Ultrasound Obstet Gynecol 2008; **31**: 549–554
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.5333

Cervical length and obstetric history predict spontaneous preterm birth: development and validation of a model to provide individualized risk assessment

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KEYWORDS: cervical length; maternal history; spontaneous preterm birth

ABSTRACT

Objectives *To evaluate the ability of combinations of cervical length and maternal history to assess the risk of spontaneous preterm birth, and to provide a simple procedure for the optimal estimation of risk.*

Methods *This prospective observational study was carried out between January 1998 and May 2006. Transvaginal sonographic measurement of cervical length at 20 + 0 to 24 + 6 weeks of gestation was carried out in 58 807 singleton pregnancies as part of routine antenatal care. The outcome measure was spontaneous extreme (< 28 weeks), early (28–30 weeks), moderate (31–33 weeks) and mild (34–36 weeks) preterm birth. Logistic regression analysis was used to derive models for the prediction of spontaneous preterm birth from the maternal obstetric history, demographic characteristics and cervical length.*

Results *The rates of extreme, early, moderate and mild spontaneous preterm birth were 0.23%, 0.24%, 0.57% and 2.93%, respectively. The best prediction of spontaneous preterm birth was provided by cervical length (area under the receiver–operating characteristics curve (AUC), extreme 0.903, early 0.816, moderate 0.784 and mild 0.617) and this was improved by adding obstetric history (AUC, extreme 0.919, early 0.836, moderate 0.819 and mild 0.650). Addition of other parameters was without material effect. For a 10% screen-positive rate, models using cervical length and obstetric history had a sensitivity of 80.6%, 58.5%, 53.0% and 28.6% for extreme, early, moderate and mild spontaneous preterm birth, respectively. These models were expressed as tables of adjusted likelihood ratios to allow simple estimation of the risk of spontaneous preterm birth.*

Conclusions *A model combining cervical length and obstetric history provides a better prediction of spontaneous preterm birth than either factor alone, and the sensitivity of screening improves for increasing degrees of prematurity. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Preterm birth is a major public health problem in terms of perinatal mortality, long-term morbidity and health economics. It is responsible for more than half of all neonatal deaths[1]. In a UK multicentre study of survivors born before 26 weeks' gestation, 80% were disabled at the age of 6 years[2]. The economic burden of prematurity relates not only to the initial neonatal intensive care but also to the longer-term increased use of medical, social and specialist educational services, as well as the lost economic productivity. In the USA the cost of preterm birth was estimated to be $26 billion per year[3].

A series of studies performed in the past 5 years have now demonstrated that administration of progestogens to high-risk women with a singleton pregnancy approximately halves the rate of spontaneous preterm birth[4–6]. In fact, the use of progestogens had been evaluated many years previously and a cumulative meta-analysis of trials of progestogens reported in 2006 showed that there had been unambiguous evidence of effectiveness by 1975[7]. The availability of an effective intervention now provides a rationale for population-based screening for preterm birth. The most widely adopted approach to identifying pregnancies at high risk of spontaneous preterm birth

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Accepted: 10 March 2008

is based on a previous history of preterm birth. Recent evidence suggests that more effective screening can be provided by the sonographic measurement of cervical length at mid-gestation[8–10]. However, there is currently no clearly accepted method for population-based screening.

The aims of the present study were, first, to evaluate the ability of combinations of cervical length and maternal history to assess the risk of extreme (< 28 weeks), early (28–30 weeks), moderate (31–33 weeks) and mild (34–36 weeks) spontaneous preterm birth, and, second, to provide a simple procedure for optimal estimation of risk.

METHODS

Participants included women undergoing routine antenatal care in seven hospitals in and around London, UK, that were collaborating in multicenter studies of screening for preterm birth and randomized interventional studies in patients found to be at high risk[6,11]. In these hospitals, women with singleton pregnancies were offered an ultrasound examination at 11 + 0 to 13 + 6 weeks, for pregnancy dating and early diagnosis of major chromosomal and other fetal abnormalities, and another scan at 20 + 0 to 24 + 6 weeks, for examination of the fetal anatomy and growth. Gestational age was determined from the menstrual history and confirmed from the measurement of fetal crown–rump length at the first-trimester scan. At the time of the second scan the women were given the option of transvaginal sonographic measurement of cervical length as a screening test for preterm delivery. The sonographers performing the scan had received extensive training, and had all passed a practical examination administered by an expert to demonstrate their competence in the technique. Each examination was performed over a period of about 3 min and the shortest of three measurements was recorded. Women with major fetal abnormalities, painful regular uterine contractions, or history of ruptured membranes or cervical cerclage *in situ* were excluded from screening.

Women with a cervical length greater than 15 mm had normal antenatal care, whereas those with a cervical length of 15 mm or less were invited to participate in randomized interventional studies of cervical cerclage and prophylactic progesterone. Randomization was to intervention or expectant management[6,11]. These studies were approved by the South Thames Multicentre Research Ethics Committee and the local ethics committees of individual hospitals. Written informed consent was obtained from all participants.

Participant characteristics, including details of maternal age, race, height, weight, smoking status, history of cervical surgery and obstetric history, were obtained from a questionnaire completed by the patients at the first ultrasound scan visit and entered into a computer database. Obstetric history was classified into five groups: primigravida or only losses before 16 weeks, previous preterm delivery in which the history was defined by the earliest birth (16–23 weeks, 24–33 weeks or 34–36 weeks) and term birth in which all deliveries were after 36 completed weeks.

Data on pregnancy outcome were collected from the hospital maternity records or general practitioners. The obstetric records of all patients delivering before 37 weeks (< 259 days) were examined to determine if the preterm birth was iatrogenic or spontaneous. The latter included those with spontaneous onset of labor and those with preterm prelabor rupture of membranes.

Quality control of screening, handling of data and verification of adherence to protocols at the different centers was performed on a regular basis by the trial coordinators.

In order to compare the prior probability of spontaneous preterm birth among the women recruited to these studies with that of the general population, we also used data from the Scottish Morbidity Record from 1985 to 2005. This data source and the definition of spontaneous preterm birth are described in detail elsewhere[12].

Data analysis

Continuous variables were summarized by the median and interquartile range, and comparisons between groups were made using the Mann–Whitney *U*-test. Univariable comparisons of dichotomous data were made using the Chi-square test. *P*-values for all hypothesis tests were two sided and statistical significance was set at $P < 0.05$.

Logistic regression analysis was used to estimate adjusted odds ratios for spontaneous preterm birth within four gestational windows: < 28 weeks, 28–30 weeks, 31–33 weeks and 34–36 weeks[13]. In these analyses, the number of spontaneous preterm births within the given range was the numerator and the number of all births at the given or later gestations was the denominator. Linearity in the log odds scale was assessed using fractional polynomials[14]. The cohort was divided into a model development group and a model validation group using a pseudorandom number for allocation. Different combinations of maternal obstetric history, demographic characteristics and cervical length were then used to estimate the probability of the given event in the model development group. The different models were compared using the estimated probabilities in the validation group (i.e. out of sample) by comparing receiver–operating characteristics curves. Statistically significant interactions were identified by backward stepwise logistic regression using the Wald test as robust standard errors were estimated (see below). Finally, after selection of the best modeling approach, logistic regression models were fitted to the entire cohort and the output converted into adjusted likelihood ratios using a method described previously[15].

The analysis excluded women with a cervix of 15 mm or less who had the active intervention in either trial[6,11]. In order to overcome the effects of this on measures of absolute and relative risk, women with a cervical length of 15 mm or less who were included in the study group were statistically weighted in proportion to the number who were excluded because they received an intervention.

This approach necessitated estimation of robust standard errors. All statistical analyses were performed using the Stata software package version 8.2 (Stata Corporation, College Station, TX, USA).

RESULTS

Complete outcome data were available for 59 313 (96.3%) of the 61 576 pregnancies examined between January 1998 and May 2006, but intrauterine fetal death occurred in 251 (0.4%) and these were excluded from further analysis. Among the 59 062 women who delivered a liveborn infant there were 657 (1.1%) with cervical length of 15 mm or less; 255 of these patients had cervical cerclage or prophylactic progesterone and 402 were managed expectantly. The characteristics of the cohort of 58 807 women included in the study are described in relation to the gestational age at birth in Table 1.

Preterm birth occurred in 3237 cases, including 2216 (68.5%) that were spontaneous and 1021 (31.5%) iatrogenic, delivered primarily owing to pre-eclampsia and/or fetal growth restriction. The overall rates of extreme (< 28 weeks), early (28–30 weeks), moderate (31–33 weeks) and mild (34–36 weeks) spontaneous birth were 0.23%, 0.24%, 0.57% and 2.93%, respectively (weighted to compensate for exclusion of women who screened positive and had an intervention). The equivalent rates in Scotland among 1 203 302 women who had a live birth (24–43 weeks gestation) between 1985 and 2005 were 0.19%, 0.22%, 0.53% and 2.60%, respectively.

Logistic regression models derived from the model development group were evaluated in the validation group. The best prediction of spontaneous preterm birth was provided by cervical length. This was improved by adding obstetric history but not maternal characteristics or statistically significant interactions (Table 2). Although the improvement provided by obstetric history was seen for all gestational age groups the effect was most marked for the least severe degrees of preterm birth. The estimated detection rates of extreme, early, moderate and mild spontaneous preterm birth by a combination of obstetric history and cervical length were 80.6%, 58.5%, 53.0% and 28.6%, respectively, for a 10% screen-positive rate (Table 3).

Having identified the optimal approach, models were then generated combining cervical length and obstetric history in the prediction of extreme, early, moderate

Table 2 Area under the receiver–operating characteristics (ROC) curve for comparison of different modeling approaches in the prediction of spontaneous preterm birth, when applied to validation sample

	Area under ROC curve				
GA at birth (weeks)	*Model 1*	*Model 2*	*Model 3*	*Model 4*	*Model 5*
< 28	0.903	0.919	0.911	*	0.649
28–30	0.816	0.836	0.826	*	0.691
31–33	0.784	0.819	0.812	0.810†	0.680
34–36	0.617	0.650	0.657	0.656‡	0.610

Model 1: cervical length alone. Model 2: cervical length plus obstetric history (nulliparous, previous term birth, previous birth at 16–23 weeks, previous birth at 24–33 weeks, previous birth at 34–36 weeks). Model 3: cervical length plus obstetric history plus maternal characteristics (age, race, smoking, body mass index). Model 4: cervical length plus obstetric history plus maternal characteristics plus statistically significant interactions. Model 5: obstetric history plus maternal characteristics (age, race, smoking, body mass index). *No statistically significant interactions. †Interaction between cervical length and maternal age in model development sample ($P = 0.002$). ‡Interaction between cervical length and maternal smoking in model development sample ($P = 0.03$). GA, gestational age.

Table 1 Characteristics of cohort in relation to gestational age at delivery

	Delivery at:					
Parameter	*< 28 weeks (n = 139)*	*28–30 weeks (n = 216)*	*31–33 weeks (n = 526)*	*34–36 weeks (n = 2356)*	*≥ 37 weeks (n = 55 570)*	P*
Age (years)	30 (24–34)	30 (25–34)	30 (25–34)	30 (25–34)	30 (26–34)	0.8
Ethnicity						
White	64 (46.0)	103 (47.7)	294 (55.9)	1459 (61.9)	37 027 (66.6)	
Black	65 (46.8)	85 (39.4)	176 (33.5)	651 (27.6)	13 427 (24.2)	< 0.001
Other	10 (7.2)	28 (13.0)	56 (10.6)	246 (10.4)	5116 (9.2)	
Body mass index (kg/m^2)	26.3 (22.6–29.5)	25.5 (22.7–28.9)	24.6 (21.7–27.6)	24.2 (21.5–27.7)	24.5 (21.9–27.8)	< 0.001
Smoker	17 (12.2)	42 (19.4)	113 (21.5)	408 (17.3)	7135 (12.8)	< 0.001
Past obstetric history						
Nulliparous	74 (53.2)	120 (55.6)	282 (53.6)	1260 (53.5)	29 032 (52.2)	
Delivery at:						
≥ 37 weeks	29 (20.9)	46 (21.3)	126 (24.0)	718 (30.5)	23 437 (42.2)	
16–23 weeks	14 (10.1)	6 (2.8)	17 (3.2)	54 (2.3)	553 (1.0)	< 0.001
24–33 weeks	16 (11.5)	28 (13.0)	46 (8.7)	114 (4.8)	876 (1.6)	
34–36 weeks	6 (4.3)	16 (7.4)	55 (10.5)	210 (8.9)	1672 (3.0)	
Cervical length (mm)	23 (6–31)	30 (23–35)	31 (25–36)	33 (28–38)	35 (31–40)	< 0.001
Spontaneous labor	107 (77.0)	127 (58.8)	313 (59.5)	1669 (70.8)	42 678 (76.8)	< 0.001

Values are median (interquartile range) or *n* (%). *Statistical comparison by Kruskal–Wallis or Chi-square test, as appropriate.

Table 3 Detection rate comparing different modeling approaches in the prediction of spontaneous preterm birth, when applied to validation sample

Method of screening	*GA at birth (weeks)*	*Detection rate (%) for fixed screen-positive rates of:*			
		1%	*5%*	*10%*	*15%*
Cervical length	< 28	53.0	66.0	75.7	77.3
	28–30	20.1	40.1	57.0	64.7
	31–33	17.2	32.6	46.8	53.0
	34–36	4.1	12.7	24.2	26.6
Obstetric history and maternal characteristics	< 28	7.5	15.0	22.5	32.1
	28–30	8.1	20.4	34.6	41.8
	31–33	7.4	24.0	32.2	37.2
	34–36	3.4	12.4	23.2	30.0
Cervical length and obstetric history	< 28	53.0	72.4	80.6	85.4
	28–30	19.1	44.7	58.5	67.7
	31–33	15.6	38.2	53.0	59.8
	34–36	4.7	15.8	28.6	33.5
Cervical length, obstetric history and maternal characteristics	< 28	52.0	69.2	82.2	82.2
	28–30	19.1	46.2	61.6	69.3
	31–33	17.2	40.0	55.3	62.9
	34–36	4.6	16.0	29.3	34.7

GA, gestational age.

and mild spontaneous preterm birth for the whole population. These were converted to adjusted likelihood ratios (Table 4). The logistic regression models used to derive these likelihood ratios are described in Table 5.

DISCUSSION

This study of about 60 000 singleton pregnancies has demonstrated that a combination of past obstetric history and cervical length provides a simple and effective method for estimating patient-specific risks of extreme, early, moderate and mild spontaneous preterm birth. The rate of preterm birth in our study of a heterogeneous inner city population was similar to the overall 6% rate in the total population in the UK[16]. Furthermore, the rates of extreme, early, moderate and mild spontaneous birth in our study were similar to those in 1 203 302 pregnancies in Scotland delivered between 1985 and 2005. The slightly higher absolute risks in our study population compared with the Scottish population probably reflect the fact that the study cohort was largely derived from urban areas with high background rates of risk factors for preterm birth, such as black ethnicity.

Evidence that the use of progesterone reduces the rate of spontaneous preterm birth provides a rationale for population-based screening for this pregnancy complication[4–7,17]. Screening on the basis of previous obstetric history and therapeutic intervention in the high-risk group is likely to have a small impact on the overall rate of prematurity because only about 10% of spontaneous early preterm births occur in women with this history[16]. Nulliparous women comprise an increasingly large proportion of the population and they have a

Table 4 Likelihood ratio-based models for prediction of spontaneous preterm birth

Parameter	*Likelihood ratio for delivery at:*			
	< 28 weeks	*28–30 weeks*	*31–33 weeks*	*34–36 weeks*
Cervical length (mm)				
< 2	745.29	74.29	44.22	99.36
2	409.86	56.10	34.78	58.12
3	258.41	48.75	30.84	35.82
4	172.11	42.36	27.35	24.60
5	119.19	36.81	24.26	18.10
6	85.02	31.99	21.51	13.96
7	62.08	27.80	19.08	11.15
8	46.20	24.16	16.92	9.15
9	34.94	20.99	15.01	7.66
10	26.79	18.24	13.31	6.53
11	20.78	15.85	11.80	5.64
12	16.29	13.77	10.47	4.93
13	12.89	11.97	9.28	4.35
14	10.28	10.40	8.23	3.87
15	8.26	9.04	7.30	3.47
16	6.68	7.85	6.48	3.14
17	5.44	6.82	5.74	2.85
18	4.45	5.93	5.09	2.60
19	3.66	5.15	4.52	2.39
20	3.03	4.48	4.01	2.20
21	2.52	3.89	3.55	2.03
22	2.10	3.38	3.15	1.89
23	1.76	2.94	2.79	1.76
24	1.48	2.55	2.48	1.64
25	1.25	2.22	2.20	1.53
26	1.05	1.93	1.95	1.44
27	0.89	1.68	1.73	1.35
28	0.76	1.46	1.53	1.28
29	0.65	1.27	1.36	1.21
30	0.56	1.10	1.21	1.14
31	0.48	0.96	1.07	1.08
32	0.41	0.83	0.95	1.03
33	0.35	0.72	0.84	0.98
34	0.31	0.63	0.75	0.93
35	0.26	0.54	0.66	0.89
36	0.23	0.47	0.59	0.85
37	0.20	0.41	0.52	0.81
38	0.17	0.36	0.46	0.78
39	0.15	0.31	0.41	0.74
40	0.13	0.27	0.36	0.71
41	0.12	0.23	0.32	0.68
42	0.10	0.20	0.29	0.66
43	0.09	0.18	0.25	0.63
44	0.08	0.15	0.22	0.61
45	0.07	0.13	0.20	0.59
46	0.06	0.12	0.18	0.57
47	0.05	0.10	0.16	0.55
48	0.05	0.09	0.14	0.53
49	0.04	0.08	0.12	0.51
50	0.04	0.07	0.11	0.49
Past obstetric history				
Nulliparous	1.07	1.00	0.98	1.03
Delivery at:				
≥ 37 weeks	0.58	0.62	0.63	0.74
16–23 weeks	4.42	1.65	1.64	1.70
24–33 weeks	1.99	3.67	3.91	2.22
34–36 weeks	0.97	1.93	2.63	2.84

The logistic regression models used to derive these likelihood ratios are described in Table 5.

Table 5 Final logistic regression models for whole cohort, used to derive the likelihood ratios in Table 4

			Coefficient						
					Previous delivery at:				
GA at birth (weeks)	*Constant*	*Cervical length transformation**	*Cervical length*	*Nulliparous*	*≥ 37 weeks*	*16–23 weeks*	*24–33 weeks*	*34–36 weeks*	P†
< 28	−7.96000	$B^{0.5-1.898619113}$	−5.44393	0.61934	0	2.03708	1.23967	0.51973	0.49
28–30	−7.13734	A − 35.0817311	−0.14044	0.47641	0	0.97466	1.77126	1.13242	0.97
31–33	−6.05034	A − 35.10576199	−0.12008	0.43554	0	0.95208	1.81838	1.42097	0.20
33–36	−3.93249	ln(B) − 1.285142045	−1.68320	0.33630	0	0.83516	1.10367	1.35008	0.20

*Where polynomial expression gave a significantly better fit than a linear model, the expressions were fitted using fractional polynomials.
†Hosmer and Lemeshow goodness of fit test. A, cervical length in mm; B, (cervical length in mm + 1)/10. GA, gestational age.

higher risk of spontaneous preterm birth than parous women. In our study more than half of all preterm births were in nulliparous women. Additionally, spontaneous preterm birth at 34–36 weeks is considerably more common than earlier delivery and recurrence tends to be observed at around the same gestational age as in the previous pregnancy[16]. Consequently, the majority of women identified through screening by obstetric history would be at risk of mild prematurity rather than delivery before 34 weeks, when perinatal mortality and morbidity are considerably higher.

Screening by cervical length, in contrast to the use of obstetric history alone, can be used in all women regardless of their parity. Furthermore, screening by a combination of obstetric history and cervical length provides a higher detection rate than either method alone. The proposed combined method is particularly effective in identifying extreme and early preterm birth and, for a screen-positive rate of 10%, the respective detection rates are about 80% and 60%. In contrast, the detection rate of late preterm birth is less than 30%. Data from neonatal units in the 1990s have demonstrated an inverse association between neonatal mortality and gestational age at delivery, with mortality rates of about 70%, 35%, 12%, 4% and 2% for babies born at 24, 26, 28, 30 and 32 weeks, respectively[18]. Similarly, the overall prevalence of cerebral palsy is about 9% for live births below 28 weeks, 6% for 28–31 weeks and 0.6% for 32–36 weeks[19].

A widely accepted method of screening in prenatal care, which combines obstetric history with ultrasound findings, is in the detection of fetal trisomy 21[20,21]. In this condition the intervention for the high-risk group is amniocentesis or chorionic villus sampling, which carry a risk of miscarriage of about 1%; such invasive intervention is therefore usually limited to 3–5% of pregnancies. In contrast, in pregnancies found to be at increased risk of preterm delivery, the intervention for the high-risk group is maternal administration of prophylactic progesterone, which is inexpensive, easy to administer, and its use in pregnancy does not appear to be associated with any adverse outcome or significant side effects[6]. Consequently, the screen-positive rate need not be limited to 3–5%, but could be increased to 10–15% with the aim of maximizing the detection rate.

Combined screening can be implemented easily into routine practice because taking an obstetric history is a regular part of antenatal care and sonographic measurement of cervical length is a simple skill to learn for sonographers undertaking routine ultrasound examination in pregnancy. The infrastructure and equipment needed for screening are readily available in all maternity units, and studies have documented that transvaginal sonography is acceptable to pregnant women[22,23]. As for the assessment of patient-specific risks for extreme, early, moderate and mild preterm birth, these can be calculated by the simple multiplication of the respective *a-priori* risk with the likelihood ratios associated with obstetric history and cervical length.

The implementation of our combined screening model into routine antenatal care and the use of prophylactic progesterone in the pregnancies at highest risk of spontaneous preterm birth has the potential, for the first time, to make a significant impact on the rate of preterm birth and its associated mortality and morbidity.

ACKNOWLEDGMENT

This study was sponsored by The Fetal Medicine Foundation (UK registered charity 1037116).

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