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The Change in Cervical Length Over Time as a Predictor of Preterm Delivery in Asymptomatic Women With Twin Pregnancies Who Have a Normal Mid-Trimester Cervical Length

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Aim: To determine whether or not the change in cervical length (CL) over time is valuable in predicting spontaneous preterm delivery (SPTD) in asymptomatic twin pregnancies with a normal mid-trimester CL (>25 mm). *Methods:* This was a prospective study including 190 consecutive asymptomatic twin gestations with a CL > 25 mm at 20–24 weeks. The women underwent an initial CL measurement at the time of routine ultrasound examination between 20 and 24 weeks' gestation, followed 4–5 weeks later by a repeat CL measurement. The primary outcome measure was SPTD at <32 completed weeks' gestation. Multicollinearity was a concern in the multivariable model since change in CL and follow-up CL were highly correlated. *Results:* The rate of SPTD at <32 weeks was 4.2%. Multiple logistic regression analyses demonstrated that the change in CL and the follow-up CL were significantly associated with SPTD before 32 weeks after adjusting for baseline covariate such as in vitro fertilization. The best cut-off values for the prediction of SPTD at <32 weeks' gestation were 13% for the change in CL with a sensitivity of 87.5% and a specificity of 63.2%. There was no significant difference in the area under the receiver operating characteristic curves between the change in CL and the follow-up CL. *Conclusions:* A greater change in CL is a good predictor of SPTD in asymptomatic twin pregnancies with a normal mid-trimester CL. However, the change in CL cannot provide data beyond the follow-up CL. In the setting of a normal mid-trimester CL, a follow-up CL measurement should be considered in asymptomatic twin pregnancies.

■ **Keywords:** cervical length, change in cervical length, prediction, preterm birth, transvaginal ultrasound, twin

Measurement of cervical length (CL) by transvaginal ultrasound (TVS) is known to be effective in identifying twin gestations at increased risk for preterm delivery (Goldenberg et al., 1996; Guzman et al., 2000; Souka et al., 1999; To et al., 2006; Yang et al., 2000). A recent meta-analysis indicated that among asymptomatic women with twin pregnancies, a CL ≤ 20 mm at 20–24 weeks' gestation is the most accurate in predicting preterm birth at <32 and <34 weeks' gestation, but a 'normal' CL (defined as a CL > 25 mm) was less accurate in predicting the absence of preterm birth (Conde-Agudelo et al., 2010). Similarly, several studies have reported that approximately one half of women with spontaneous preterm delivery (SPTD) at < 32 weeks have a CL > 25 mm at 20–24 weeks (Conde-Agudelo et al., 2010; Fox et al., 2009; Goldenberg et al., 1996; Yang et al., 2000). At present, however, there is no effective tool to predict the risk of SPTD in the absence of a short CL, despite the fact that by identifying such a high-risk group for SPTD, possible interventions in this cohort can be studied to test their effectiveness.

Recent studies involving singleton pregnancies have shown that a reduction in CL over time is associated with SPTD (Fox et al., 2007; Naim et al., 2002). However, with respect to twin pregnancies, there is limited data on the relationship between the change in CL and SPTD, and the

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results are conflicting; some studies have shown a significant association (Bergelin & Valentin, 2003; Fox et al., 2010; Gibson et al., 2004), while another study has failed to do so (Ong et al., 2000). This disagreement may be due to the relatively small sample size, study design (i.e., prospective or retrospective), and different definitions for the change in CL (i.e., absolute or percentage change in CL over time) in previous studies. The purpose of the current study was to determine whether or not the change in CL over time is valuable in predicting SPTD in asymptomatic women with twin pregnancies and a CL > 25 mm at 20–24 weeks' gestation.

Materials and Methods

This was a prospective observational study which was conducted at the Seoul National University Bundang Hospital in Seongnamsi, Korea between September 2004 and February 2011. Women with twin gestations attending the antenatal clinic were consecutively enrolled in the study at 20–24 weeks' gestation. The inclusion criteria were as follows: (1) a viable twin gestation; (2) a CL > 25 mm at 20–24 weeks' gestation; (3) no history of prophylactic cervical cerclage; (4) intact amniotic membranes; (5) absence of regular uterine contractions; (6) no evidence of major fetal anomalies, suspected twin-to-twin transfusion syndrome, monoamniotic placenta, or placenta previa; and (7) well documented obstetric dates (by reliable menstrual history in agreement with an ultrasonographic examination before 20 weeks of gestation or in vitro fertilization dating). The women underwent an initial CL measurement at the time of routine ultrasound examination between 20 and 24 weeks' gestation, followed 4–5 weeks later by a repeat CL measurement. All CL measurements were performed in an outpatient setting on asymptomatic women. The change in CL (expressed as a percentage) was defined as the decrement in sonographic CL between the initial and follow-up measurements and was calculated using the following formula: $([CL_{initial} - CL_{follow\text{-}up}]/CL_{initial}) \times 100$, where CL is the cervical length in millimeters. A short CL was defined as ≤25 mm at 20–24 weeks' gestation, which has been validated in several studies (Goldenberg et al., 1996; Imseis et al., 1997). The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (Seongnamsi, Korea), and written informed consent was obtained from all study participants prior to enrollment.

The data on subject characteristics, including demographic data, previous obstetric history, and infertility treatment, were obtained at the first antenatal visit to the hospital and were entered into a computerized database. Data on the obstetric outcomes were obtained from a computerized system in the delivery ward; and in women delivering at another hospital, directly from the patients or the medical practitioners. The primary outcome measure was SPTD at <32 completed weeks' gestation (224 days); SPTD was defined as delivery after spontaneous onset of preterm labor or premature rupture of membranes. Additional analysis of SPTD at <34 completed weeks of gestation was also performed. Women who were delivered for maternal or fetal indications were excluded from the analysis of SPTD at all later gestational ages. For example, if a woman had an indicated preterm delivery at 33 weeks' gestation, such as a pregnancy complicated by pre-eclampsia, she was included in the analysis for SPTD at <32 weeks' gestation, but not included in the analysis for SPTD at <34 weeks' gestation.

Assessment of CL was performed by Maternal Fetal Medicine faculties or fellows using an Aloka SSD 5500 ultrasound machine equipped with a 6.0-MHz transducer (Aloka Co. Ltd, Tokyo, Japan). All women were asked to empty their bladders prior to the scan. The method used for measurement of CL has been described previously (Suh et al., 2007). Three measurements were performed and the shortest length was taken as the CL. The initial and follow-up CL measurements were made available to the responsible obstetrician and any interventions were instituted at their discretion. In our practice, women with a short cervix (≤25 mm) were referred to their obstetrician for expectant management. Of note, progesterone administration or hospitalization was not included in our practice for asymptomatic twin pregnancies with a short cervix.

We assumed that 5% of women with twin pregnancies and a CL > 25 mm at 20–24 weeks gestation have SPTDs at <32 weeks' gestation because previous studies have reported that the rate was 8.5–9.2% (Goldenberg et al., 1996; Guzman et al., 2000), and one half of women with SPTDs at <32 weeks' gestation have a CL > 25 mm at 20–24 weeks' gestation (Conde-Agudelo et al., 2010; Fox et al., 2009; Goldenberg et al., 1996; Yang et al., 2000). Therefore, using an alpha of 0.05 and a power of 0.8, we calculated that a sample size of 189 women would be needed to detect a 15% difference in the change in CL with a standard deviation (*SD*) of 16% (based on a pilot study).

Univariate analysis was performed with a Student's *t*-test, Mann–Whitney U test, χ^2 test, or Fisher's exact test. Shapiro–Wilk and Kolmogorov–Smirnov tests were used to affirm a normal distribution of the data. A Pearson correlation analysis was used to determine the relationship between the follow-up CL and the change in CL. Overall, logistic regression analysis was used to examine the relationship between the change in CL and SPTD at <32 and <34 weeks' gestation after adjusting for the effect of the confounders. Variables found to have a significant correlation or a tendency towards an association with SPTD at <32 and <34 weeks' gestation in univariate analysis ($p < .25$) were entered into a logistic regression model. A receiver operating characteristic (ROC) curve analysis was used to determine the relationship between the sensitivity (true-positive rate) and the false-positive rate, and to select the best cut-off values for the change in CL and the follow-up CL in the

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TABLE 1

Clinical Characteristics of the Study Population

Characteristics	Delivery <32 weeks (n = 8)	Delivery ≥32 weeks (n = 182)	p values	Delivery <34 weeks (n = 11)	Delivery ≥34 weeks (n = 175)	p values
Age (years)	33.1 ± 1.9	32.4 ± 3.4	.472	32.8 ± 2.0	32.4 ± 3.4	.658
Nulliparous	87.5% (7/8)	78.6% (143/182)	1.000	72.7% (8/11)	80.0% (140/175)	.699
Prior preterm birth before 37 weeks	0% (0/8)	1.6% (3/182)	1.000	0% (0/11)	1.7% (3/175)	1.000
Monochorionic	37.5% (3/8)	23.6% (43/182)	.404	36.4% (4/11)	23.4% (41/175)	.466
In vitro fertilization	25.0% (2/8)	53.3% (97/182)	.156	45.5% (5/11)	53.1% (93/175)	.759
Body mass index at initial TVS (kg/m^2)	24.5 ± 2.4	23.8 ± 2.9	.442	24.6 ± 2.4	23.8 ± 2.9	.359
Gestational age at initial TVS (weeks)	21.8 ± 1.4	21.9 ± 1.4	.828	21.7 ± 1.2	21.9 ± 1.4	.615
Initial CL (mm)	36.9 ± 5.5	38.5 ± 6.1	.493	37.0 ± 6.1	38.6 ± 6.1	.390
Gestational age at follow-up TVS (weeks)	25.8 ± 1.2	26.0 ± 1.4	.745	25.7 ± 1.0	26.1 ± 1.4	.413
Follow-up CL (mm)	27.7 ± 8.1	35.1 ± 7.9	.016	29.7 ± 9.8	35.1 ± 7.9	.032
Change in CL (percent)	25.7 ± 14.9	8.7 ± 15.7	.005	20.7 ± 17.8	9.3 ± 15.4	.019
Weeks between CL measurements	4.1 ± 0.4	4.2 ± 0.4	.505	4.1 ± 0.3	4.2 ± 0.4	.272
Gestational age at delivery (weeks)	30.3 ± 1.6	36.4 ± 1.3	<.001	31.0 ± 1.8	36.6 ± 1.1	<.001

Note: Values are given as mean ± standard deviation or % (n/N). TVS, transvaginal ultrasound; CL, cervical length.

prediction of SPTD at <32 weeks' gestation. Diagnostic indices were calculated (sensitivity, specificity, positive predictive value, negative predictive value, positive-likelihood ratio, and negative-likelihood ratio) for the change in CL and the follow-up CL to predict SPTD at <32 and <34 weeks' gestation. The McNemar's test was used to compare the sensitivity and specificity of the change in CL and the follow-up CL, alone or in combination, for predicting SPTD at <32 and <34 weeks' gestation. A univariate z-score test was used to estimate the statistical significance of the difference between the areas under the two ROC curves (DeLong et al., 1988). Note that, p values <.05 were considered statistically significant. SPSS 15.0.1 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

Results

During the study period, a total of 244 consecutive women were recruited at 20–24 weeks gestation for this study; 22 women (6 had cervical cerclages placed and 16 were managed expectantly) were excluded from the analysis secondary to a short initial CL (≤25 mm). Of the 222 women with a CL > 25 mm at 20–24 weeks gestation, 26 were excluded for a history-indicated cerclage ($n = 3$), occurrence of SPTD before follow-up measurement ($n = 2$), and loss to ultrasound follow-up ($n = 21$). Furthermore, six women were excluded due to development of twin-to-twin transfusion syndrome ($n = 2$), one fetal demise ($n = 1$), or an incomplete data set ($n = 3$), leaving 190 women suitable for evaluation. The mean gestational age at the time of initial TVS was 21.9 weeks (*SD*, 1.8 weeks; range, 20.0–24.6 weeks) and 26.0 weeks (*SD*, 1.4 weeks; range, 24.0–29.2 weeks) at the second examination. There were no indicated preterm deliveries in women who delivered preterm at <32 weeks' gestation. However, there were 4 indicated preterm deliveries in women who delivered preterm between 32^{+0} and 33^{+6} weeks' gestation, all of which were for pre-eclampsia. Thus, these women were excluded from the study evaluating the relationship between SPTD at <34 weeks and covariates. SPTDs at <32 and <34 weeks' gestation occurred in 4.2% (8/190) and 5.9% (11/186) of women with a CL > 25 mm at the initial CL measurement, respectively.

Table 1 lists the clinical characteristics of the study population stratified according to SPTD at <32 and <34 weeks' gestation. There were no significant associations between SPTD at <32 weeks' gestation and maternal age, initial CL, nulliparity, prior preterm births, chorionicity, in vitro fertilization, body mass index, and gestational ages at the time of initial and follow-up TVSs. However, women with a SPTD at <32 weeks' gestation had a significantly shorter mean follow-up CL and a higher mean change in CL than those who did not deliver spontaneously at <32 weeks' gestation. The same results were obtained using the secondary endpoint (SPTD at <34 weeks' gestation). The initial CL was significantly correlated with the follow-up CL ($r = .679$, $p < .001$) but not with the change in CL ($r = .032$, $p = .639$).

Multiple logistic regression analyses were performed to examine the relationship between SPTD before 32 and 34 weeks' gestation and the change in CL and follow-up CL after adjusting for the effect of other confounders (Table 2). The change in CL and the follow-up CL appear to be highly correlated ($r = .729$, $p < .0001$), suggesting multicollinearity issues in our subsequent regression analysis and thus making it difficult to identify the independent effect of each variable on the outcome. Therefore, two separate models were constructed and each model consisted of the change in CL (model 1) or the follow-up CL (model 2) in addition to another confounding variable (in vitro fertilization). The change in CL and the follow-up CL were significantly

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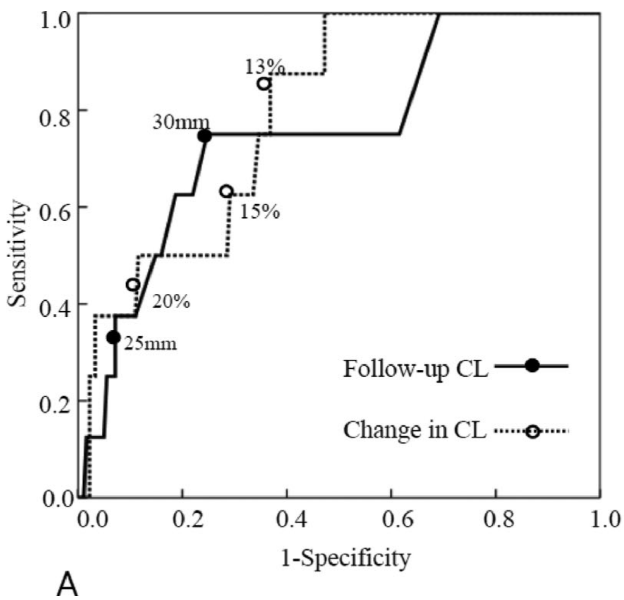

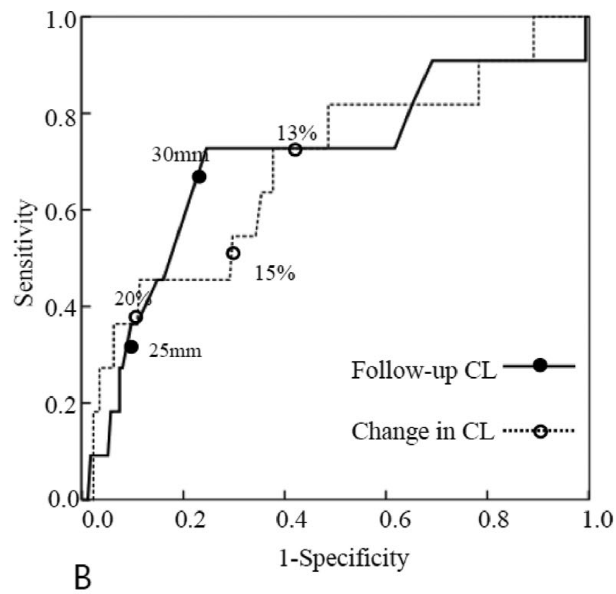

FIGURE 1

Receiver operating characteristic curves for follow-up cervical length (——) and change in cervical length (-----) in predicting spontaneous preterm delivery (A) before 32 weeks' gestation (follow-up cervical length: area under curve (AUC), 0.752; *SE*, 0.088; $p = .016$; change in cervical length: AUC, 0.793; *SE*, 0.063; $p = .005$) and (B) before 34 weeks' gestation (follow-up cervical length: AUC, 0.703; *SE*, 0.094; $p = .024$; change in cervical length: AUC, 0.688; *SE*, 0.090; $p = .037$). CL = cervical length.

TABLE 2

Logistic Regression Analysis of Independent Variables in Predicting Spontaneous Preterm Delivery Before 32 and 34 Weeks' Gestation

Predictor	Odds ratio	95% confidence interval	*p* values
	Spontaneous preterm delivery <32 weeks		
Model 1			
Change in CL (%)	1.055	1.013–1.098	.009
In vitro fertilization	0.373	0.070–1.984	.248
Model 2			
Follow-up CL (mm)	0.906	0.831–0.988	.025
In vitro fertilization	0.371	0.071–1.954	.242
	Spontaneous preterm delivery <34 weeks		
Model 1			
Change in CL (%)	1.041	1.005–1.079	.025
In vitro fertilization	0.937	0.265–3.312	.920
Model 2			
Follow-up CL (mm)	0.926	0.860–0.997	.041
In vitro fertilization	0.909	0.258–3.202	.881

Note: CL = cervical length.

associated with SPTD before 32 and 34 weeks after adjusting for in vitro fertilization.

Figure 1 displays the ROC curves for the change in CL and a follow-up CL in predicting SPTD at <32 and <34 weeks' gestation. All the curves were above the 45° line, indicating a significant relationship between these variables and SPTD at <32 and <34 weeks' gestation. The best cut-off values for the prediction of SPTD at <32 weeks' gestation were 13% for the change in CL with a sensitivity of 87.5% and a specificity of 63.2%, and 30 mm for a follow-up CL with a sensitivity of 75.0% and a specificity of 75.3%. There was no significant difference in the AUCs between the change in CL and the follow-up CL to predict SPTD before 32 weeks ($p = .432$) and before 34 weeks of gestation ($p = .824$).

Table 3 presents the following diagnostic indices predicting SPTD at <32 and <34 weeks' gestation: the change in CL; the follow-up CL; and a combination of both variables (change in CL $\geq$ 13% and CL $\leq$ 30 mm). There were no significant differences in sensitivity among the change in CL, the follow-up CL, and the combination. However, the specificity of the change in CL was significantly lower than the follow-up CL and the combination of both parameters ($p < .001$ by McNemar test).

Discussion

The results of the current study clearly demonstrate that in asymptomatic women with twin pregnancies and a normal CL at 20–24 weeks' gestation (>25 mm), a greater change in CL after the initial CL measurement is a significant predictor of preterm delivery. Nevertheless, a change in CL was not superior to a follow-up CL in predicting preterm delivery. These findings confirm and extend the previous reports by other investigators (Bergelin & Valentin, 2003; Fox et al., 2010). Further, these observations suggest that in the setting of a normal mid-trimester CL, a follow-up CL measurement should be considered in asymptomatic twin pregnancies to identify another group of twin pregnancies at risk for preterm delivery.

One of the major advantages of CL is that serial measurements can be made non-invasively as a marker of SPTD. The current study suggests that by using repeated CL measurements 4–5 weeks after a baseline CL at 20–24 weeks'

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TABLE 3

Diagnostic Indices in the Prediction of Spontaneous Preterm Delivery <32 and <34 Weeks' Gestation

Test cut-off	Sensitivity (% (*n*/*N*))	Specificity (% (*n*/*N*))	PPV (% (*n*/*N*))	NPV (% (*n*/*N*))	LR+ (95% CI)	LR– (95% CI)
Spontaneous preterm delivery <32 weeks						
Change in CL ≥13%	87.5 (7/8)	63.2 (115/182)	9.5 (7/74)	99.1 (115/116)	2.38 (1.72–3.29)	0.20 (0.03–1.24)
CL ≤ 30mm	75.0 (6/8)	75.3 (137/182)*	11.8 (6/51)	98.6 (137/139)	3.03 (1.89–4.87)	0.33 (0.10–1.11)
Change in CL ≥ 13% and CL ≤ 30 mm	75.0 (6/8)	79.1 (144/182)*	13.6 (6/44)	98.6 (144/146)	3.59 (2.20–5.86)	0.32 (0.09–1.05)
Spontaneous preterm delivery <34 weeks						
Change in CL ≥ 13%	72.7 (8/11)	62.3 (109/175)	10.8 (8/74)	97.3 (109/112)	1.93 (1.28–2.90)	0.44 (0.17–1.16)
CL ≤ 30mm	72.7 (8/11)	75.4 (132/175)*	15.7 (8/51)	97.8 (132/135)	2.96 (1.90–4.62)	0.36 (0.14–0.95)
Change in CL ≥ 13% and CL ≤ 30 mm	63.6 (7/11)	78.9 (138/175)*	15.9 (7/44)	97.2 (138/142)	3.01 (1.77–5.12)	0.46 (0.21–1.01)

Note: PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; CL, cervical length. *$p < .001$ compared with the change in CL ≥ 13% by McNemar test.

gestation, asymptomatic women with twin pregnancies can be reclassified as low or high risk for SPTD, leading to a significant improvement in risk stratification. At present, objective risk assessment has been developed mainly for women with twin gestation at 20–24 weeks gestation. The finding in our study that women in whom the change in CL is ≥13% within 4–5 weeks of an initial CL measurement at 20–24 weeks' gestation have an increased risk for SPTD could be of enormous value to clinicians. Given the significant treatment effect with preservation of the CL at 28 weeks in women who were administered intravaginal progesterone (O'Brien et al., 2009), further studies are required to determine whether or not vaginal progesterone in this subgroup can reduce the rate of early preterm birth.

A major finding of the current study was that in asymptomatic women with twin pregnancies and a CL > 25 mm at 20–24 weeks' gestation, a greater change in CL after the baseline CL measurement contributes significantly to the prediction of preterm birth. These findings are consistent with a report by another investigator (Fox et al., 2010), who demonstrated that the change in CL over time is a significant predictor of SPTD, even in the absence of a short cervix. These observations were novel, but not unexpected because a previous study revealed that independent of the baseline CL, more rapid shortening of the cervix increases the risk of preterm birth (Naim et al., 2002). However, the current results are different from the findings of Gibson et al. (Gibson et al., 2004) who showed that the change in CL from 18–24 weeks or 24–28 weeks has poor predictive value for SPTD prior to 35 weeks' gestation. The basis for the discrepancy between these two studies is not clear, but it may be related to sample size (91 women vs. 190 women) and the different definitions for change in CL over two measurements. In the current study, the change in CL was defined as a percentage change in the CL over time, while according to Gibson et al., the change in CL was defined as an absolute change. Cervical changes might be better represented by assessing a percentage change rather than an absolute change, especially when the baseline values are low. This is because for any given absolute change in length, a smaller baseline length yields a larger measure of percentage change.

In our population of patients with a CL > 25 mm, a greater change in CL was detected in 87% of women with SPTD at <32 weeks' gestation, with a 4.2% risk of SPTD at <32 weeks' gestation overall. Adding a follow-up CL ≤ 30 mm as a screening criterion significantly increased the specificity from 63% to 79%. Indeed, it is of clinical importance to define the subgroup of women with twin pregnancies at low risk for SPTD based on the well-known a priori odds of complications. In the current study, the false-negative rate was very low; the values were nearly the same whether using the change in CL or the follow-up CL. Although, higher negative predictive values in the current study may have been achieved because our patients had a lower incidence of SPTD at <32 weeks' gestation and were at low-risk twins for SPTD at <32 weeks' gestation, it appears that CL shortening and/or a CL on a follow-up scan within the normal range is reassuring.

Our study had several limitations. First, the results of the ultrasound examinations were not blinded to clinicians, and consequently patients with very short cervices may have been recommended to bed rest. Although no beneficial effect of bed rest has been identified in prolonging twin pregnancies or improving fetal outcomes (Crowther et al., 1990), such a recommendation may lead to a bias in our results. Second, interobserver variability could not be evaluated in the present study, although all measurements were performed using a standardized protocol by experienced faculties or fellows with specialization in maternal-fetal medicine. The use of the same observer for serial measurements for CL would be important in reducing variance. Finally, prediction of preterm births based on serial CL measurements does not necessarily lead to the prevention of preterm births because of the current lack of effective interventions.

In conclusion, our study suggested that in asymptomatic women with twin pregnancies and a CL > 25 mm at 20–24 weeks gestation, a follow-up CL measurement 4–5 weeks after the baseline CL measurement gives useful clinical information on the likelihood of SPTD at <32 and <34 weeks' gestation. Specifically, we noted that a CL ≤ 30 mm on follow-up and CL shortening ≥13% between late second trimester measurements with an interval of approximately

4 weeks suggests an increased risk for SPTD. However, the change in CL could not provide data beyond that provided by the follow-up CL alone. The findings of this study must be confirmed in large, prospective, fully blinded studies.

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