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First-Trimester Screening for Spontaneous Preterm Delivery with Maternal Characteristics and Cervical Length

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Key Words
First-trimester screening · Preterm delivery · Cervical length · Pyramid of pregnancy care

Abstract
Objective: It was the aim of this study to examine the potential value of cervical length at 11–13 weeks' gestation in the prediction of spontaneous preterm delivery. ***Methods:*** This was a screening study for spontaneous preterm delivery in singleton pregnancies from cervical length measured by transvaginal ultrasound at 11–13 weeks' gestation. The performance of screening for preterm delivery by cervical length alone and with maternal characteristics was estimated. ***Results:*** In the 9,974 pregnancies included in the study, spontaneous delivery before 34 weeks occurred in 104 (1.0%) cases. Multivariate regression analysis in the term delivery group demonstrated that for the $\log_{10}$ cervical length, significant independent contributions were provided by fetal crown-rump length, maternal height, age, racial origin and parity. The median cervical length multiple of the median (MoM), corrected for maternal characteristics, was significantly lower in the preterm (0.892 MoM, 95% CI 0.829–0.945) than in the term delivery group (0.994 MoM, 95% CI 0.919–1.082; $p < 0.0001$). In screening by a combination of maternal characteristics and cervical length, the estimated detection rate of preterm delivery was 54.8% (95% CI 44.7–64.6), at a false-positive rate of 10%. ***Conclusions:*** Effective first-trimester screening for spontaneous early preterm delivery can be provided by a combination of maternal characteristics and cervical length.

Introduction

Preterm birth is the main cause of neonatal death and neurological handicap in children [1–3]. Consequently, prediction and prevention of this complication is a major challenge in pregnancy care. Whilst all births before 37 weeks' gestation are defined as preterm, the vast majority of mortality and morbidity relates to early delivery before 34 weeks.

The risk of spontaneous preterm birth is inversely related to the cervical length measured by transvaginal sonography at 20–24 weeks' gestation [4–7]. In women with a short cervix, administration of progesterone reduces the risk of spontaneous early preterm delivery by about 45% [8, 9]. However, progesterone is not as effective in women with cervical length <10 mm as in those with a length of 10–20 mm. Consequently, it may be preferable to measure cervical length in earlier pregnancy before the critical length of 10 mm is reached. Several studies reported that measurement of cervical length in the first

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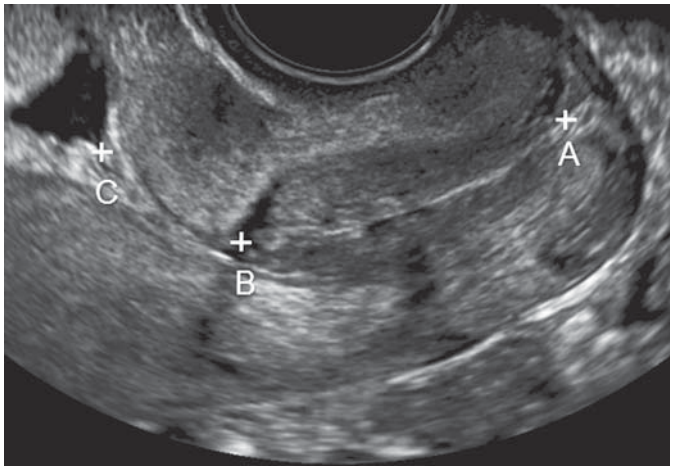

Fig. 1. Ultrasound picture illustrating the measurement of the length of the cervix (A to B) and the isthmus (B to C).

trimester is not predictive of preterm delivery [10–14]. However, in these studies, the mean or median cervical length was 40–44 mm, which is considerably longer than in the second trimester suggesting that in the measurement of cervical length, sonographers may have inadvertently included the uterine isthmus. In a study of 1,508 singleton pregnancies, we reported that the median lengths of the cervix and the cervico-isthmic complex at 11–13 weeks were 32 and 45 mm, respectively [15]. In the 16 (1.1%) cases that subsequently delivered spontaneously before 34 weeks, the median cervical length (28 mm) was shorter [15].

The aim of this screening study is to examine the potential value of cervical length at 11–13 weeks' gestation in the prediction of spontaneous preterm delivery.

Methods

This was a prospective screening study for spontaneous preterm delivery in pregnant women attending their routine first hospital visit at King's College Hospital, University College London Hospital and Medway Maritime Hospital Gillingham. At this visit, which is held at 11^{+0}–13^{+6} weeks' gestation, we recorded maternal characteristics and medical history and performed transabdominal and transvaginal sonography to firstly determine gestational age from the measurement of the fetal crown-rump length (CRL), secondly, diagnose any major fetal abnormalities, thirdly, measure fetal nuchal translucency thickness as part of screening for aneuploidies, and fourthly, measure endocervical length [15–19]. The policy was to refer women with a cervical length <15 mm to a specialist high-risk for preterm delivery clinic. However, in this study, none of the patients had such a short cervix. All women were offered another scan at 20–24 weeks' gestation for the diagnosis of fetal abnormalities, assessment of fetal growth and transvaginal measurement of cervical length, and if the length was <15 mm, the women were treated by cervical cerclage or vaginal progesterone.

Measurement of Endocervical Length

The measurement of endocervical length by transvaginal sonography was performed as previously described [15]. First, the women were asked to empty their bladder and were placed in the dorsal lithotomy position. Second, the vaginal transducer (2.7–9.3 MHz) was introduced in the anterior fornix of the vagina and adjusted to obtain a sagittal view of the entire length of the cervical canal, which may be either translucent or echodense. The canal is bordered by the endocervical mucosa, which is usually of decreased but occasionally of increased echogenicity compared to the surrounding tissues. Third, the probe was withdrawn until the image was blurred and then advanced gently until the image was restored without exerting undue pressure on the cervix. Fourth, the settings of the ultrasound machine were altered to obtain the widest viewing angle and the magnification was increased so that most of the screen was occupied by the tissues between the external cervical os at one end of the picture and the gestational sac at the other end. Fifth, callipers were used to measure in sequence the linear distance between the two ends of the glandular area around the endocervical canal (fig. 1). All the operators performing the scans had received extensive training and had all passed a practical examination administered by an expert to demonstrate their competence in the technique.

Outcome Measures

The outcome measures were spontaneous preterm delivery before 34 weeks (early preterm) and at 34^{+0}–36^{+6} weeks (late preterm). Data on pregnancy outcome were obtained from the maternity computerized records or the general medical practitioners of the women and were also recorded in our database. The obstetric records of all patients delivering before 37 weeks (<259 days) were examined to determine whether the preterm delivery was medically indicated or spontaneous. The latter included those with spontaneous onset of labour and those with preterm prelabour rupture of membranes.

Statistical Analysis

Descriptive data were presented as medians and interquartile ranges for continuous variables and as numbers and percentages for categorical variables. Comparison between the outcome groups was done by χ^2 or Fisher's exact test for categorical variables and by the Mann-Whitney U test for continuous variables.

The distribution of cervical length was logarithmically transformed to obtain a symmetric distribution of residuals with approximately constant standard deviation. This was assessed by inspecting histograms and probability plots. Multivariate regression analysis was used to determine which of the factors among the maternal characteristics, obstetric history and gestation were significant predictors of $\log_{10}$ cervical length in the term delivery group. The distribution of $\log_{10}$ cervical length, expressed as multiple of the median (MoM) of the term delivery group, was determined in the early and late spontaneous preterm delivery groups. Comparison of cervical length MoM between outcome groups was done by the Mann-Whitney U test, with post-hoc Bonferroni correction. The a priori risk for early spontaneous preterm deliv-

Table 1. Maternal characteristics in the three outcome groups

Maternal variables	Delivery >37 weeks (n = 9,657)	Spontaneous delivery	
		<34 weeks (n = 104)	34–36 weeks (n = 213)
Maternal age, years	31.9 [28.0–35.4]	31.4 [27.4–35.5]	30.6 [26.6–34.2]*
Maternal weight, kg	64.6 [58.0–74.1]	65.3 [57.3–78.1]	62.7 [56.5–72.7]
Maternal height, cm	164 [160–169]	163 [158–167]	164 [159–168]
Racial origin			
Caucasian	7,214 (74.7)	58 (55.8)*	138 (64.8)*
African	1,179 (12.2)	30 (28.8)*	30 (14.1)
South Asian	639 (6.6)	8 (7.7)	22 (10.3)
East Asian	392 (4.1)	4 (3.8)	11 (5.2)
Mixed	233 (2.4)	4 (3.8)	12 (5.6)*
Cigarette smoker	597 (6.2)	8 (7.7)	20 (9.4)
Assisted conception	437 (4.5)	8 (7.7)	9 (4.2)
Obstetric history			
No delivery at or beyond 16 weeks	5,313 (55.0)	51 (49.0)	123 (57.7)
Delivery at 16–30 weeks (1 event)	95 (1.0)	6 (5.8)*	4 (1.9)
Delivery at 16–30 weeks (2 events)	0	4 (3.8)*	0
Delivery at 16–30 weeks (1 event) plus ≥37 weeks	7 (0.1)	3 (2.9)*	0
Delivery at 31–36 weeks	118 (1.2)	14 (13.5)*	14 (6.6)*
Delivery at 31–36 weeks plus ≥37 weeks	17 (0.2)	3 (2.9)*	1 (0.5)
Delivery at ≥37 weeks	4,107 (42.5)	23 (22.1)*	71 (33.3)*

Data are medians with interquartile ranges in brackets, or number of patients with percentages in parentheses. Comparison between the outcome groups was done by χ^2 or Fisher's exact test for categorical variables and by Mann-Whitney U test for continuous variables. * $p < 0.0167$, post-hoc Bonferroni correction.

ery based on maternal characteristics and obstetric history was determined as previously described [20]. Likelihood ratios were computed from the fitted distributions of $\log_{10}$ MoM values in the term delivery group and in each of the two preterm delivery groups. The a posteriori risks for early and late spontaneous preterm delivery were derived by multiplying the a priori risk with the likelihood ratio. The performance of screening was determined by the area under the receiver operating characteristic curve (AUROC) [21].

The statistical software package SPSS 18.0 (SPSS Inc., Chicago, Ill., USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.

Results

We prospectively examined 10,870 singleton pregnancies between July 2009 and March 2011. We excluded 896 (8.2%) because they had missing outcome data (n = 423), the pregnancies resulted in miscarriage before 24 weeks' gestation (n = 91) or termination (n = 105), because there was iatrogenic delivery at 24–33 weeks (n = 192) or the women had either cervical cerclage (n = 37) or vaginal progesterone (n = 48). In the remaining 9,974 pregnancies included in the study, spontaneous preterm delivery before 34 weeks occurred in 104 (1.0%) cases and delivery between 34 and 36 completed weeks in 213 (2.1%) cases. The maternal characteristics of each of the outcome groups are compared in table 1.

Multivariate regression analysis in the term delivery group demonstrated that for the $\log_{10}$ cervical length significant independent contributions were provided by fetal CRL, maternal height, age, racial origin and parity ($R^2 = 0.018$; table 2). The median cervical length MoM was significantly lower in both the early ($p < 0.0001$) and late ($p = 0.009$) spontaneous preterm delivery groups than in the term delivery group (table 3).

In the term delivery group, African women had shorter cervical length than Caucasian women (table 3) but cervical length MoM was not significantly different between the two racial groups ($p = 0.628$; fig. 2). Similarly, in the early and late preterm delivery groups, the median cervical length MoM was not significantly different between African and Caucasian women ($p = 0.264$ and 0.966, respectively; fig. 2).

Table 2. Multivariate regression analysis for the prediction of log_{10} cervical length in the term delivery group

Independent variable	Coefficient	Standard error	p
Intercept	1.360143	0.017832	<0.0001*
Fetal CRL	0.000222	0.000066	0.0008*
Maternal height	0.000480	0.000078	<0.0001*
Maternal age	0.002926	0.000800	0.0003*
(Maternal age)^2	–0.000036	0.000013	0.0047*
Racial origin			
Caucasian	0		
African	–0.004102	0.001591	0.0099*
South Asian	–0.008513	0.002117	0.0001*
East Asian	–0.004224	0.002651	0.1112
Mixed	–0.001738	0.003349	0.6038
Cigarette smoking	0.002660	0.002195	0.2256
Assisted conception	0.000432	0.002902	0.8816
Obstetric history			
No delivery at or beyond 16 weeks	0		
Delivery at 16–30 weeks (1 event)	–0.005124	0.005220	0.3263
Delivery at 16–30 weeks (1 event) plus ≥37 weeks	–0.036067	0.018994	0.0576
Delivery at 31–36 weeks	0.002786	0.004678	0.5515
Delivery at 31–36 weeks plus ≥37 weeks	–0.021189	0.012219	0.0829
Delivery at ≥37 weeks	0.003595	0.001059	0.0007*

* $p < 0.05$.

Table 3. The median and interquartile range of cervical length in the three outcome groups

	Number	Term delivery	Spontaneous delivery			
			n	<34 weeks	n	34–36 weeks
Cervical length, mm						
Total	9,657	32 (30–35)	104	29 (26–30)*	213	31 (29–34)*
Caucasian	7,214	32 (30–35)	58	29 (27–31)*	139	31 (29–34)*
African	1,179	31 (29–35)**	30	27 (25–30)*	30	31 (28–34)
Cervical length, MoM						
Total	9,657	0.994 (0.919–1.082)	104	0.892 (0.829–0.945)*	213	0.977 (0.892–1.059)*
Caucasian	7,214	0.995 (0.921–1.081)	58	0.894 (0.832–0.984)*	139	0.967 (0.890–1.057)
African	1,179	0.992 (0.911–1.087)	30	0.863 (0.769–0.944)*	30	0.962 (0.884–1.066)

Comparison between the outcome groups was done by the Mann-Whitney U test. * $p < 0.0167$, post-hoc Bonferroni correction. Comparison between Caucasian and African racial groups in each outcome group was done by the Mann-Whitney U test. ** $p < 0.05$.

The frequency distributions of cervical length MoM in the term delivery group and early spontaneous preterm delivery group are presented in figure 3. The overlapping Gaussian distributions of log_{10} cervical length MoM in the term delivery group and each of the spontaneous preterm delivery groups were used to calculate the likelihood ratios for preterm delivery (fig. 4, table 4).

The a priori risk for early spontaneous preterm delivery based on maternal characteristics and obstetric history was determined as previously described [20], and using this model, the expected number of early spontaneous preterm delivery was 101 cases (95% prediction interval 83–123), which is similar to the observed number of 104 cases. The a posteriori risks for spontaneous pre-

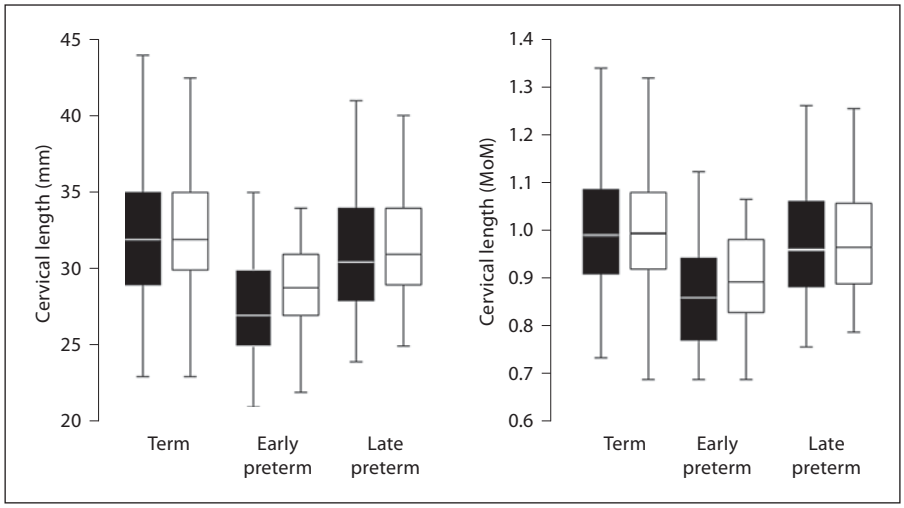

Fig. 2. Box-whisker plot of cervical length and its MoM values of Caucasian (□) and African (■) women in the three outcome groups.

term delivery were derived by multiplying the a priori risk by the likelihood ratio for cervical length.

The AUROC and the detection rates of early and late spontaneous preterm delivery for false-positive rates of 5 and 10% in screening by maternal characteristics, cervical length and their combination are given in figure 5 and table 5. In the prediction of early spontaneous preterm delivery, the AUROC was significantly improved to 0.840 (95% CI 0.833–0.847) when maternal characteristics (0.714, 95% CI 0.705–0.723) were combined with cervical length (0.782, 95% CI 0.774–0.790; $p < 0.0001$). In the prediction of late spontaneous preterm delivery, the AUROC was significantly improved to 0.583 (95% CI 0.573–0.593) when maternal characteristics (0.563, 95% CI 0.553–0.573) were combined with cervical length (0.551, 95% CI 0.541–0.561; $p = 0.042$).

In the 85 patients with cervical length <15 mm at 20–24 weeks' gestation who were treated with either cervical cerclage or vaginal progesterone, there were 3 with spontaneous delivery before 34 weeks, 2 with delivery between 34 and 36 completed weeks and 80 with delivery at or after 37 weeks. In the 85 cases, the cervical length at 11–13 weeks was <32 mm, which is the median of the normal range, and <25 mm, which is the 1st centile, in 65 (76.5%) and 18 (21.2%) women, respectively.

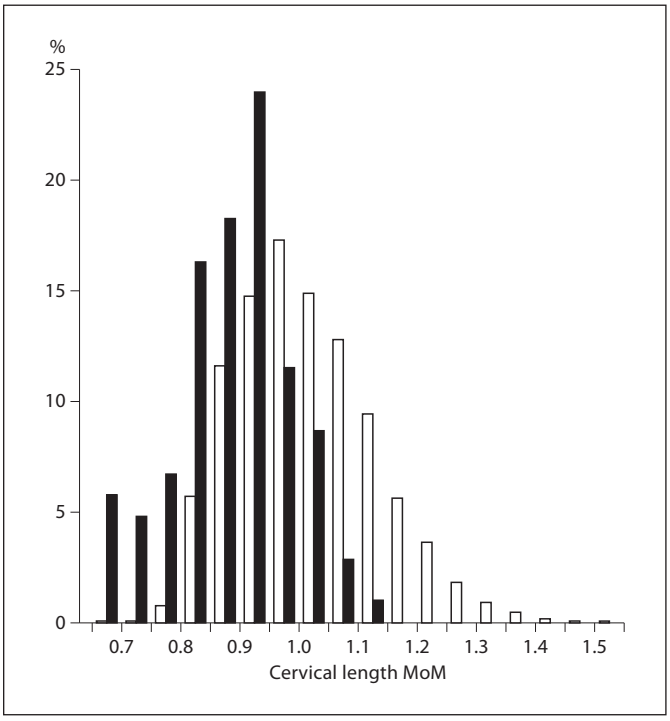

Fig. 3. Frequency distributions of cervical length MoM in the term delivery group (□) and early spontaneous preterm delivery group (■).

Discussion

The findings of this screening study demonstrate that in singleton pregnancies resulting in spontaneous preterm delivery, cervical length at 11–13 weeks' gestation is shorter than that in women delivering at term. An algorithm combining maternal characteristics and cervical length can identify about 55% of pregnancies resulting in delivery before 34 weeks, at a false-positive rate of 10%. The detection rate for delivery at 34–36 weeks was only

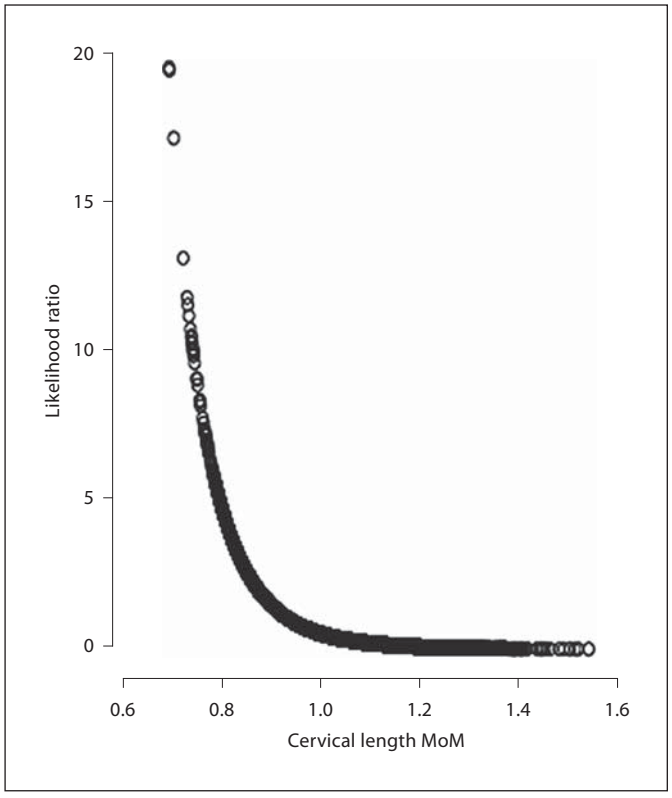

Fig. 4. Likelihood ratios for early spontaneous preterm delivery from cervical length MoM.

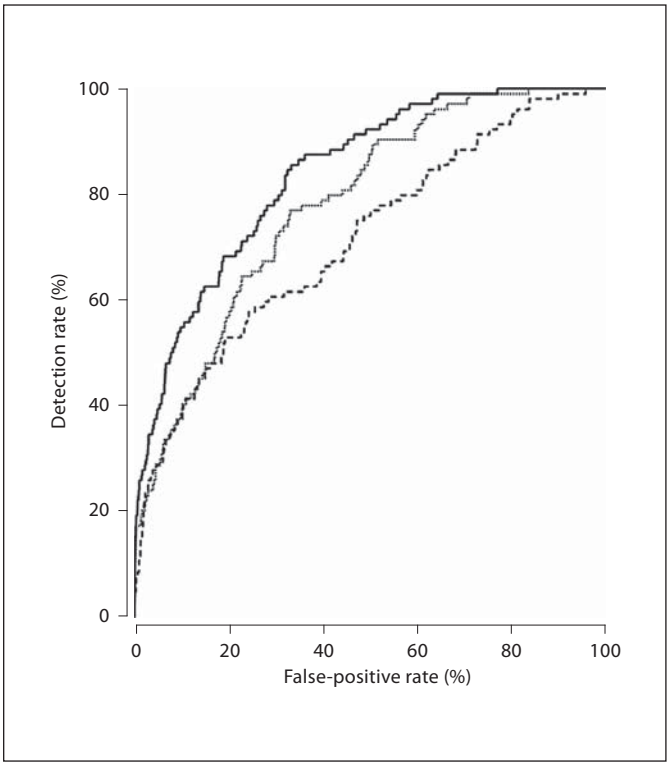

Fig. 5. Receiver operating characteristics curves of maternal characteristics (– – – – –), cervical length (· · · · ·) and their combination (———) in the prediction of early spontaneous preterm delivery.

20%. It is likely that the performance of screening would have been higher if some of the women with a short cervix were not excluded from the study because they were treated with cervical cerclage or progesterone.

The study confirmed that spontaneous preterm delivery is associated with certain maternal characteristics, and the observed number of preterm deliveries in this study was similar to that predicted from a multivariable regression model published previously [20]. The risk for spontaneous early preterm delivery increases with maternal age and decreases with height; it is higher in women of African and South Asian racial origin than in Caucasians, in cigarette smokers and in those conceiving after the use of ovulation induction drugs. The risk of preterm delivery is also influenced by the outcome of previous pregnancies. The risk is inversely related to gestation at previous spontaneous delivery decreasing from about 7% if the gestation was 16–24 weeks to 3% if 31–33 weeks and to 0.6% if all deliveries were at term. Additionally, the risk is affected by the number of previous spontaneous deliveries at 16–30 weeks, increasing from about 6–19% if there are two rather than

Table 4. Likelihood ratios for early and late spontaneous preterm delivery from $\log_{10}$ cervical length MoM

$\log_{10}$ cervical length MoM	Likelihood ratio	
	early spontaneous preterm delivery	late spontaneous preterm delivery
–0.16	19.76 (18.80–20.72)	2.04 (2.02–2.06)
–0.14	12.17 (10.52–13.82)	1.82 (1.76–1.88)
–0.12	7.82 (6.74–8.90)	1.64 (1.59–1.69)
–0.10	5.00 (4.36–5.64)	1.49 (1.45–1.53)
–0.08	3.22 (2.81–3.63)	1.35 (1.31–1.39)
–0.06	2.04 (1.78–2.30)	1.24 (1.21–1.27)
–0.04	1.29 (1.12–1.46)	1.13 (1.10–1.16)
–0.02	0.82 (0.72–0.92)	1.04 (1.02–1.06)
0	0.52 (0.45–0.59)	0.97 (0.95–0.99)
0.02	0.33 (0.29–0.37)	0.90 (0.88–0.92)
0.04	0.21 (0.18–0.24)	0.84 (0.82–0.86)

Figures in parentheses are 95% CIs.

Table 5. Comparison of the performance of screening for early and late spontaneous preterm delivery by maternal characteristics, cervical length and their combination

Screening test	AUROC	
	early spontaneous preterm delivery	late spontaneous preterm delivery
Maternal history		
Total	0.714 (0.705–0.723)	0.563 (0.553–0.573)
Caucasian	0.692 (0.682–0.703)	0.533 (0.522–0.545)
African	0.729 (0.703–0.754)	0.645 (0.617–0.672)
Cervical length		
Total	0.782 (0.774–0.790)	0.551 (0.541–0.561)
Caucasian	0.772 (0.762–0.781)	0.563 (0.552–0.575)
African	0.797 (0.773–0.820)	0.553 (0.525–0.581)
Combined test		
Total	0.840 (0.833–0.847)	0.583 (0.573–0.593)
Caucasian	0.836 (0.828–0.845)	0.565 (0.553–0.576)
African	0.829 (0.806–0.850)	0.662 (0.635–0.689)

	Detection rate for fixed false-positive rate			
	5%	10%	5%	10%
Maternal history				
Total	28.9 (20.4–38.6)	37.5 (28.2–47.5)	9.9 (6.2–14.7)	19.7 (14.6–25.7)
Caucasian	25.9 (15.3–39.0)	34.5 (22.5–48.1)	8.0 (4.1–13.8)	12.3 (7.3–19.0)
African	26.7 (12.3–45.9)	26.7 (12.3–45.9)	16.7 (5.7–34.7)	20.0 (7.8–38.6)
Cervical length				
Total	28.9 (20.4–38.6)	38.5 (29.1–48.5)	9.4 (5.8–14.1)	14.6 (10.1–20.0)
Caucasian	25.9 (15.3–39.0)	39.7 (27.1–53.4)	8.7 (4.6–14.7)	15.2 (9.7–22.3)
African	40.0 (22.7–59.4)	50.0 (31.3–68.7)	10.0 (2.2–26.6)	13.3 (3.8–30.7)
Combined test				
Total	39.4 (30.0–49.5)	54.8 (44.7–64.6)	12.2 (8.1–17.4)	20.2 (15.0–26.2)
Caucasian	41.4 (28.6–55.1)	53.5 (39.9–66.7)	10.1 (5.7–16.4)	13.0 (7.9–19.8)
African	43.3 (25.5–62.6)	60.0 (40.6–77.3)	13.3 (3.8–30.7)	26.7 (12.3–45.9)

Figures in parentheses are 95% CIs.

one such delivery. In women with previous preterm deliveries, there is a protective effect against recurrence if they also had a delivery at term, and for women with one or two deliveries at 16–30 weeks, the risk of recurrence decreases from about 6 to 1.5% and from 19 to 10%, respectively. Screening at 11–13 weeks by an algorithm combining maternal characteristics and obstetric history [20] identified about 38% of our pregnancies resulting in spontaneous delivery before 34 weeks and 20% of those delivering at 34–36 weeks, at a false-positive rate of 10%.

In the measurement of cervical length, care was taken to include only the portion of the cervix where the canal is bordered by the endocervical mucosa [15, 22]. At 11–13 weeks' gestation, the median cervical length in women delivering at term was 32 mm. Multivariate regression analysis in the normal outcome group demonstrated that cervical length increases with fetal CRL, maternal age and height and is lower in women of African and South Asian racial origin than in Caucasians. After adjustment for these maternal characteristics, the median cervical length MoM was significantly reduced in the early and to a lesser extent in the late spontaneous preterm delivery groups. The patient-specific risk for spontaneous preterm delivery was inversely related to the cervical length MoM, and the individual risk can be derived by multiplying the a priori risk, obtained from maternal characteristics and obstetric history, by the likelihood ratio for cervical length.

In women of African racial origin, the cervical length in both the term and early spontaneous preterm delivery groups was shorter than in Caucasians. In the calculation

of MoMs, after correction for maternal characteristics including racial origin, the cervical length in those with spontaneous delivery before 34 weeks was shorter in women of African than of Caucasian origin, but this difference was not significant. Similarly, the performance of screening for preterm delivery in women of African origin was higher, but not significantly so, than in Caucasians. The extent to which larger studies will demonstrate significant differences between racial groups in the short cervical length related preterm delivery rate and therefore in the mechanisms leading to preterm delivery remains to be determined.

The study has provided evidence that spontaneous preterm delivery can be added to the list of pregnancy complications that can now be identified by screening at 11–13 weeks' gestation [23]. Randomized studies, based on first-trimester screening to identify the high-risk group for subsequent early delivery, will investigate the extent to which pregnancy outcome would improve through early intervention with such measures as prophylactic use of progesterone.

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