Ultrasound Obstet Gynecol 2009; **33**: 459–464
Published online 10 March 2009 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.6332

Reference range for cervical length throughout pregnancy: non-parametric LMS-based model applied to a large sample

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KEYWORDS: cervical length; LMS; preterm delivery; transvaginal ultrasound; *Z*-scores

ABSTRACT

Objective *Short cervical length is an important risk factor for preterm delivery. However, because cervical length changes throughout pregnancy, adequate risk estimation needs to take into account the gestational age (GA) at which the measurement is taken. We aimed to model cervical changes throughout pregnancy in order to be able to use Z-scores, avoiding the confounding effect of GA.*

Methods *Cervical length was prospectively measured in singleton pregnancies, as part of routine antenatal care over a 3-year period. Measurements were taken at GA ranging from 16 to 36 weeks and only one measurement per pregnancy was used in the analysis. Because cervical length measurements are not normally distributed, we used a non-parametric approach (LMS method) to best describe the distribution of the measurements with gestation.*

Results *We included 6614 cervical length measurements. The LMS method identified changes in cervical length measurement across GA. We computed new reference charts and provide L, M and S values that allow the calculation of Z-score at any GA from any cervical length measurement 'Y' using the formula:* $Z\text{-score} = ((Y/M)^L - 1)/(L \times S)$.

Conclusion *Cervical length measurements do not have a normal distribution at a given GA and so require a statistical model that takes this into account. The model that we developed allows easy Z-score calculation, therefore avoiding the confounding effect of GA and allowing straightforward monitoring of cervical length.*

INTRODUCTION

Preterm birth is the main cause of perinatal morbidity and mortality[1]. Cervical length measured by transvaginal sonography (TVS) has been reported to be inversely correlated with spontaneous preterm delivery[1–4]. However, cervical length changes with gestational age (GA). Most published studies show that cervical length normally decreases throughout pregnancy[5–8]. It has been shown that for a given cervical length measurement, the GA at which TVS is performed significantly affects the calculation of risk of spontaneous preterm birth[9]; for the same short cervix measurement, the earlier the measurement the greater the risk of spontaneous preterm birth[9]. Therefore, a nomogram of cervical length for each week of pregnancy is essential for determining the risk of preterm delivery when using this method. Several studies have aimed to develop reference values for cervical length, based on a cross-sectional or longitudinal approach. However, these studies were based on a limited number of cases or range of GA[5,7,8,10–14] and statistical modeling was inappropriate because normal ranges for cervical length were usually based on parametric methods, defining cut-off values based on mean and standard deviations[6,15,16].

This study was undertaken to provide reference values for cervical length based on a large sample and using a statistical approach that is not based on the usual assumption of normality.

PATIENTS AND METHODS

Over a 3-year period four trained operators, unaware of the subsequent analysis, prospectively and routinely performed cervical length measurements using TVS. This sonographic examination was part of our routine prenatal management policy and oral informed consent from the

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Accepted: 3 November 2008

 ORIGINAL PAPER

patients was sought prior to ultrasound examination in all cases.

Measurements were obtained in all cases by TVS examination using a 7-MHz probe (Voluson 730 Expert, GE Healthcare, Buc, France). Operators were specialists in prenatal ultrasound, each having performed more than 2000 prenatal examinations per year over the past 10 years. Freeze-frame and cine-loop capabilities as well as electronic on-screen callipers were used for the measurements. Cervical length was measured by TVS as described previously[8] as part of routine prenatal examination. In brief, each examination was performed with the patient in the dorsal lithotomy position and with an empty bladder. The pressure of the probe on the cervix was kept as low as possible. Cervical length was recorded as the distance (mm) between the furthest points at which the proximal and distal endocervical walls are juxtaposed. Endocervical funneling was also recorded but was not included in the calculation of cervical length. All measurements were performed to the nearest 0.1 mm. Included were all cervical lengths measured during a routine prenatal ultrasound examination at between 16 and 36 weeks. GA was determined from the earliest available ultrasound scan[17]. If more than one scan was done in that period, only the first cervical length measurement was used for this study. Exclusion criteria were: known abnormal growth or karyotype, congenital malformation, abnormal uterine contraction, preterm labor, no first-trimester dating based on crown–rump length (CRL), and multiple pregnancies. GA in weeks was used; i.e., fractions of weeks were computed to the nearest week, with fractions of ≤ 4 days and > 5 days assigned to the lower and higher week, respectively. Women with measurements < 25 mm at any GA were referred to our high-risk pregnancy unit for management and follow-up. These patients were included in the analysis but the outcome of such pregnancies is not within the scope of this article.

The normality of cervical length measurements was assessed by using the Shapiro–Wilk test at each gestational week. Skewness was also calculated and tested at each gestational week. The mean, median, standard deviation, interquartile range (IQR) and range of cervical length measurements were computed at each gestational week. To investigate the relationship between cervical length and GA, the mean measurement was fitted using a polynomial of the form $y = a + \Sigma b_i x^i$[18,19]. Regression models with robust estimation (Huber–White sandwich estimators[20,21]) were used and increasing order terms for GA were added in the model as long as they were significant as based on the likelihood-ratio test. Parity (categorized into nulliparous, primiparous and multiparous) was added into this robust regression model and its effect, adjusted on GA, was evaluated.

The cervical length across gestation was then analyzed by the LMS method[22] using the LMS ChartMaker[23]. The LMS method summarizes the changing distribution of the variable of interest (i.e. cervical length) according to the covariate (i.e. GA) by three curves. These three curves represent the median (M), coefficient of variation (S) and skewness (L), the latter expressed as a Box–Cox power transformation. Cole and Green[22] added a non-parametric aspect to the original LMS method by using maximum penalized likelihood to estimate the age-related curves for each of the parameters by natural cubic splines. Therefore the three curves can be fitted as cubic splines by non-linear regression, and the extent of smoothing required can be expressed in terms of smoothing parameters or equivalent degrees of freedom. The best model was determined by comparing the difference in deviance (−2 log (penalized likelihood)) between two models where the total number of degrees of freedom differed by e to a χ^2_e distribution[22,24].

The median (M), the generalized coefficient of variation (S), and the power in the Box–Cox transformation (L) parameters can be used to calculate values of interest. To obtain the value (Y) of a cervical length measurement at a particular *Z*-score or percentile, we used the following equation[22,23]:

$$Y = M\,(1 + (L \times S \times Z))^{(1/L)}$$

where L, M, and S are the values at the corresponding GA and Z is the *Z*-score that corresponds to the particular percentile. Cervical length measurements corresponding to the 1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th and 99th centiles were calculated and plotted against GA.

In addition, in order to obtain the *Z*-score (Z) and corresponding percentile for a given cervical length measurement (Y), we used the following equation[22,23]:

$$Z = \frac{(Y/M)^L - 1}{S \times L}$$

where L, M and S are taken at the corresponding GA. *Z*-scores and centiles corresponding to the usual cut-off of 25 mm were computed across gestation.

The goodness of fit of our LMS-based model was assessed by using a graphical representation of the calculated *Z*-scores in our population, globally and across GA[25]. All tests were two-tailed and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata 9.2 for Windows (StataCorp LP, College Station, TX, USA) and LMS ChartMaker Light 2.1 (Medical Research Council, London, UK).

RESULTS

During the study period 6614 examinations met the inclusion criteria. Table 1 shows the number, mean, median, standard deviation, IQR and range of measurements at each gestational week. Results of the Shapiro–Wilk test as well as skewness are also given at each week. Mean (± SD) maternal age was 30.1 ± 4.3 years. Overall, the mean ± SD and median (IQR) cervical length were 36.9 ± 9.3 and 38 (31–43) mm, respectively. There were 653 patients (9.9%) with cervical

Table 1 Descriptive statistics of cervical length measurements across gestation

GA (weeks)	n	*Mean (SD)*	*Median (range)*	*Q25*	*Q75*	P *for Shapiro–Wilk test*	*Skewness*	P *for skewness*
16	79	43.3 (6.7)	43 (25–55)	31	53	0.24	—0.35	0.31
17	99	41.7 (6.6)	42 (23–60)	25	53	0.04	−0.46	0.06
18	68	42.8 (6.3)	42 (27–58)	39	47	0.05	0.08	0.57
19	61	41.5 (8.2)	42 (20–65)	27	47	0.05	−0.40	0.04
20	108	42.5 (6.9)	42 (25–58)	38	48	0.75	−0.03	0.16
21	142	41.3 (8.0)	42 (8–62)	37	46	$< 10^{-4}$	−0.82	$< 10^{-4}$
22	979	40.3 (7.5)	40 (5–68)	36	45	$< 10^{-4}$	−0.32	$< 10^{-4}$
23	1149	40.6 (7.7)	41 (5–66)	36	45	$< 10^{-4}$	−0.24	$< 10^{-4}$
24	309	39.7 (7.8)	40 (1–61)	35	45	$< 10^{-4}$	−0.84	$< 10^{-4}$
25	123	39.9 (9.5)	41 (2–62)	36	46	$< 10^{-4}$	−1.14	$< 10^{-4}$
26	119	36.6 (9.4)	36 (6–56)	32	43	0.01	−0.58	$< 10^{-4}$
27	136	37.2 (8.3)	38 (4–55)	33	43	0.001	−0.80	$< 10^{-4}$
28	156	35.7 (9.3)	37 (10–59)	28	43	0.32	−0.25	0.11
29	120	35.9 (9.4)	36.5 (9–58)	31	43	0.02	−0.55	$< 10^{-4}$
30	79	32.8 (9.1)	33 (9–51)	27	39	0.38	−0.35	0.04
31	95	34.4 (9.3)	36 (9–62)	30	40	0.24	−0.31	0.10
32	940	34.1 (8.9)	34 (3–61)	29	40	$< 10^{-4}$	−0.33	$< 10^{-4}$
33	1405	33.2 (9.4)	34 (5–62)	27	40	$< 10^{-4}$	−0.34	$< 10^{-4}$
34	324	30.8 (9.8)	31 (3–54)	24	38	0.61	−0.08	0.54
35	65	39.3 (10.4)	30 (5–57)	21	37	0.64	0.1	0.37
36	58	29.5 (9.7)	31 (11–49)	22	36	0.26	−0.12	0.88
Total	6614	36.9 (9.3)	38 (1–68)	31	43	$< 10^{-4}$	−0.48	$< 10^{-4}$

GA, gestational age; *n*, number of observations; Q25, 25th percentile; Q75, 75th percentile. Lengths are given in mm.

length below 25 mm. Data demonstrated significant non-normality ($P < 10^{-4}$) and significant negative skewness (-0.48, $P < 10^{-4}$).

Funneling was observed in 431/6614 cases (6.5%). There were 3226 (48.8%) nulliparous, 2405 (36.4%) primiparous and 983 (14.9%) multiparous patients, respectively.

Robust regression of cervical length on GA demonstrated a significant relationship between the variables: linear regression found a significant decrease in cervical length with GA (beta coefficient for GA (± SD): -0.69 ± 0.019 mm/week, $P < 10^{-4}$). The relationship between cervical length and GA was, however, best described with a second-order polynomial (beta coefficient for GA (± SD): 0.29 ± 0.02, beta coefficient for GA^2: -0.019 ± 0.004 mm/week, $P < 10^{-4}$). Higher-order terms did not improve the model as based on the pseudo log-likelihood ratio test. In this second order GA-adjusted model, parity was a significant predictor for cervical length (average ± SD difference: 1.9 ± 0.23 mm, $P < 10^{-4}$ and 3.4 ± 0.31 mm, $P < 10^{-4}$, for primiparous and multiparous women, respectively, as compared to nulliparous).

Based on maximum penalized likelihood, the L, M and S curves were best fitted with a series of spline curves with three, five and three degrees of freedom, respectively. Table 2 shows the values of the median (M), the generalized coefficient of variation (S) and the power in the Box–Cox transformation (L) parameters at each gestational week. Based on these results, the cervical length corresponding to the 1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th and 99th centiles are given for each gestational week in Table 2. Also shown in Table 2 is the *Z*-score corresponding to a cervical length of 25 mm at each week of gestation, and the percentage of women that would be included using this value as a cut-off.

The reference charts based on this LMS model are shown in Figure 1, and Figure 2 illustrates the goodness of fit of our model. Overall, the mean (SD) of the calculated *Z*-scores was 0.0002 (1.0001).

DISCUSSION

Cervical length measured by TVS has proven to be useful in predicting the risk of premature delivery, i.e. the shorter

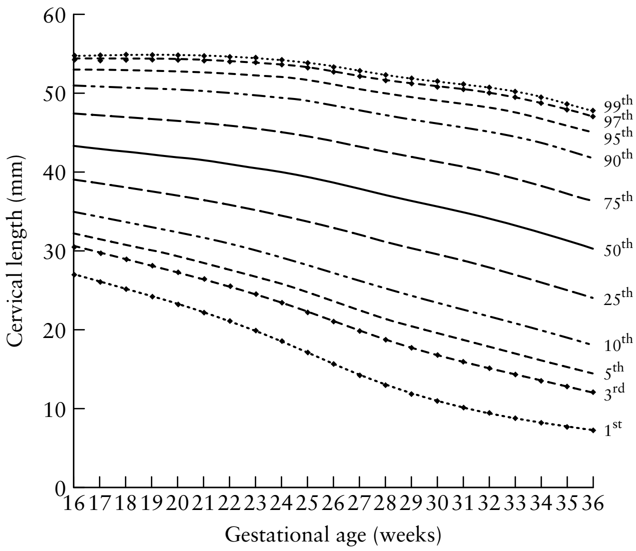

Figure 1 Reference ranges for cervical length across gestation. First to 99th percentiles are indicated.

Table 2 Results of the LMS analysis

GA (weeks)	L	M	S	Percentile											25-mm cut-off	
				1st	3rd	5th	10th	25th	50th	75th	90th	95th	97th	99th	Z-score	% selected
16	1.531	43.299	0.144	27.0	30.5	32.2	34.9	39.0	43.3	47.4	50.9	53.0	54.3	54.8	−2.58	0.5
17	1.519	42.957	0.150	26.1	29.7	31.5	34.2	38.5	43.0	47.2	50.8	53.0	54.3	54.8	−2.46	0.7
18	1.506	42.628	0.156	25.2	28.9	30.8	33.6	38.0	42.6	47.0	50.8	53.0	54.4	54.8	−2.35	0.9
19	1.496	42.287	0.162	24.2	28.1	30.1	33.0	37.6	42.3	46.8	50.7	52.9	54.4	54.9	−2.24	1.2
20	1.487	41.908	0.169	23.2	27.3	29.3	32.3	37.0	41.9	46.5	50.5	52.9	54.3	54.8	−2.14	1.6
21	1.482	41.480	0.175	22.2	26.4	28.5	31.6	36.5	41.5	46.2	50.3	52.7	54.2	54.7	−2.04	2.1
22	1.480	41.032	0.182	21.1	25.5	27.7	30.9	35.9	41.0	45.9	50.1	52.6	54.1	54.6	−1.93	2.7
23	1.483	40.582	0.189	19.9	24.5	26.8	30.1	35.3	40.6	45.6	49.9	52.4	54.0	54.5	−1.83	3.4
24	1.493	40.033	0.196	18.6	23.4	25.8	29.2	34.6	40.0	45.1	49.6	52.1	53.7	54.3	−1.72	4.2
25	1.501	39.374	0.204	17.1	22.2	24.7	28.3	33.8	39.4	44.6	49.1	51.7	53.3	53.9	−1.61	5.3
26	1.503	38.621	0.212	15.6	21.0	23.5	27.2	32.9	38.6	43.9	48.5	51.1	52.8	53.4	−1.50	6.6
27	1.495	37.841	0.221	14.2	19.8	22.4	26.2	32.0	37.8	43.2	47.9	50.6	52.2	52.8	−1.40	8.1
28	1.477	37.077	0.229	13.0	18.7	21.4	25.2	31.2	37.1	42.6	47.3	50.0	51.7	52.3	−1.30	9.6
29	1.449	36.342	0.238	11.9	17.7	20.4	24.3	30.3	36.3	41.9	46.8	49.5	51.3	51.9	−1.21	11.2
30	1.412	35.628	0.247	10.9	16.8	19.5	23.5	29.5	35.6	41.3	46.3	49.1	50.9	51.5	−1.13	12.9
31	1.369	34.919	0.256	10.1	15.9	18.6	22.6	28.7	34.9	40.7	45.8	48.7	50.5	51.2	−1.05	14.7
32	1.323	34.165	0.265	9.4	15.1	17.8	21.8	27.9	34.2	40.1	45.2	48.2	50.1	50.8	−0.96	16.8
33	1.275	33.305	0.275	8.8	14.3	17.0	20.9	27.0	33.3	39.3	44.5	47.6	49.5	50.2	−0.87	19.1
34	1.226	32.329	0.285	8.2	13.5	16.1	19.9	26.0	32.3	38.4	43.7	46.8	48.8	49.5	−0.77	22.0
35	1.177	31.309	0.295	7.7	12.7	15.2	19.0	25.0	31.3	37.4	42.8	46.0	48.0	48.7	−0.67	25.1
36	1.128	30.280	0.305	7.2	12.0	14.4	18.1	24.0	30.3	36.4	41.8	45.1	47.1	47.8	−0.56	28.6

The median (M), the generalized coefficient of variation (S) and the power in the Box–Cox transformation (L) parameters are given at each gestational week. Calculated centiles are all based on the LMS parameters[22,23]: $Y = M\,(1 + (L \times S \times Z))^{1/L}$, where L, M, and S are the values at the corresponding gestational age (GA) and *Z* is the *Z*-score that corresponds to the intended percentile. Percentile values are given in mm. Also shown is the *Z*-score corresponding to a cervical length of 25 mm at each week of gestation, and the percentage of women who would be included using this value as a cut-off.

the cervix the higher the predicted risk[1,3,4,8]. However, accurate recognition of cervical length abnormality must proceed from a precise understanding of the normal range of cervical length measurements.

Our study confirms that cervical length changes throughout pregnancy, in accordance with most published studies, which show a physiological decrease in cervical length[5–8,26]. It is therefore essential to adjust for GA when using cervical length measurement in the risk assessment for preterm delivery. Shorter cervical length is associated with an increase in the risk of spontaneous preterm birth, with the risk increasing the earlier, in terms of GA, that the short cervical length measurements are obtained[8,9]. It has been reported that the cervical parameter with the best predictive accuracy for preterm birth is cervical length below 25 mm, irrespective of the GA at measurement[27]. However, according to our data, this single cut-off value corresponds to the 0.5^{th}, 3^{rd}, 10^{th} and 20^{th} percentiles at 16, 22, 28 and 33 weeks, respectively. Therefore, accounting for the GA at which this measurement is found should further improve the risk prediction. Iams *et al.*[8] suggested that the length of the cervix is an indirect indicator of its competence and should be seen as a continuous rather than a dichotomous variable. Our LMS method allowed adequate centile calculations that fit this hypothesis. We found that there is only a mild effect of parity on cervical length measurement, as suggested by other reports[7,8,15], and no distinction should be made on parity when assessing cervical length.

Although our data are in agreement with those reported by other authors[6,26,28,29], our large cohort provides evidence that cervical length measurements are not normally distributed, and this should be taken into account when using this method of risk estimation. Hasegawa *et al.*[6] and Okitsu *et al.*[26] included 729 and 129 women, respectively, in their studies, whereas Cook and Ellwood[28] and Bergelin and Valentin[29] studied 41 and 19 women longitudinally, respectively. The assumption of normality may remain unrejected in small samples and the normal approximation could definitely hold if we were to compute statistics on the mean values. Indeed, in such cases, statistically significant non-normality can easily be accepted unless the normal plot shows clear deviation from a straight line[19]. However, when deciding upon cut-off values for cervical length, our interest lies in the detection of extreme values, possibly indicating a higher risk for preterm delivery. Although this was not noticed by the authors, there is also evidence of non-normality in reports that considered measurements to be normally distributed. As an example, Hibbard *et al.*[15] reported that the mean ± SD cervical length in their study population of 760 women was 38.5 ± 8.0 mm, and the 10^{th}, 5^{th} and 2.5^{th} percentiles of cervical length were 30, 27 and 22 mm, respectively. If the population was normally distributed, the 10^{th}, 5^{th} and 2.5^{th} percentiles of cervical length should have been: mean − (1.28 × SD), mean − (1.645 × SD) and mean − (1.96 × SD), respectively, i.e. 28, 25 and 23 mm. Iams *et al.* described cervical length as normally distributed[8], but the percentiles reported by them do not

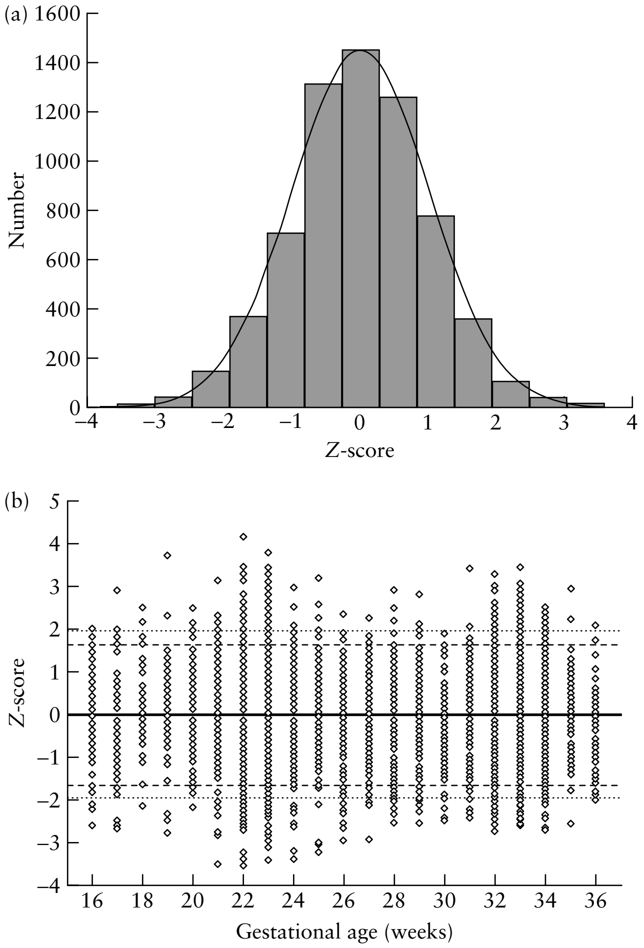

Figure 2 Distribution of *Z*-scores: globally (a) and across gestation (b). Overall, the mean (SD) *Z*-score was 0.0002 (1.0001).

correspond to a normal distribution. They reported mean cervical length (± SD) to be 35.2 ± 8.3 mm at 24 weeks, based on a sample of 2915 women. Therefore, the 10th, 5th and 1st percentiles should have been 24.5, 21.5 and 16 mm, whereas they report values of 26, 22 and 13 mm, respectively.

The LMS method with penalized likelihood that we used is extremely flexible and widely applicable. It produces centile curves even when the data appear to have a complex shape. Furthermore, time-varying skewness, which cannot be taken into account with classical log transformation, is easily dealt with. The LMS method has been increasingly used in recent years and it was the chosen procedure to compute the 2000 CDC Growth Charts for the United States[30]. Our results allow for easy and automated calculation of *Z*-scores, avoiding the confounding effect of GA when assessing cervical length. The use of exact percentiles and *Z*-scores permits optimal assessment of cervical length. In addition, *Z*-scores allow the precise description of length outside of the 3rd and 97th percentiles of a growth reference. Such *Z*-score calculation could also make quality-control programs and population comparison easier, allowing for the analysis of cervical length distribution among operators or populations[31,32].

The main weakness of our study is that we chose a cross-sectional design that estimates 'measurement distance', whereas longitudinal or mixed longitudinal designs provide information on both distance and velocity of changes[33]. Our model may therefore be inadequate for longitudinal cervical length monitoring as it gives no clue as to whether or not a given rate of percentile crossing is unusual. Another limitation is that only four operators performed all the examinations. This might slightly impact on the variability of the measurements.

Our study provides new reference values for cervical length based on a large sample. The centiles based on the LMS method can be used to decide on the policy of interventions for reducing the morbidity and mortality of preterm birth. Consideration of most variables in medicine and particularly in obstetrics has evolved from a fixed threshold to a continuous variable with a risk of adverse outcomes changing with the measurement. It is likely that the same will apply to the risk for preterm delivery, and our results should allow further studies to investigate this risk in relation to *Z*-scores/centiles of cervical length. Validation of the chart provided, followed by large prospective cohorts, are now required to investigate whether the risk of preterm delivery remains constant at a given *Z*-score, independent of GA.

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