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ORIGINAL ARTICLE

Associations of temporal changes in cervical length and lower uterine segment length with spontaneous preterm delivery risk: a prospective study of 727 Japanese women

Rie Oi[1,2] · Naoyuki Miyasaka[2] · Takahiro Yamashita[1] · Tomoko Adachi[1]

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Abstract

Purpose A prospective assessment of the risk of spontaneous preterm delivery (sPTD) by evaluating temporal changes in cervical measurements.

Methods We analyzed clinical variables, focusing on cervical length (CL) and lower uterine segment (LUS) length (LUSL) as measured by transvaginal ultrasonography in 727 pregnant Japanese women.

Results In women undergoing term deliveries, CL increased from gestational week (GW) 8–25. In contrast, the combination of CL and LUSL (ComL for "combined length") gradually decreased and sole LUSL became almost 0 mm by GW 25. Univariate logistic regression analysis suggested that a history of PTD was a risk factor for sPTD. CL, LUSL, and ComL were not significant predictors of sPTD.

Conclusion To assess the risk of sPTD in the second trimester, it is not necessary to distinguish the cervix from the LUS.

Keywords Premature birth · Cervix uteri · Second trimester of pregnancy · Ultrasonography · Diagnostic imaging

Introduction

Premature birth is the most common cause of neonatal morbidity and mortality [1]. Decreasing the risk of premature birth will improve newborns' prognoses. Several factors predict spontaneous preterm delivery (sPTD), including a history of preterm delivery (PTD) [2–5], measurement of cervical length (CL) [6–33], and measurement of lower uterine segment length (LUSL) [34]. One-time measurements of CL and LUSL in the first [6–17] and second trimesters [6, 18–30], and serial measurements to determine the rate of shortening [4, 6, 15, 18, 31–33], may predict sPTD risk.

Transvaginal ultrasonography (TVUS) can distinguish the cervix from the lower uterine segment (LUS) during pregnancy. One study reported that decreased LUSL in the first trimester was associated with an increased risk of sPTD [34]. On the other hand, another study reported an association between a decrease in CL, as measured independently from the LUSL in the first trimester, and an increased risk of sPTD [16]. Therefore, the distinction between decreases in CL and LUSL may be important. However, the association between temporal changes in CL and LUSL and pregnancy outcome have not been investigated in a large-scale study.

The objective of this study was to analyze temporal changes in CL and LUSL by TVUS in Japanese women with singleton pregnancies to identify sPTD risk factors.

Methods

The study protocol was approved by our institution's Ethics Committee. The study cohort was limited to Japanese women with a singleton pregnancy who visited our hospital during the period from August 2015 to January 2017. Those who underwent cervical conization were excluded from analysis. All participants underwent measurements of CL and LUSL by TVUS at least three times at gestational week (GW) $8^{0/7}$–$13^{6/7}$, $15^{0/7}$–$19^{6/7}$, and $20^{0/7}$–$24^{6/7}$. The combination of CL and LUSL was referred to as combined length (ComL). More specifically, the lengths measured at

✉ Rie Oi
oirie1023@yahoo.co.jp

1 Maternal and Child Health Center Aiiku Hospital, 1-16-10 Shibaura, Minato-ku, Tokyo 105-0023, Japan

2 Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan

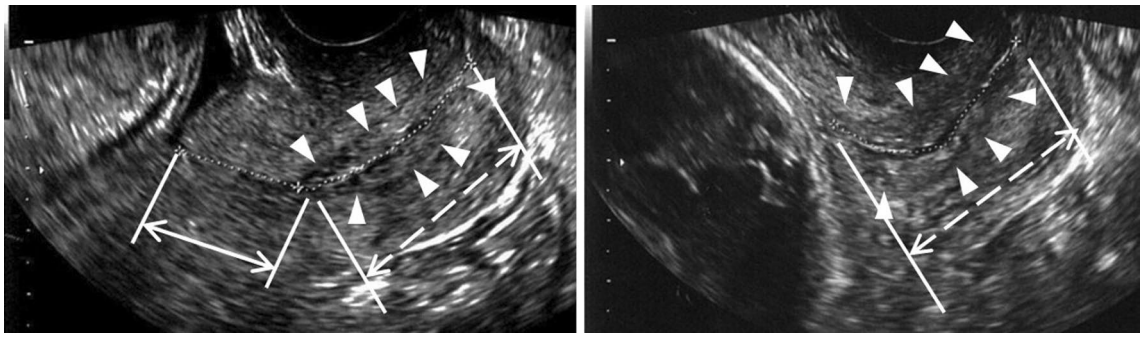

Fig. 1 Identification of the cervix and the lower uterine segment (LUS). The cervical glandular area (CGA) is the spindle-shaped area surrounded by triangles. The central linear anechoic area of the CGA is the cervical canal. The part cranial to the CGA is the LUS. The left image shows a well-defined cervix and LUS. The right image shows a well-defined cervix without the LUS

Table 1 Univariate analysis of maternal characteristics by group

	Term delivery ($n=705$)	Spontaneous PTD ($n=22$)	p
Maternal age (years)	34 (31–37)	33 (29.25–37.75)	0.609
Primigravida	354 (50.2%)	8 (36.4%)	0.279
Primipara	503 (71.3%)	14 (63.6%)	0.475
Maternal height (cm)	160 (156–163)	160 (153.5–161)	0.832
Maternal weight (kg)	50.0 (47–54)	49.5 (47.25–52)	0.398
Maternal BMI (kg/m^2)	19.75 (18.48–21.22)	19.53 (18.45–20.65)	0.517
ART	121 (17.2%)	2 (9.1%)	0.561
History of PTD	14 (2.0%)	2 (9.1%)	0.0812

ART includes egg donation

PTD preterm delivery, *BMI* body mass index, *ART* artificial reproductive treatment

GW $8^{0/7}$–$13^{6/7}$, $15^{0/7}$–$19^{6/7}$, and $20^{0/7}$–$24^{6/7}$ were referred to as CL1, LUSL1, and ComL1; CL2, LUSL2, and ComL2; and CL3, LUSL3, and ComL3, respectively. The rate of shortening between GW $8^{0/7}$–$13^{6/7}$ and $15^{0/7}$–$19^{6/7}$ was referred to as ΔCL1-2, ΔLUSL1-2, and ΔComL1-2, and that between $15^{0/7}$–$19^{6/7}$ and $20^{0/7}$–24 as ΔCL2-3, ΔLUSL2-3, and ΔComL2-3 (mm/week). The values determined for CL, LUSL, ComL, ΔCL, ΔLUSL, ΔComL, pregnancy outcome, and other relevant clinical variables were prospectively recorded.

CL and LUSL were measured using a Voluson P8 US system (GE Healthcare, Buckinghamshire, England). The probe frequency was set as high as possible (7–9 MHz) to obtain the best graphic resolution. After ensuring that the urinary bladder was empty, the probe was inserted into the vagina and moved slowly to the anterior fornix, and then to the right and left to identify the central part of the cervix and the internal os. The thin, spindle-shaped area, as confirmed by a slight hyperechoic signal on a vertical image of the cervix, was identified as the cervical glandular area (CGA), while the central linear anechoic area was identified as the cervical canal. Afterward, the length of the linear anechoic area was measured as the CL. The cranial end point of the glandular area was identified as the histological internal os. In cases with a narrow segment of the uterus from the internal os further cranially, the LUS was detected and the length of its linear anechoic area was measured as the LUSL (Fig. 1). CGA was clearly visualized in most cases in the measurement before GW 25, and only in cases in which CGA could not be clearly visualized, we measured total length as CL. The CL and LUSL were measured independently, and the values were recorded in an electronic chart. Each clinician researcher recorded the measurements in the outpatient clinic. The first author collected all images and values and confirmed the accuracy of measurements. When the clinician's measurement was inaccurate, the author remeasured the length. Before the study, the accuracy of the first author's measurements was confirmed by the following experiment. The author measured CL and LUSL three times using 10 images each from GW $8^{0/7}$–$13^{6/7}$, GW $15^{0/7}$–$19^{6/7}$, and GW $20^{0/7}$–$24^{6/7}$. The interclass correlation coefficient 1 (ICC1) was found to be 0.826 for CL1, 0.814 for LUSL1, 0.891 for CL2, 0.869 for LUSL2, 0.902 for CL3, and 0.927 for LUSL3. Ten well-trained clinicians from our

institute measured the 30 images that were used to evaluate the author's ICC1. The 95% confidence intervals (CI) of each measured value were calculated with Mann–Whitney's *U* test, which confirmed that the mean value of the three measurements taken by the first author were within 95% CI.

Statistical analysis

Continuous variables were analyzed using Mann–Whitney's *U* test and are expressed as the median with interquartile range. Categorical variables were analyzed with Fisher's exact test and are expressed as the number of patients with the percentage in parentheses. Temporal changes in the CL, LUSL, and ComL by gestational age are depicted as scatter plots. The approximate curves and straight lines were drawn using the least squares method. Univariate logistic regression analysis was performed to identify predictive sPTD factors. The lengths measured after any intervention for threatened sPTD were excluded from the univariate and logistic regression analyses. The graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), was used for statistical analyses.

Results

In total, 754 women with a singleton pregnancy underwent three measurements at GW $8^{0/7}$–$13^{6/7}$, $15^{0/7}$–$19^{6/7}$, and $20^{0/7}$–$24^{6/7}$. Of these, 27 were excluded from analysis; 16 women's pregnancy outcomes were unknown and 11 women who delivered before GW 37 experienced iatrogenic indications such as maternal hypertensive disorder or fetal distress. Ultimately, data from 727 women were included in the analysis. All participants had delivered before the end of September 2017. Of these, 705 were term deliveries and 22 were sPTDs. The univariate analysis results of the maternal characteristics of the term delivery group and the sPTD group are shown in Table 1. Among the variables, only a history of PTD tended to be marginally significant.

Figure 2 shows a scatter plot of the temporal (GW 8–25) changes in CL, LUSL, and ComL in women who delivered at term without intervention against threatened preterm labor. Intervention included admission, cerclage, intravenous administration of tocolytic agents, and intravaginal administration of urinastatine or progesterone. The CL of the term delivery without intervention group was approximately 35–37 mm in the first trimester and increased very slowly to > 40 mm at around GW 25. The LUS effaced completely, LUSL became 0 mm by GW 25, and the ComL value showed a near linear decrease.

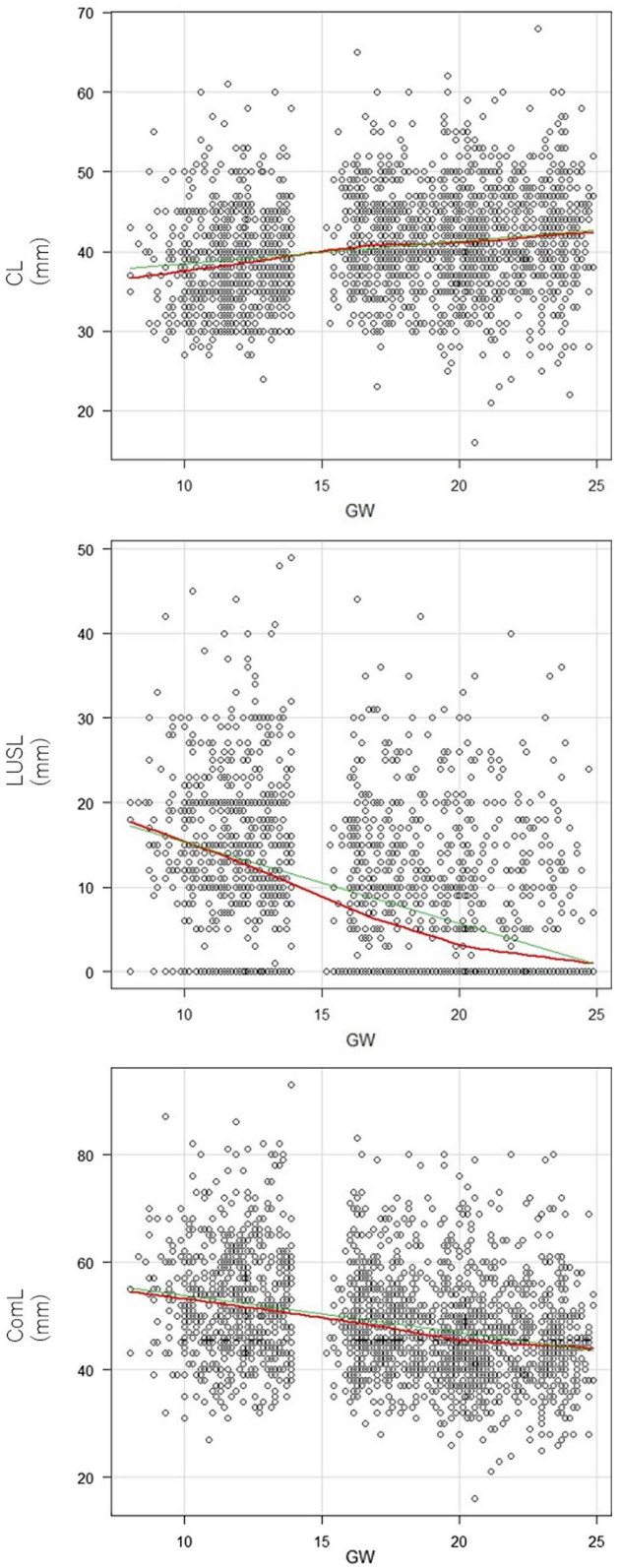

Fig. 2 Temporal changes in cervical length (CL), lower uterine segment length (LUSL), and combined length (ComL) of women who delivered at term without intervention for threatened preterm labor between GW 8–25. ComL is defined as the combination of CL and LUSL

Table 2 Univariate analysis of cervical and lower segment length and the rates of shortening by group

	Term delivery	Spontaneous PTD	*p*
CL1 (mm)	38 (34–42)	39.5 (34.25–44.5)	0.714
CL2 (mm)	40 (37–45)	39 (35–43)	0.203
CL3 (mm)	41 (37–46)	40 (33.5–44)	0.187
LUSL1 (mm)	13 (8–20)	14 (1.5–20)	0.626
LUSL2 (mm)	2 (0–13)	0 (0–10.75)	0.426
LUSL3 (mm)	0 (0–5)	0 (0–8.25)	0.741
ComL1 (mm)	52 (45–60)	49.5 (44–59)	0.683
ComL2 (mm)	46 (41–54)	44.5 (37.5–51.75)	0.184
ComL3 (mm)	44 (39–50)	43.5 (36.75–51.25)	0.554
ΔCL1-2 (mm/w)	−0.29 (−1.05 to 0.18)	−0.13 (−0.8 to 0.66)	0.280
ΔCL2-3 (mm/w)	0 (−1.11 to 0.56)	−0.18 (−0.67 to 0.71)	0.439
ΔLUSL1-2 (mm/w)	1.13 (0–2.33)	0.88 (0–2.83)	0.861
ΔLUSL2-3 (mm/w)	0 (0–2.04)	0 (0–0)	0.101
ΔComL1-2 (mm/w)	0.78 (−0.52 to 1.98)	1.67 (−0.58 to 2.7)	0.325
ΔComL2-3 (mm/w)	0.5 (−0.78 to 2.0)	0 (−0.82 to 2.44)	0.550

CL1, LUSL1, and ComL1 were measured at $8^{0/7}$–$13^{6/7}$ weeks of gestation. CL2, LUSL2 and ComL2 were measured at $15^{0/7}$–$19^{6/7}$ weeks of gestation. CL3, LUSL3, and ComL3 were measured at $20^{0/7}$–$24^{6/7}$ weeks of gestation. ΔCL, ΔLUSL, and ΔComL are the rates of shortening between two periods, with the numbers indicating the two periods

PTD preterm delivery, *CL* cervical length, *LUSL* lower uterine segment length, *ComL* combined length (of CL and LUSL)

Table 2 shows the univariate analysis results of CL, LUSL, ComL, ΔCL, ΔLUSL, and ΔComL in the term delivery group and the sPTD group. Values measured after any intervention were excluded from the analysis. CL2 and ComL2 tended to be shorter in the sPTD group than in the term delivery group. Regarding to the sPTD group, LUSL decreased similarly to the term delivery group and reached to 0 mm by GW 25.

Table 3 shows the results of univariate logistic regression analyses of predicting sPTD on the basis of maternal characteristics, obstetrical history, and measured values (CL, LUSL, ComL, ΔCL, ΔLUSL, and ΔComL). A history of PTD was predictive of sPTD [odds ratio (OR) = 4.940; 95% CI = 1.05–23.20; $p = 0.0431$]. CL2 (OR = 0.936; 95% CI = 0.87–1.00; $p = 0.0681$) and ComL2 (OR = 0.953; 95% CI = 0.91–1.00; $p = 0.0539$) were also possibly predictive of sPTD. Since the number of sPTDs was small ($n = 22$), multivariate logistic regression analysis was not performed.

Discussion

Temporal changes in the CL, LUSL, and ComL values were investigated until GW 25. This is the first large-scale report of not only CL but also LUSL among 700 Japanese women. The reliability of the measurements between examiners was confirmed by the first author, who reviewed and measured the lengths of all images.

A novel finding of this research is that the CL had increased in the term delivery group by GW 25. In contrast, Souka et al. [15] reported that the CL had decreased by an average of 2.36 mm from GW 11–24, but this report did not describe extension. There are two differences between the results obtained by us and those by Souka et al. First, we measured the cervical canal with a curved trace, whereas Souka et al. measured it in a straight line, which might have led to an underestimated curved canal. Adding to that, the time and frequency of TVUS up to GW 25 were about the same in the present study and in the report by Souka et al., but the latter did not plot the measurement results at every week of gestation, so the transition of CL was not obtained. Temporary elongation of CL at this time may occur as the entire uterus, including the cervical canal, expands with pregnancy. The univariate analysis results showed that there was no significant difference in CL1 between the term delivery group and the sPTD group, as reported by Greco et al. [16], and CL2 had a tendency to shorten, but not to the extent reported by Iams et al. [6]. The total number of participants in the present study ($n = 727$) and the incidence of sPTD ($n = 22$) may be too small to show a sufficiently significant difference. In this study, the CL1, CL2, and CL3 measurements were longer than those reported elsewhere, but the reason remains unclear. It is desirable to accumulate the data of Japanese women with the curve tracing measurement.

The univariate analysis results of the association between LUSL1 and sPTD indicated no significant shortening of LUSL1 in the sPTD group as reported by Sananes et al. [34]. Moreover, LUSL3 was somewhat longer in the sPTD group than in the term delivery group. In both groups, LUSL decreased to 0 mm by GW 25, and the lower segment showed complete effacement. In this study, however, LUSL at each gestational age did not predict sPTD. Because the pattern of LUSL shortening to 20 mm within 10 weeks was considerably similar in the term delivery group and the sPTD group, we could not find a significant difference in LUSL from only 22 sPTD cases.

Several studies reported that the CL shortening rate after GW 20 was more rapid in the sPTD group than in the term delivery group [6, 31, 32]. However, in the present study, there were no significant differences in the ΔCL1-2 and ΔCL2-3 values between the term delivery group and the sPTD group. As a possible reason, the number of sPTD might be too small to show significance between the two groups. Also, there was no significant difference in the ΔLUSL value between the term delivery group and the sPTD group.

Although multivariate analysis was not performed because the number of sPTD cases was too small ($n = 22$), the univariate analysis results suggested that a history of PTD and the CL2 and ComL2 values were predictive of sPTD. In fact, a history of PTD increases risk of recurrent sPTD [2–5]. However, it has been pointed out that the sensitivity of recurrent sPTD as a predictor of preterm birth is insufficient only with a history of PTD [3, 4]. A number of studies have reported TVUS usefulness to screen for sPTD in the second trimester [6, 19–22, 25] and predict preterm birth by the combination of a history of PTD and TVUS at GW 20–24 [5]. In some of these studies, CL was measured with an awareness of LUSL, while others had measured ComL without an awareness of LUSL. However, no study has examined the usefulness of distinguishing between CL and ComL in the second trimester. As shown by the univariate analysis results, the *p* value of ComL2 was slightly lower than that of CL2, so efforts to distinguish between CL and LUSL to predict sPTD at GW 15–19 may be unnecessary. There are two reasons for this: one is that there was not much difference between the CL2 and ComL2 measurements of normal pregnant women because most women have LUSL shortening at this time as the lower segment was effaced, and second, CL shortening occurred after complete effacement of the lower segment. In pregnant women with CL shortening at GW 15–19, LUSL may have already become 0 mm. Because women with high-risk of sPTD may have short CL and LUSL of 0 mm, the difference in the ComL2 between normal pregnant women and high-risk sPTD women may be obviously larger than the one in the CL2.

Table 3 Univariate logistic regression analysis predicting spontaneous preterm delivery

	OR	95% CI	*p*
Maternal age (years)	0.969	0.88–1.07	0.518
Maternal weight (kg)	0.965	0.90–1.04	0.337
Maternal BMI (kg/m^2)	0.912	0.74–1.12	0.373
ART	0.483	0.11–2.09	0.330
History of PTD	4.940	1.05–23.20	0.0431
CL1 (mm)	1.010	0.95–1.08	0.719
CL2 (mm)	0.936	0.87–1.00	0.0681
CL3 (mm)	0.972	0.91–1.04	0.414
LUSL1 (mm)	0.982	0.94–1.03	0.431
LUSL2 (mm)	0.975	0.92–1.03	0.369
LUSL3 (mm)	1.040	0.99–1.09	0.134
ComL1 (mm)	0.989	0.95–1.03	0.616
ComL2 (mm)	0.953	0.91–1.00	0.0539
ComL3 (mm)	1.010	0.97–1.06	0.534
ΔCL1-2 (mm/w)	1.280	0.95–1.75	0.110
ΔCL2-3 (mm/w)	1.100	0.83–1.45	0.502
ΔLUSL1-2 (mm/w)	1.000	0.83–1.20	0.997
ΔLUSL2-3 (mm/w)	0.869	0.32–1.03	0.106
ΔComL1-2 (mm/w)	1.070	0.91–1.25	0.419
ΔComL2-3 (mm/w)	0.914	0.78–1.07	0.518

CL1, LUSL1, and ComL1 were measured at $8^{0/7}$–$13^{6/7}$ weeks of gestation. CL2, LUSL2, and ComL2 were measured at $15^{0/7}$–$19^{6/7}$ weeks of gestation. CL3, LUSL3, and ComL3 were measured at $20^{0/7}$–$24^{6/7}$ weeks of gestation. ΔCL, ΔLUSL, and ΔComL are the rates of shortening between two periods, with the numbers indicating the two periods

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *ART* artificial reproductive treatment, *PTD* preterm delivery, *CL* cervical length, *LUSL* lower uterine segment length, *ComL* combined length (of CL and LUSL)

Conclusion

A history of PTD is a predictor of sPTD. Distinguishing CL from LUSL in the 2nd trimester is not necessarily useful to predict sPTD. The usefulness of distinguishing between CL and LUSL to predict sPTD is likely to be demonstrated by accumulating data within the first trimester, when most pregnant women have not achieved effacement of the LUS.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical statements All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent was obtained from all patients before inclusion in this study.

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