Published in final edited form as:

Am J Obstet Gynecol. 2016 November ; 215(5): 616.e1–616.e14. doi:10.1016/j.ajog.2016.06.034.

Do Serial Measurements of Cervical Length Improve the Prediction of Preterm Birth in Asymptomatic Women with Twin Gestations?

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Abstract

Objective—To determine whether serial measurements of cervical length can improve the prediction of preterm birth in asymptomatic women with twin gestations compared with a single measurement of cervical length at mid-gestation.

Materials and Methods—This was a retrospective cohort study of women with twin pregnancies followed in a tertiary medical center between 2012 and 2014. All participants underwent routine measurement of cervical length at mid-gestation and every 2–3 weeks thereafter until 28–32 weeks. For each patient, cervical length was determined at the following time periods: 18+0 to 21+6 weeks (Period 1, routine exam), 22+0 to 24+6 weeks (Period 2), 25+0 to 27+6 weeks (Period 3) and 28+0 to 32+0 weeks (Period 4). Measurements of cervical length at Periods

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Disclosure statement: The authors report no conflict of interest.

Presentation: This paper was presented as a poster at the 35th Annual Meeting of the Society for Maternal Fetal Medicine, Feb 2–7th, 2015, San-Diego.

2–4 were analyzed in the form of either absolute length (in mm) or percent shortening relative to cervical length at Period 1. The performance of a stepwise algorithm that incorporates serial measurements of cervical length for the prediction of preterm birth was compared to that achieved with a single measurement of cervical length at Period 1.

Results—Overall 441 women with twin pregnancies who were eligible for the study underwent a total of 2,374 cervical length measurements. The association of a short cervix (<10th percentile) with preterm birth at <32 weeks persisted in each of the four periods of gestation [Odds ratio (95%-confidence interval): 7.2 (3.1–16.5), 15.3 (6.4–36.7), 10.3 (4.4–24.3) and 23.1(8.3–64.1), respectively]. Compared with a single measurement of cervical length at mid-gestation (Period 1), a stepwise algorithm integrating serial cervical length measurements from all four successive gestational age periods resulted in a significant increase in the area under the ROC curve (0.917 vs. 0.613, $p<0.001$). Similarly, when a target false positive rate of 5% was used, the same stepwise algorithm was associated with a higher detection rate (69% vs. 28%, $p<0.001$), higher positive likelihood ratio (14.54 vs. 5.12) and a lower negative likelihood ratio (0.32 vs. 0.76) for preterm birth at <32 weeks compared with a single measurement of cervical length at Period 1.

Conclusions—Integration of serial measurements of cervical length using a stepwise algorithm in asymptomatic women with twin gestations can improve the detection of women at risk of preterm birth. Prospective studies are needed to validate these findings, and to investigate whether improved risk assessment performance is sufficient to offset the additional costs associated with serial cervical length measurements.

Condensation

Serial measurements of sonographic cervical length improve the predictive accuracy for preterm birth in twin gestations.

Keywords

cervical shortening; cervix; labor; prematurity; screening; prediction; preterm labor; cervical ripening; biomarker; longitudinal study; pregnancy; ultrasound

INTRODUCTION

Preterm birth (PTB) is the main cause of neonatal mortality and morbidity in twin pregnancies.^{1–16} Although current interventions for the prevention of PTB in women with twins are of limited success,^{17–36} early prediction of PTB in these pregnancies can assist care providers in identifying those women with twin gestation who are at the highest risk of PTB and who may benefit from closer monitoring and administration of antenatal corticosteroids for fetal lung maturation.^{29, 37–47} Furthermore, identification of patients at risk is a prerequisite for testing interventions to reduce the rate of preterm birth.

Cervical length (CL) at midtrimester, as measured by transvaginal ultrasound, is a powerful predictor of PTB in both singleton^{23, 48–68} and twin gestations.^{37, 42, 69–92} However, given the fact that, in some cases, cervical shortening may become evident only later during the second trimester, it seems reasonable that serial monitoring of CL may improve the overall detection of women who are at high risk of PTB.^{93–97} In an effort to improve the predictive

accuracy of CL, measurement of CL is often repeated during the second and early third trimester.^{78, 81, 98–106} However, evidence that serial measurements of CL improve the prediction of PTB is limited, and the results of available studies are conflicting.^{107–109} In a recent systematic review and meta-analysis on the predictive accuracy of changes in sonographic CL over time in singleton and twin pregnancies, Conde-Agudelo and Romero found that the shortening of cervical length over time had only a low to moderate predictive accuracy for preterm birth.¹¹⁰ The contradictory results may be related to the limitations of some of the studies which have been subject to systematic review and meta-analysis. For example, some studies have a small sample size, and there is variability in the timing of CL measurement, the definition of cervical shortening, and the cutoff of CL used to define a short cervix. In addition, in most of these studies, the analysis of the predictive value of serial measurements of CL was limited to data derived from only two sequential measurements of CL.

The aim of the current study was to determine whether the integration of information obtained from serial measurements of CL can improve the prediction of PTB in asymptomatic women with twin gestations compared to a single measurement of cervical length at 18+0 to 21+6 weeks of gestation.

MATERIALS AND METHODS

Study population

This was a retrospective study of all women with twin gestations who were followed in the Twins Clinic in a single referral center between January 2012 and December 2014. Pregnancies complicated by any of the following conditions were excluded: less than 3 measurements of cervical length during gestation, cervical cerclage, uncertain pregnancy dating, indicated preterm delivery at <34 weeks for maternal or fetal indications, birth weight of either twin <500g, gestational age at delivery <24 weeks, stillbirth of one or both fetuses, monoamniotic twins, monochorionic twins complicated by twin-to-twin transfusion syndrome (TTTS), or genetic or structural anomalies. The rationale for the exclusion of women who gave birth before 24 weeks is that in most cases these women would not have multiple measurements of cervical length (which is the focus of the current study). In addition, these women most likely represent a different subgroup of pregnancies resulting in late miscarriage or pre-viable preterm birth for whom the cervical changes will be seen very early and will be very evident, and so the contribution of serial monitoring of cervical length in these cases is expected to be minor. The study was approved by the Sunnybrook Health Sciences Center Research Ethics Board.

Monitoring of cervical length

All women were followed by a single physician in the Twins Clinic of the Sunnybrook Health Sciences Center during the study period. All women who are being followed in this clinic undergo serial transvaginal measurement of CL every 2–3 weeks between 14–18 weeks and 28–32 weeks of gestation. Progesterone was not used in the management of women with twins and a short cervix given the lack of solid evidence regarding the benefit of progesterone in this context. Cervical cerclage was performed in selected cases of women

with suspected mechanical cervical insufficiency (N=18), and these cases were excluded from the analysis. Women who were noted to have a short cervix were recommended to decrease the level of activity, although it was advised to avoid strict bed rest. There was no standardized protocol with respect to activity restriction. All sonographic measurements included in the study involved only asymptomatic women. Women with preterm labor and women receiving tocolysis for premature contractions were not included in the analysis. The obstetrician in the Twins Clinic was not blinded to the results of CL measurement.

All sonographic examinations were performed by experienced sonographers. Sonographic CL measurement was performed transvaginally with an empty bladder, according to a standard technique.¹¹¹ Briefly, the measurement of cervical length was performed in a sagittal plane, visualizing the full length of the cervical canal from the internal os to the external cervical os while exerting as little pressure with the transducer as possible. Unless there was evidence of severe cervical shortening, the measurement of cervical length is repeat following fundal pressure or the Valsalva maneuver. At least three measurements were obtained and the shortest measurement was recorded.

Data collection

Data were extracted from the medical charts and included demographic and obstetrical characteristics, chorionicity, validation of gestational age by first trimester ultrasound, pregnancy complications, presence of cervical cerclage, and neonatal outcome. The reports of all ultrasound examinations performed during pregnancy were reviewed in detail for information on CL.

Predictive value of cervical length at each period

For each patient, CL was determined at 4 time periods along gestation: 18+0 to 21+6 weeks (Period 1), 22+0 to 24+6 weeks (Period 2), 25+0 to 27+6 weeks (Period 3) and 28+0 to 32+0 weeks (Period 4). When more than one measurement of CL was available within any of these periods, the value that was recorded for that period was the average of all CL measurements performed for the individual patient within this time period. The degree of cervical shortening between two given time periods was calculated as follows: $(\text{cervical length in later period} - \text{cervical length in earlier period}) / \text{cervical length in earlier period} \times 100$. Thus, lower (more negative) values reflect greater cervical shortening.

To determine whether CL has a predictive role at each of the 4 periods, the following measures of accuracy were determined for CL and percent shortening of CL at each of the 4 periods: 1) The association of short cervix ($<10^{\text{th}}$ percentile within each specific period) with delivery <32 weeks using logistic regression analysis; 2) The correlation between CL and gestational age at birth (using Pearson's correlation coefficient); and 3) The area under the ROC curve (AUC) for delivery <32 weeks.

Integration of serial measurements of cervical length

To determine whether integration of serial measurements of CL can improve the predictive accuracy for PTB compared with a single measurement of CL at Period 1, we compared the

performance of 4 models/algorithm that integrated increasing numbers of CL measurements using a stepwise approach (Supplemental Figure 1):

1. $CL_{\text{Period1}} < \text{threshold1}_{\text{mm}}$ (Supplemental Figure 1A);
2. $CL_{\text{Period1}} < \text{threshold1}_{\text{mm}}$ OR $CL_{\text{Period2}} < \text{threshold2}_{\text{mm}}$ (Supplemental Figure 1B);
3. $CL_{\text{Period1}} < \text{threshold1}_{\text{mm}}$, $CL_{\text{Period2}} < \text{threshold2}_{\text{mm}}$, OR $CL_{\text{Period3}} < \text{threshold3}_{\text{mm}}$ (Supplemental Figure 1C);
4. $CL_{\text{Period1}} < \text{threshold1}_{\text{mm}}$, $CL_{\text{Period2}} < \text{threshold2}_{\text{mm}}$, $CL_{\text{Period3}} < \text{threshold3}_{\text{mm}}$, OR $CL_{\text{Period4}} < \text{threshold4}_{\text{mm}}$ (Supplemental Figure 1D).

These models/algorithms were designed using a pragmatic stepwise approach that can be easily applied to clinical practice. Once CL at any given period was below the threshold for that specific period, that result of the model was classified as POSITIVE, and no further CL measurements were required. If all CL measurements included in the model were equal or above their corresponding thresholds, the result of the model was classified as NEGATIVE. Women who had missing CL measurements in the later periods because they gave birth prematurely (e.g., women who gave birth at 27 weeks of gestation and therefore could not have a CL measurement in Period 4) were classified as either TRUE POSITIVE (if any of the previous CL measurements were below their corresponding threshold) or FALSE NEGATIVE (if all of the previous CL measurements prior to the premature birth were equal or above their corresponding threshold) (Supplemental Figure 1). Women for whom information on CL in one or more periods was missing for reasons other than preterm birth, were not included in the calculation of the performance of models that were based on CL measurements in these periods. For this reason, the number of women used for the calculation of the performance of the four models was highest for model 1 and lowest for model 4.

To facilitate comparison of the detection rate of the different models, the predictive accuracy of each of the 4 models was determined for the same target false positive rate (2% and 5%). Practically, the only way on to maintain such a fixed false positive rate for models that integrate serial measurements of CL was through the use of lower CL threshold values for the early periods (i.e., Periods 1 and 2) in these models compared with the threshold values used during the same periods for models that integrate only one or two measurements of CL (i.e., models 1 and 2). Thus, for example, the threshold of CL used in Period 1 was highest in the case of model 1 and lowest in the case of model 4. An iteration process was used to identify the set of thresholds of CL at each of the periods that yields the highest detection rate for the target false positive rate for each of the four models.

The following measures of predictive accuracy for PTB were calculated for each of the models: 1) area under the ROC curve (AUC), 2) Detection rate (DR, or sensitivity), 3) False-positive rate (FPR, or 1-specificity), 4) Positive and negative predictive values (PPV and NPV, respectively), and 5) Positive and negative likelihood ratios (LR+ and LR-, respectively). A LR+ >10 and a LR- <0.1 were considered to provide strong predictive

evidence; LR+ of 5–10 and LR– of 0.1–0.2 were considered to reflect moderate predictive value; and LR+ <5 and LR– >0.2 reflect only low predictive value.

The same process described above was performed for another set of 4 models that similarly integrated increasing number of CL measurements but analyzed the percent shortening of CL rather than absolute CL:

1. $CL_{\text{Period1}} < \text{threshold1}_{\text{mm}}$;
2. $CL_{\text{Period1}} < \text{threshold1}_{\text{mm}}$ OR percent shortening Periods 1→2 < threshold2%;
3. $CL_{\text{Period1}} < \text{threshold1}_{\text{mm}}$, percent shortening Periods 1→2 < threshold2% OR percent shortening Periods 1→3 < threshold3%;
4. $CL_{\text{Period1}} < \text{threshold1}_{\text{mm}}$, percent shortening Periods 1→2 < threshold2%, percent shortening Periods 1→3 < threshold3% OR percent shortening Periods 1→4 < threshold4%.

Statistical analysis

Student's t-test was used for comparison of mean cervical length at each of the four periods in women who did or did not delivery at <32 weeks. The McNemar's test for correlated proportions was used to compare the detection rate of the different models using the model that is based on a single measurement of CL at Period 1 (model 1) as reference. The AUC of the different models were compared based on the method of Hanley¹¹² and using the AUC of the model that is based on a single measurement of CL at Period 1 (model 1) as reference.

Statistical analysis was performed with SPSS v21.0 software (Armonk, NY: IBM Corp). Results were considered significant when the P-value was less than 0.05.

RESULTS

Characteristics of study population

A total of 586 women with twin pregnancies were identified during the study period, of whom 441 (75.3%) were eligible for the study and contributed 2,374 measurements of CL (Table 1). The rate of PTB at less than 34 and 32 weeks was 15.9% and 7.9%, respectively (Table 1).

Relationship between cervical length at different periods of gestation and risk of preterm birth

The first question that we addressed was whether measurement of CL at different periods of gestation can identify women who will give birth prematurely. Figure 1 presents the mean CL at each of the four periods of gestation in women who did or did not give birth prior to 32 weeks of gestation. The mean CL was significantly lower in women who gave birth prior to 32 weeks at each of the four gestational age periods and these differences increased with gestational age (Figure 1). The fact that measurement of CL at any of the 4 periods is predictive of PTB is also reflected by the observation that a short cervix (<10th percentile) at each of the 4 periods was significantly associated with PTB <32 weeks, by the significant

correlation between CL at each of the 4 periods and gestational age at birth, and by the AUC for PTB<32 weeks at each of the 4 periods (Table 2).

Relationship between cervical shortening and the risk of preterm birth

The value of serial CL measurements can also be analyzed by means of the relative degree of cervical shortening between successive periods rather than the absolute CL at each period. Similar to the absolute measurements of CL at each period of gestation, the degree of cervical shortening between successive periods (expressed as percent shortening) discriminated between women who did or did not give birth prematurely (Figure 2). The fact that the degree of cervical shortening is predictive of PTB is also reflected by the significant association of a high degree of cervical shortening (<10th percentile) with PTB <32 weeks, by the significant correlation between percent shortening at each of the 4 periods and gestational age at birth, and by the AUC for PTB<32 weeks at each of the 4 periods (Table 3).

Does the integration of serial measurements of cervical length improve the predictive accuracy for preterm birth?

Finally, given that measurement of CL at each of the 4 periods was found to be predictive of PTB, we questioned whether integration of serial measurements of CL at each of these periods using a stepwise algorithm can improve the prediction of PTB (Supplemental Figure 1).

We first addressed this question by comparing the predictive accuracy of models that integrated two (Periods 1 and 2), three (Periods 1, 2 and 3) and four (Periods 1, 2, 3 and 4) successive measurements of CL with that achieved by a single measurement of CL at mid gestation (Period 1). The AUC for the prediction of PTB <32 weeks increased with the number of CL measurements included in the model (0.795, 0.815 and 0.917 for integration of two, three and four measurements, respectively) and was significantly higher than that achieved with a single measurement of CL at Period 1 (0.613, $p<0.005$) (Figure 3). Similarly, for a given target false positive rate (2% or 5%), integration of each additional measurement of CL increased the detection rate and the positive likelihood ratio, and decreased the negative likelihood ratio for PTB <32 weeks (Table 4). The detection rate achieved with a model that integrated all 4 measurements of CL was significantly higher than that achieved with a single measurement of CL at period 1 (for false positive rate 2%: 62% vs. 19%, $p=0.025$; for false positive rate 5%: 69% vs. 28%, $p=0.019$) (Table 4). Measurement of CL at Period 2 and Period 4 had the largest relative contribution to the overall detection rate (Table 4).

Findings were similar when the serial measurements of CL were analyzed as percent shortening (relative to CL at period 1) rather than absolute length (Figure 4 and Table 5). The AUC for the prediction of PTB <32 weeks increased with the number of CL measurements (analyzed as percent shortening relative to CL at Period 1) included in the model (0.784, 0.830 and 0.929 for integration of two, three and four measurements, respectively) and was significantly higher than that achieved with a single measurement of CL at Period 1 (0.613, $p<0.007$) (Figure 4). Similarly, for a given target false positive rate

(2% or 5%), integration of each additional measurement of CL increased the detection rate and the positive likelihood ratio, and decreased the negative likelihood ratio for PTB <32 weeks (Table 5). The detection rate achieved with a model that integrated all 4 measurements of CL was significantly higher than that achieved with a single measurement of CL at period 1 (for false positive rate 2%: 69% vs. 19%, $p=0.016$; for false positive rate 5%: 77% vs. 28%, $p=0.016$) (Table 5).

COMMENTS

Principal findings of the study

1) Cervical length measured in asymptomatic women with twin gestations is associated with PTB at < 32 weeks of gestation, even when measurements are performed during the late second or early third trimester; 2) Integration of the information obtained from serial measurements of CL in asymptomatic women with twins, either in the form of absolute values of CL or relative degree of cervical shortening, can improve the prediction of PTB at <32 weeks (i.e., increase the detection rate without increasing the false positive rate) compared with a single measurement of CL at mid-gestation.

Results of the study in the context of other observations

CL was predictive of PTB when measured during late 2nd trimester or early 3rd trimester. This finding is in agreement with previous studies.^{81, 100, 104} For example, Levêque et al., in a study of 120 asymptomatic women with twin pregnancies found that measurement of CL at either 22 weeks or 27 weeks was associated with the risk of PTB at <34 weeks.¹⁰⁴

Since cervical shortening may only become evident for the first time late in the second trimester, it is reasonable to assume that serial measurement of CL will detect more women who are at risk of PTB that were not identified as such based on CL measurement at mid-gestation. A potential concern, however, is that repeated measurements of CL would also increase the overall false positive rate for PTB compared with a single measurement of CL at mid-gestation. However, we have demonstrated that integration of the information obtained from serial measurements of CL improves the detection of women at risk of PTB (compared with a single measurement of CL at mid-gestation) without increasing the overall false positive rate. The reason for this is that when serial measurements of CL are employed, lower thresholds of CL can be used to define the test as positive when CL is measured during the second trimester (e.g., Periods 1 and 2), thereby decreasing the overall false positive rate.

Although the use of such lower thresholds would decrease the detection rate of each individual measurement of CL, the overall cumulative detection rate achieved with the multiple measurements of CL is higher than that achieved with a single measurement of CL at Period 1 that uses a higher threshold. This is demonstrated clearly in Tables 4 and 5 where in models that integrated more than one measurement of CL, the thresholds used for CL at Period 1 were lower than that used by the model that included only a single measurement of CL at Period 1.

In contrast to our findings, previous studies, including a recent meta-analysis, concluded that information on cervical shortening between successive measurements of CL in twins is not beneficial and provides only little added benefit over a single measurement of CL.^{100–102, 104, 110} However, in addition to the small number of available studies, the interpretation of these data is limited by small sample size and variation in the number and timing of CL measurement, the definition of cervical shortening (e.g., mm/week vs. percent shortening), and definition of the outcome measures (e.g., some studies used delivery at less than 35 or 36 weeks as the primary outcome measure which is of questionable clinical significance).^{78, 81} Most importantly, in all of these studies, the analysis of cervical shortening was limited to the change in CL between only two time points, so that data regarding the integration of multiple (more than two) serial measurements of CL in twins, as was done in the current study, are lacking.

Strengths and Limitations

This is the largest study on serial measurements of CL in asymptomatic women with twins, and the first to assess the effect of integration of multiple (>2) measurements of CL on the predictive accuracy for PTB. Another advantage is that all women were followed in a single clinic dedicated to twin pregnancies according to a standardized protocol, and all sonographic measurements of CL were performed by experienced sonographers.

The main limitations of the study include its retrospective design, those related to missing information, unknown generalizability to broader populations, and that care providers were not blinded to cervical length measurements. Although we included only asymptomatic women, it cannot be ruled out that, given the retrospective design, a small number of women with some degree of uterine activity were included in the study either because they did not report it to their care provider or because the care provider did not mention it in the chart. Another limitation relates to fact that the number of women used for the calculation of the performance of the models was not identical for all four models and decreased with the number of measurements included in the model (i.e., the number of women was highest for model 1 and lowest for model 4). This was the result of the fact that for some women information of CL was not available for all four gestational age periods, mainly due to missed visits. The variation in the size of the study groups used to assess the performance of the four models may complicate the direct comparison between the models and may result in a detection rate that might be optimistically high. In addition, the use of lower thresholds of CL in the earlier periods of gestation (such as in the case of models that integrate 3 or 4 measurements of CL) may delay the detection of some women who are at risk of early PTB.

Conclusion and clinical implications

Integration of serial CL measurements can improve the detection rate for PTB in asymptomatic women with twin gestations, without increasing the fraction of women who receive false positive risk determinations. Better detection of women at risk of PTB is important for patient counseling and can guide decisions regarding patient transfer, admission, frequency of monitoring, and administration of corticosteroids for fetal lung maturation. Indeed, in a recent study, serial monitoring of CL in twins was associated with improved rates of exposure to corticosteroids in women who delivered preterm,⁴⁶ although

data regarding the beneficial effects of antenatal corticosteroids in twins pregnancies are conflicting.^{113–123} In addition, in a recent individual-patient meta-analysis, Romero et al. found that the use of progesterone in asymptomatic women with twin pregnancy and a short cervix decreased the rate of PTB at <33 weeks by 30% and the rate of neonatal morbidity by approximately 50%.⁶⁶ Similarly, in a recent randomized controlled trial of women with twin pregnancy and a short cervix, it was found that administration of progesterone decreased the likelihood of preterm birth and the rate of neonatal morbidity.¹²⁴ Finally, there is recent evidence that cervical pessary may decrease the likelihood of preterm birth in women with twin pregnancies.^{36, 125–129} Thus, the improved prediction of PTB using serial measurement of CL may facilitate treatment with progesterone if more evidence becomes available to support the use of progesterone in that context.^{22, 26, 66, 124, 130, 131} Still, it should be emphasized that there is currently no level-I evidence that routine monitoring of cervical length in women with twin pregnancies improves pregnancy outcome,¹³² and therefore current recommendations do not support such a practice.¹³³

Prospective studies are required to confirm our findings, and to determine whether the enhanced risk assessment translates into health benefits sufficient to offset the additional costs or burden incurred by incorporating serial cervical length measurement into routine practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of financial support: This research was supported, in part, by the Perinatology Research Branch, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services (NICHD/NIH); and, in part, with Federal funds from NICHD, NIH under Contract No. HSN27520130000

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Figure 1. Cervical length at each period of gestation in women who did or did not deliver at < 32 weeks

* $p < 0.001$ (Student's t-test).

Data reflect the mean cervical length at each gestational age period.

Similar findings were observed for women who did or did not deliver at < 34 weeks (data not shown).

Figure 2. Change in cervical length between successive periods of gestation in women who did or did not deliver at <32 weeks

* $p < 0.001$

** $p < 0.01$

Data reflect the change in cervical length between different period of gestation. The change in cervical length was calculated as follows: $(\text{cervical length in later period} - \text{cervical length in earlier period}) / \text{cervical length in earlier period} \times 100$. Thus, lower (more negative) values reflect greater cervical shortening.

Similar findings were observed for women who did or did not deliver at <34 weeks (data not shown).

Figure 3. Effect of serial measurements of cervical length (interpreted as absolute length in mm) on the ROC curve for the prediction of preterm birth <32 weeks

ROC, Receiver operating characteristic; AUC, area under the ROC curve; CL cervical length

ROC curves are presented for: single measurement of CL in Period 1 (blue line), combination of CL in periods 1 and 2 (green line), combination of CL in periods 1, 2 and 3 (orange line), and combination of CL in periods 1, 2, 3 and 4 (red line).

* $p < 0.001$ compared with AUC of single measurement of cervical length in period 1

** $p = 0.004$ compared with AUC of single measurement of cervical length in period 1

Figure 4. Effect of serial measurements of cervical length (interpreted as percentage shortening compared with period 1) on the ROC curve for the prediction of preterm birth <32 weeks
 ROC, Receiver operating characteristic; AUC, area under the ROC curve; CL cervical length
 ROC curves are presented for: single measurement of CL in Period 1 (blue line), combination of CL in period1 and percentage shortening between period 1→2 (green line), combination of CL in period1 and percentage shortening between periods 1→2 and 1→3 (orange line), and combination of CL in period1 and percentage shortening between periods 1→2, 1→3 and 1→4 (red line).

* $p < 0.001$ compared with AUC of single measurement of cervical length in period 1

** $p = 0.007$ compared with AUC of single measurement of cervical length in period 1

Table 1

Characteristics of the study group

Characteristic	Value
N	441
Maternal age (years)	32.9 ± 4.1
Chorionicity	
DC/DA	358 (81.2)
MC/DA	83 (18.8)
Number of Cervical length measurements	
Total	2,374
Period 1: 18+0 to 21+6	688
Period 2: 22+0 to 24+6	605
Period 3: 25+0 to 27+6	620
Period 4: 28+0 to 32+0	461
GA at delivery (weeks)	35.4 ± 2.4
<34 weeks	70 (15.9)
<32 weeks	35 (7.9)
Birthweight (gr)	
Twin A	2389 ± 557
Twin B	2333 ± 567

DC, di-chorionic; DA, di-amniotic; MC, mono-chorionic

Values are presented as N (%) or mean ± SD unless stated otherwise.

Risk of preterm delivery in women with short cervix (<10th percentile) diagnosed at different periods of gestation

Table 2

Gestational age period	Mean $\pm$ SD (mm)	10 th percentile (mm)	Association of CL <10 th percentile with delivery < 32 weeks OR (95%-CI)	Correlation with GA at delivery	AUC for delivery <32 weeks (95%-CI)
Period 1: 18+0 to 21+6	37.3 $\pm$ 7.1	30	7.2 (3.1–16.5)	0.166 *	0.72 (0.55–0.88)
Period 2: 22+0 to 24+6	36.4 $\pm$ 8.7	25	15.3 (6.4–36.7)	0.286 *	0.85 (0.73–0.98)
Period 3: 25+0 to 27+6	33.5 $\pm$ 10.4	19	10.3 (4.4–24.3)	0.290 *	0.85 (0.71–0.98)
Period 4: 28+0 to 32+0	29.7 $\pm$ 11.4	13	23.1 (8.3–64.1)	0.350 *	0.89 (0.78–1.00)

CL, cervical length; GA, gestational age; AUC, area under the receiver operating characteristics (ROC) curve

* Pearson's correlation coefficient , p-value <0.01

Table 3

Risk of preterm delivery in women with cervical shortening between different periods of gestation

Gestational age periods [†]	Mean ± SD (%)	10 th percentile (%) [‡]	Association of percentage shortening <10 th percentile with delivery < 32 weeks [‡] OR (95%-CI)	Correlation with GA at delivery	AUC for delivery <32 weeks (95%-CI)
Change in CL between periods 1 → 2	-0.2% ± 20.8%	-26.8%	7.1 (3.0–17.1)	0.178 **	0.76 (0.59–0.94)
Change in CL between periods 1 → 3	-8.6% ± 26.0%	-43.3%	7.5 (3.0–18.9)	0.215 **	0.74 (0.55–0.92)
Change in CL between periods 1 → 4	-19.8% ± 27.9%	-57.2%	17.0 (6.0–48.0)	0.301 **	0.85 (0.71–0.99)
Change in CL between periods 2 → 3	-7.0% ± 21.9%	-31.6%	6.7 (2.7–17.6)	0.132 *	0.62 (0.44–0.80)
Change in CL between periods 2 → 4	-18.5% ± 23.2%	-50.0%	10.5 (3.2–34.1)	0.258 **	0.85 (0.73–0.97)
Change in CL between periods 3 → 4	-10.3% ± 25.6%	-41.0%	8.1 (2.8–23.3)	0.124 **	0.74 (0.57–0.91)

CL, cervical length; GA, gestational age; AUC, area under the receiver operating characteristics (ROC) curve

* p-value <0.05,

** Pearson's correlation coefficient, p-value <0.01

[†] Calculated as follows: [(cervical length in later period – cervical length in earlier period) / cervical length in earlier period] x 100. Thus, lower (more negative) values reflect greater cervical shortening.

[‡] Values below the 10th percentile reflect cases with the greatest (most negative) cervical shortening.

Table 4

Effect of serial measurements of cervical length (interpreted as absolute length in mm) on the predictive accuracy for preterm birth <32 weeks

Model	Thresholds* (mm)				Predictive accuracy										Relative contribution to DR			
	P1	P2	P3	P4	TP (n)	FP (n)	TN (n)	DR (%)	FPR (%)	PPV (%)	NPV (%)	LR+	LR-	P-value	P1	P2	P3	P4
For FPR of 2%																		
CL on Period 1 < threshold	26				6	8	26	374	19%	2%	43%	8.95	0.83	Ref	19%			
CL on Periods 1 OR 2 < thresholds	23	20			10	8	17	333	37%	2%	56%	15.79	0.64	0.13	13%	37%		
CL on Periods 1, 2 OR 3 < thresholds	20	15	10		7	5	14	313	33%	2%	58%	21.20	0.68	0.24	6%	22%	33%	
CL on Periods 1, 2, 3 OR 4 < thresholds	15	14	12	10	8	5	5	226	62%	2%	62%	28.43	0.39	0.025	6%	19%	32%	62%
For FPR of 5%																		
CL on Period 1 < threshold	29				9	21	23	361	28%	5%	30%	5.12	0.76	Ref	28%			
CL on Periods 1 OR 2 < thresholds	26	25			13	18	14	323	48%	5%	42%	9.12	0.55	0.22	19%	48%		
CL on Periods 1, 2 OR 3 < thresholds	25	23	17		10	15	11	303	48%	5%	40%	10.10	0.55	0.22	13%	44%	48%	
CL on Periods 1, 2, 3 OR 4 < thresholds	25	20	15	10	9	11	4	220	69%	5%	45%	14.54	0.32	0.019	13%	37%	40%	69%

CL, cervical length; TP, true positive; FP, false positive; FN, false negative; TN, true negative; DR, detection rate (=sensitivity); FPR, false positive rate (=1-specificity); PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; P1, Period 1 (18+0 to 21+6 weeks); P2, Period 2 (22+0 to 24+6 weeks); P3, Period 3 (25+0 to 27+6 weeks); P4, Period 4 (28+0 to 32+0 weeks).

The predictive accuracy of serial measurements of cervical length (interpreted as absolute length in mm) for preterm birth <32 weeks was calculated for 4 combinations of serial measurements of cervical length: Period 1 only, Periods 1+2, Periods 1+2+3, and Periods 1+2+3+4.

*For each of the 4 combinations, the predictive accuracy was calculated using different sets of thresholds. These thresholds were determined using an iteration process that identified the set of thresholds that is associated with the highest detection rate for each of the following target levels of false positive rate: 2% and 5%.

Table 5

Effect of serial measurements of cervical length (interpreted as percentage shortening compared with period 1) on the predictive accuracy for preterm birth <32 weeks

Model	Thresholds *					Predictive accuracy										Relative contribution to DR			
	P1 (mm)	P2 (%)	P3 (%)	P4 (%)	TP (n)	FP (n)	FN (n)	TN (n)	DR (%)	FPR (%)	PPV (%)	NPV (%)	LR+	LR-	P- value	P1	P2	P3	P4
For FPR of 2%																			
CL on Period 1 < threshold	26mm				6	8	26	374	19%	2%	43%	94%	8.95	0.83	Ref	19%			
CL on Periods 1 < threshold OR percentage shortening between Periods 1→2 < threshold	20mm	-40%			9	6	18	335	33%	2%	60%	95%	18.94	0.68	0.15	6%	33%		
CL on Periods 1 < threshold OR percentage shortening between Periods 1→2 or 1→3 < threshold	15mm	-40%	-60%		8	6	13	312	38%	2%	57%	96%	20.20	0.63	0.063	6%	33%	38%	
CL on Periods 1 < threshold OR percentage shortening between Periods 1→2, 1→3 or 1→4 < threshold	20mm	-60%	-70%	-72%	9	5	4	226	69%	2%	64%	98%	31.98	0.31	0.016	6%	7%	25%	69%
For FPR of 5%																			
CL on Period 1 < threshold	29mm				9	21	23	361	28%	5%	30%	94%	5.12	0.76	Ref	28%			
CL on Periods 1 < threshold OR percentage shortening between Periods 1→2 < threshold	25mm	-32%			12	17	15	324	44%	5%	41%	96%	8.92	0.58	0.17	13%	44%		
CL on Periods 1 < threshold OR percentage shortening between Periods 1→2 or 1→3 < threshold	25mm	-34%	-60%		9	16	12	302	43%	5%	36%	96%	8.52	0.60	0.16	13%	42%	43%	
CL on Periods 1 < threshold OR percentage shortening between Periods 1→2, 1→3 or 1→4 < threshold	15mm	-34%	-60%	-74%	10	12	3	219	77%	5%	45%	99%	14.81	0.24	0.016	6%	41%	45%	77%

CL, cervical length; TP, true positive; FP, false positive; FN, false negative; TN, true negative; DR, detection rate; FPR, false positive rate; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; P1, Period 1 (18+0 to 21+6 weeks); P2, Period 2 (22+0 to 24+6 weeks); P3, Period 3 (25+0 to 27+6 weeks); P4, Period 4 (28+0 to 32+0 weeks). The predictive accuracy of serial measurements of cervical length (interpreted as percentage shortening compared with period 1) for preterm birth <32 weeks was calculated for 4 combinations of serial measurements: Period 1 only, Period 1 + %shortening between period 1→2, Period 1 + %shortening between periods 1→2 and 1→3, and Period 1 + %shortening between periods 1→2, 1→3 and 1→4.

* For each of the 4 combinations, the predictive accuracy was calculated using different sets of thresholds. These thresholds were determined using an iteration process that identified the set of thresholds that is associated with the highest detection rate for each of the following target levels of false positive rate: 2% and 5%.