9−10.4) at 32 to 35 6/7 weeks of gestation, yet it decreased from 7.2 (95% CI, 6.0−8.7) to 2.7 (95% CI, 2.4−3.2) for the CL of <25 mm.

When the CL of <25 mm approach was compared to the customized screening approach at 20 to 23 6/7 weeks of gestation using a percentile cutoff value that ensured the same −LR for both methods, we found that the customized approach had a significantly higher +LR in predicting sPTB at <33 (12.3 vs 7.2), <34 (13.2 vs 7.2), <35 (12.1 vs 7.0), <36 (12.5 vs 7.5), and <37 (12.5 vs 7.8) weeks of gestation (*P*<.05 for all differences) (Table 5).

Analysis of time to delivery in symptomatic patients

The analyses reported thus far have focused on asymptomatic patients. We next analyzed CL in patients who experienced an episode of spontaneous preterm labor. Therefore, we considered all women diagnosed with an episode of preterm labor who had a subsequent scan at 28 to 31 6/7 weeks of gestation (n=41) or at 32 to 35 6/7 weeks (n=75) and did not deliver during the same day of the scan. The scans obtained at 28 to 31 6/7 weeks of gestation and used in this analysis were performed at a median of 4.7 weeks of gestation (IQR, 1.9−6.7) following the diagnosis of preterm labor, whereas the scans acquired at 32 to 35 6/7 weeks were performed at a median of 1.4 weeks of gestation (IQR, 0.0−2.9) after the diagnosis of preterm labor. As shown in Figure 5, the differences in survival curves (the proportion of women not yet delivered) between women with a negative test result and those with a positive test result were overall greater for the customized CL percentile <10th percentile test than for the CL of <25 mm test. Although the difference in survival (log-rank test) was significant between women with a customized CL percentile of ≥10th and those with a customized CL percentile of <10th at 28 to 31 6/7 weeks of gestation (*P*=.006) and 32 to 35 6/7 weeks of gestation (*P*<.001), they were nonsignificant (*P*=.219) or marginally so (*P*=.04) between women with a CL of ≥25 mm and those with a CL of <25 mm at the same gestational-age intervals, respectively. For example, the difference in 1 week survival of delivery from the date of the scan between symptomatic women with a negative test and those with a positive test at 32 to 35 6/7 weeks of gestation was 18% for the customized approach and only 6% for the noncustomized approach (Figure 5).

Discussion

Principal findings

(1) Sonographic CL increases with parity and maternal weight and decreases with gestational age and maternal height, provided that all other covariates remain constant; (2) the effects of maternal

TABLE 3
Comparison of AUCs and sensitivity at fixed specificity between customized and noncustomized cervical length screening

Gestational age at measurement (wk)	Number of pregnancies with a scan in this interval (% of sPTB cases)	AUC			Sensitivity at 10% FPR				
					Noncustomized		Customized		
		Noncustomized	Customized	*P* value	Cutoff (mm)	Sensitivity	Cutoff (percentile)	Sensitivity	*P* value
20–23 6/7	4169 (12.0%)	71%	72%	.001	28	40%	15	50%	<.001
24–27 6/7	4338 (11.7%)	71%	72%	<.001	25	36%	14	50%	<.001
28–31 6/7	4209 (10.7%)	70%	72%	<.001	21	33%	16	53%	<.001
32–35 6/7	3956 (7.5%)	67%	71%	<.001	18	29%	21	54%	<.001

AUC, area under the ROC curve; *FPR*, false positive rate; *ROC*, receiver operating characteristic; *sPTB*, spontaneous preterm birth.

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weight, height, and parity are more pronounced during the third trimester of pregnancy; (3) at 20 to 23 6/7 weeks of gestation to 32 to 35 6/7 weeks of gestation, the customized CL screening detects 50% to 54% of women at risk for sPTB (<37 weeks of gestation) compared to the detection rate of 29% to 40% for screening by CL based on cutoff values that ensure an FPR of 10% for both methods; (4) compared to the CL of <25 mm approach, for the same −LR, the customized cervical screening at 20 to 23 6/7 weeks of gestation resulted in almost a doubling of the +LR for sPTB at <33, <34, <35, <36, and <37 weeks of gestation; and (5) for women already diagnosed with an episode of preterm labor, the difference in survival curves between those with a negative test result and those with a positive test result at 28 to 31 6/7 weeks of gestation or at 32 to 35 6/7 weeks of gestation was greater for the customized CL percentile of <10th test compared to the CL of <25 mm test; and (6) we provide a calculator for the customized assessment of CL in clinical practice.

Our findings in the context of what is already known

Our findings about the relationship between sonographic CL and maternal characteristics are in agreement with those reported in other studies.[25,40,41,70] The data support using customization of CL to account for these sources of variability. Rosenbloom et al[25] found differences in the predictive performance of CL for sPTB between nulliparous and multiparous women. Palatnik et al[71] reported the effect of maternal characteristics on the CL in 18,100 pregnant women at 18 to 24 weeks of gestation. They found that an increased maternal body mass index had a positive effect on CL[71] and similar observations were reported by Venkatesh et al.[72] In a study performed in the Netherlands[40] in a group of low-risk women, maternal factors were evaluated for their impact on CL during the midtrimester. The authors reported that maternal weight, parity, and Caucasian ethnicity were associated with a longer CL, but there was no association between CL and gestational age or maternal height. These observations are in line with the findings herein that show a systematic effect of parity throughout gestation and a positive effect of weight and parity starting with the second trimester of pregnancy. Our study, however, is unique, given the longitudinal design that allowed the assessment of how the effects of maternal characteristics on CL become modified with advancing gestation. Although reference ranges for CL that account for gestational age have been previously reported,[46–48] these studies did not take into account differences in maternal characteristics. Moreover, the current findings demonstrate that the predictive accuracy for sPTB increases with advancing gestational age at CL evaluation (50% sensitivity at 20–23 6/7 weeks of gestation vs 54% at 32–35 6/7 weeks of gestation; FPR=10%). Our results are consistent with those of Hassan et al[31] who reported that cervical ultrasound performed later in gestation predicts sPTB better than when performed earlier in gestation.

Clinical implications

Andersen et al[62] performed one of the first studies to evaluate the relationship between a sonographic short cervix and the risk of preterm birth. The authors reported that a CL of <39 mm was associated with a 25% risk of preterm birth. Iams et al[45] evaluated the cervix with transvaginal ultrasound at 24 and 28 weeks of gestation in 2915 patients and reported an exponential increase in the relative risk of preterm birth as the CL shortened. This association between cervical shortening and preterm birth has been further confirmed by other investigators in both low-risk[31,73–81] and high-risk[82–87] asymptomatic patients.

Our group evaluated 6877 women between 14 and 24 weeks of gestation and reported an odds ratio (OR) of 13.4 (95% CI, 8.8–20.6) for preterm birth with a CL of ≤25 mm and an OR of 24.3 (95% CI, 12.9–45.9) for a CL of ≤15 mm at ≤32 weeks of gestation. Here, 47.6% of patients with a CL of ≤15 mm underwent sPTB at ≤32

TABLE 4
Prediction of spontaneous preterm birth (<37 weeks of gestation) by customized CL percentile and CL

Gestational age at measurement	Screening method	Sensitivity	Specificity	+LR	−LR	PPV	NNE
20−23 6/7	CL<15 mm	0.24 (0.20−0.28)	0.99 (0.98−0.99)	17.40 (12.70−23.80)	0.77 (0.73−0.81)	0.70 (0.63−0.77)	1.40
	CL<25 mm	0.35 (0.31−0.40)	0.95 (0.94−0.96)	7.20 (60−8.70)	0.68 (0.64−0.73)	0.50 (0.44−0.55)	2.00
	Customized CL of <10th percentile	0.45 (0.41−0.50)	0.93 (0.93−0.94)	6.90 (5.90−8.10)	0.59 (0.54−0.64)	0.49 (0.44−0.53)	2.00
24−27 6/7	CL<15 mm	0.20 (0.16−0.24)	0.98 (0.97−0.98)	8.50 (6.50−11.10)	0.82 (0.79−0.86)	0.53 (0.4−0.6)	1.90
	CL<25 mm	0.36 (0.31−0.40)	0.92 (0.91−0.93)	4.60 (3.90−5.40)	0.70 (0.65−0.75)	0.38 (0.33−0.42)	2.60
	Customized CL of <10th percentile	0.46 (0.42−0.51)	0.93 (0.92−0.93)	6.20 (5.30−7.20)	0.58 (0.54−0.63)	0.45 (0.41−0.49)	2.20
28−31 6/7	CL<15 mm	0.21 (0.17−0.25)	0.97 (0.96−0.97)	6.80 (5.30−8.70)	0.81 (0.78−0.85)	0.45 (0.38−0.52)	2.20
	CL<25 mm	0.42 (0.37−0.46)	0.89 (0.88−0.90)	3.70 (3.20−4.30)	0.66 (0.61−0.71)	0.31 (0.27−0.35)	3.20
	Customized CL of <10th percentile	0.45 (0.41−0.50)	0.94 (0.94−0.95)	8.00 (6.80−9.40)	0.58 (0.53−0.63)	0.49 (0.44−0.54)	2.00
32−35 6/7	CL<15 mm	0.19 (0.15−0.24)	0.96 (0.95−0.96)	4.50 (3.40−6.00)	0.84 (0.80−0.89)	0.27 (0.21−0.33)	3.70
	CL<25 mm	0.45 (0.39−0.51)	0.84 (0.82−0.85)	2.70 (2.40−3.20)	0.66 (0.59−0.73)	0.18 (0.15−0.21)	5.60
	Customized CL of <10th percentile	0.39 (0.33−0.44)	0.95 (0.95−0.96)	8.50 (6.90−10.40)	0.64 (0.59−0.70)	0.41 (0.35−0.47)	2.40

CL, cervical length; *−LR*, negative likelihood ratio; *+LR*, positive likelihood ratio; *NNE*, number needed to evaluate (1/PPV); *PPV*, positive predictive value.
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weeks of gestation.[31] Heath et al[75] reported that a CL of ≤15 mm at 23 weeks of gestation was observed in 58% of women who delivered at ≤32 weeks of gestation and in 86% of women who delivered at ≤28 weeks of gestation.

Although studies that evaluated the prediction of a short cervix for sPTB are difficult to compare directly given the differences in study design (ie, gestational age at CL measurement and outcomes), there is consistency in the inverse relationship between CL and risk of sPTB. The high positive predictive value of a short cervix (nearly 50% for sPTB at <32 weeks of gestation with a CL of ≤15 mm) has justified trials of intervention (progesterone,[39,88,89] cerclage,[43,90] and pessary[91,92]) to prevent prematurity.

The current study demonstrates for the first time that customized CL screening at 20 to 23 6/7 weeks of gestation identifies more women at risk of sPTB who can benefit from a therapeutic intervention. For the same −LR (0.68), the customized approach had a +LR of 12.3 (95% CI, 9.8−15.5) compared to a +LR of 7.2 (95% CI, 6.0−8.7) for the CL of <25 mm approach in predicting sPTB at <37 weeks of gestation. This finding is of clinical importance because women identified at this gestational age can benefit from vaginal progesterone treatment and thus reduce the incidence of sPTB.[29,37−39] Moreover, among patients with an episode of preterm labor (referred to as symptomatic patients), a shorter CL during the third trimester of pregnancy is associated with earlier delivery,[93] and knowledge of the CL improves patient outcomes.[94,95] Here, we show that improved prediction of an imminent delivery in symptomatic patients can be achieved by the customization of CL assessment. Therefore, the customized approach proposed herein also has value for patient management, such as the administration of antenatal corticosteroids.[96,97]

Of note, although the use of a fixed cutoff value (25 mm) to define a short cervix is convenient, the customized approach described herein can also be easily applied by using the calculator we

TABLE 5
Prediction of sPTB by customized CL percentile and CL based on measurements at 20 to 23 6/7 weeks of gestation

Gestational age at spontaneous preterm birth	Screening method	+LR	−LR
<37 wk	CL<25	7.20 (6.00−8.70)	0.68 (0.64−0.73)
	Customized CL of <Pth percentile (*P*=2.0)	12.30 (9.80−15.50)	0.68 (0.64−0.73)
	Customized CL of <10th percentile	6.90 (5.90−8.10)	0.59 (0.54−0.64)
<36 wk	CL<25	7.20 (6.20−8.30)	0.56 (0.52−0.61)
	Customized CL of <Pth percentile (*P*=1.8)	13.20 (10.90−16.00)	0.58 (0.54−0.62)
	Customized CL of <10th percentile	6.80 (6.00−7.70)	0.47 (0.43−0.52)
<35 wk	CL<25	7.00 (6.00−8.10)	0.54 (0.49−0.59)
	Customized CL <Pth percentile(*P*=1.8)	12.10 (10.10−14.50)	0.55 (0.51−0.61)
	Customized CL of <10th percentile	6.60 (5.80−7.40)	0.45 (0.40−0.50)
<34 wk	CL<25	7.50 (6.60−8.70)	0.49 (0.44−0.55)
	Customized CL of <Pth percentile (*P*=1.9)	12.50 (10.50−14.80)	0.50 (0.45−0.55)
	Customized CL of <10th percentile	6.80 (6.00−7.60)	0.41 (0.36−0.46)
<33 wk	CL<25	7.80 (6.80−8.90)	0.44 (0.39−0.50)
	Customized CL of <Pth percentile (*P*=2.0)	12.50 (10.60−14.70)	0.45 (0.39−0.51)
	Customized CL of <10th percentile	6.90 (6.20−7.80)	0.36 (0.31−0.42)

Pth percentile was set to match the −LR for the 25 mm cutoff.

CL, cervical length; *−LR*, negative likelihood ratio; *+LR*, positive likelihood ratio.

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have provided and could be integrated within the software operating the ultrasound scanners. Regarding the option of the customized percentile cutoff for screening in asymptomatic women, 1 option would be to use the cutoffs shown in Table 3 that give an FPR of 10% throughout gestation and detect 50% to 54% of the cases. This approach could be suitable while screening at 20 to 24 weeks of gestation when women found at risk could benefit from progesterone treatment; hence, the control of false positives is not of major concern. Alternatively, the use of a customized CL percentile <10th percentile would provide a lower FPR (5%−7%) similar to the one of a CL of <25 mm, yet, in this case, the sensitivity would be somewhat lower but still superior to the use of a CL of <25 mm (Table 4).

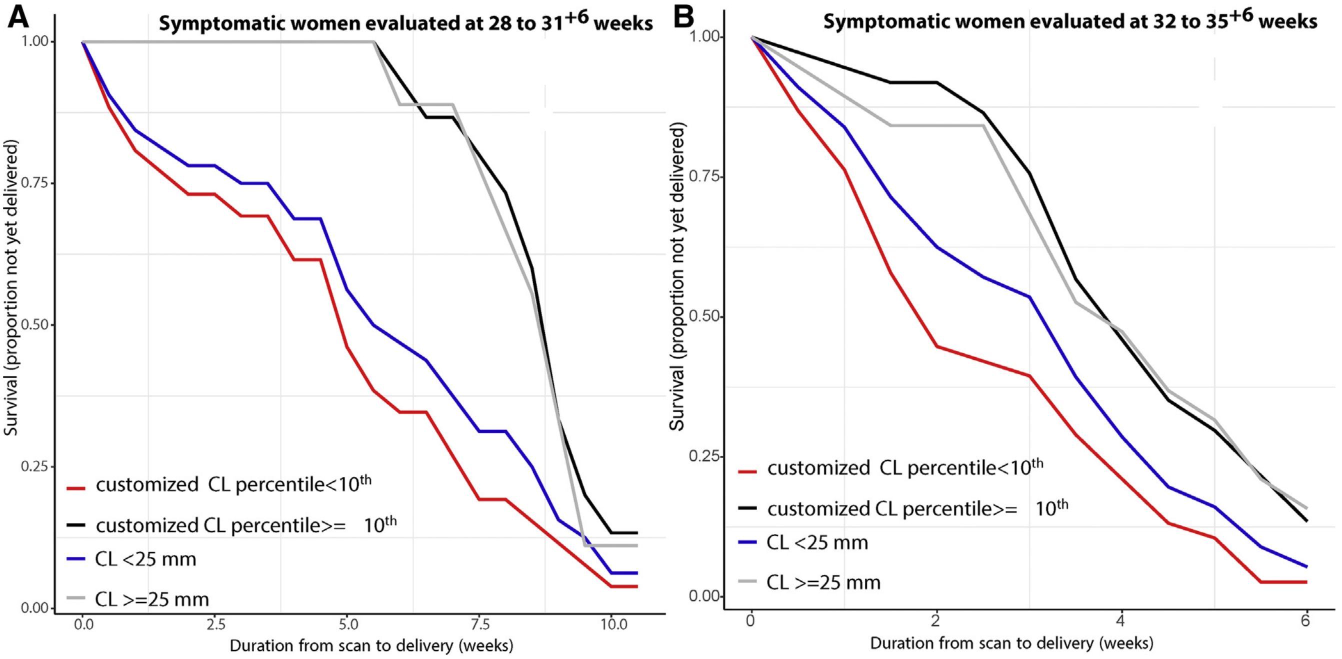
Research implications

The current results open several lines of investigation, for example, an assessment of the applicability of these findings to twin pregnancies. Moreover, a significant reduction in the rate of sPTB at <33 weeks of gestation has been demonstrated in asymptomatic patients with a CL of <25 mm[39] after treatment with vaginal progesterone; therefore, further studies are necessary to determine whether the additional patients identified as at-risk by the customized CL assessment, relative to the clinical standard, could also benefit from progesterone treatment.

Study limitations

Although CL differences were previously reported among ethnic groups even after adjusting for maternal weight, height, and parity,[40] this study did not detect such differences, likely because of the low frequency of ethnic groups other than African American. Moreover, although the standard was derived on the basis of data collected mostly from African-American patients, we concluded that the prediction performance of the customized approach likely generalizes to other ethnic groups as well, based on the sensitivity analysis (Supplemental Figure). We consider the risk of overfitting to the current cohort as being low given the reduced number of variables used for customization, variables previously associated with CL in multiple studies. The simplicity of the customization model in terms of the number of coefficients relative to the number of patients was also key to preventing overfitting. The internal generalization of the approach was proven by the use of cross-validation that yielded prediction performance estimates very similar to those reported in the primary analysis, hence, indicating a lack of overfitting. However, further studies are warranted to assess the applicability of our customized CL screening to other populations. Although we have also demonstrated that a customized CL of <10th percentile is a more effective predictor of early delivery than a CL of <25 mm in women already diagnosed with an episode of preterm labor, possible limitations in assessing the clinical significance of this finding must

FIGURE 5
Survival analysis for patients with spontaneous preterm labor



The figures show the percentage of patients with an episode of preterm labor who had not yet delivered as a function of the time from the sonographic CL evaluation. The average survival to delivery was lower for women with a customized CL percentile <10th percentile than for those with a CL of <25 mm (median [interquartile range], 0.42 [0.19—0.72] vs 0.53 [0.31—0.77], $P<.001$, and 0.39 [0.13—0.58] vs 0.54 [0.2—0.71], $P=.003$) for measurements in symptomatic women at 28 to 31 6/7 weeks of gestation **(A)** and 32 to 35 6/7 weeks of gestation **(B)**, respectively.

CL, cervical length.

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be considered: (1) not all women who delivered preterm had scans collected after presentation of an episode of preterm labor and (2) for some of the women, the CL scans were obtained several weeks after the diagnosis of preterm labor.

Conclusion

Customized CL screening identifies more pregnant women at risk for sPTB who could benefit from treatment, thus reducing the impact of prematurity. ■

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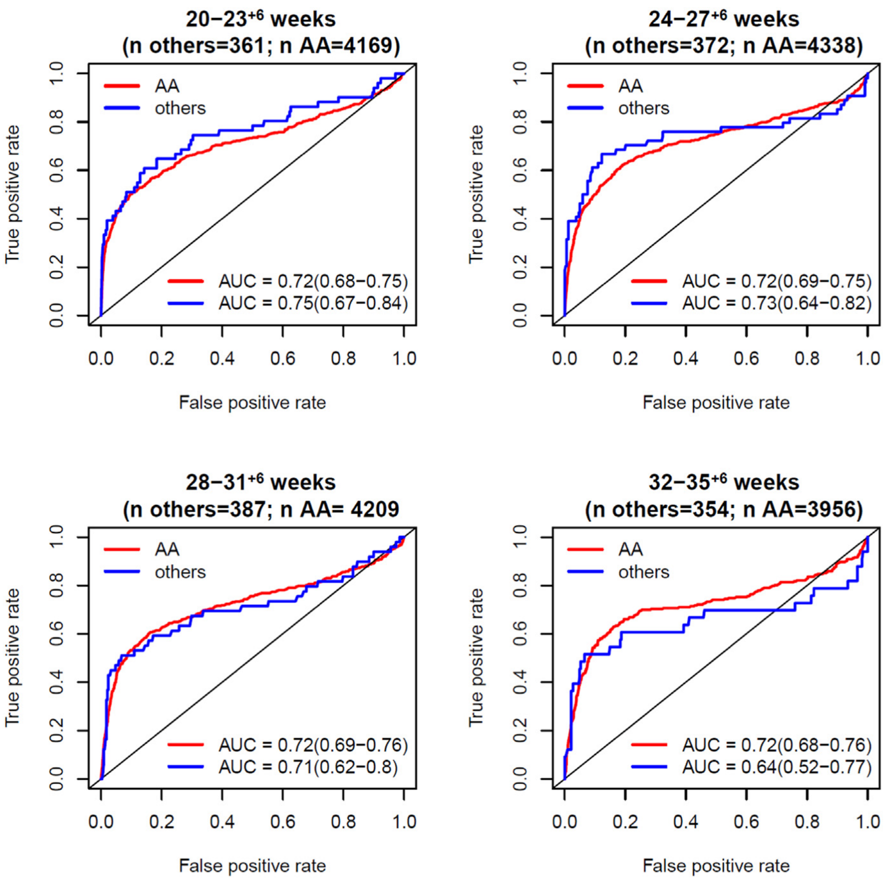
SUPPLEMENTAL FIGURE

Sensitivity analysis for prediction of spontaneous preterm birth by ethnic groups



The customized CL standard was derived from a cohort that included 90% of women self-identified as African American (AA). The prediction performance for spontaneous preterm birth at <37 weeks of gestation based on a low customized CL percentile was evaluated separately for the AA women (*red*) and all other ethnic groups (*blue*) separately. No significant difference in AUC statistics were observed (DeLong test *P*>.05) for all gestational age intervals at screening.

AUC, area under the receiver operating characteristic curve; *CL*, cervical length.

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SUPPLEMENTAL TABLE
Customized cervical length standard coefficients

Coefficients	Estimate	Standard error	*P* value
(Intercept)	25.592	0.176	<.001
t	−1.560	0.054	<.001
t^2	−0.474	0.014	<.001
t^3	−0.033	0.004	<.001
Weight	1.671	0.137	<.001
$Weight^2$	−0.160	0.071	.024
Height	−0.307	0.105	.001
Parity=1	1.631	0.238	<.001
Parity≥2	2.886	0.244	<.001
Weight×t	0.362	0.045	<.001
$Weight \times t^2$	−0.061	0.014	<.001
$Weight \times t^3$	−0.011	0.004	.013
$Weight^2 \times t$	−0.061	0.019	.001
Height×t	−0.125	0.028	<.001
(Parity=1)×t	0.005	0.062	.942
(Parity≥2)×t	0.172	0.065	.008

t=(GA−28)/4, where GA is considered in weeks. Weight=(actual weight[kg]−77)/22.5. Height=(actual height[cm]−163)/7.2. The corresponding variance of the predicted value obtained from the model above is given by $Var=69.623+10.310 \times t+1.457 \times t^2$. Note that the centering and scaling of weight and height are based on the mean and standard deviation, whereas Table 1 shows medians and interquartile ranges.

GA, gestational age.

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