Original Article

Reference Range of the Cervical Length Measured by Transvaginal Ultrasound in Twin Pregnancies

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Objective: To construct the reference range for cervical length (CL) measured by transvaginal ultrasound (TVS) in twin pregnancies at 16- to 34-weeks' gestation.

Material and Methods: The present study was a retrospective cohort study performed on 123 uncomplicated twin pregnancies delivered at 34-weeks' gestation or beyond. All twin pregnancy women's CL at 16- to 34-weeks' gestation who delivered at Ramathibodi Hospital between February 22, 2016 and March 5, 2019 were examined. The study excluded those who had abortion, history of previous preterm delivery (PTD), monoamniotic twins, single twin demised, history of cervical insufficiency, history of cervical surgery, cervical cerclage, cervical pessary placement, fetal anomaly, fetal chromosome abnormality, fetoscopic surgery or unknown pregnancy outcome. Five hundred seventy-nine CL measurements were analyzed for constructing the mean CL, standard deviation, 95% confidence intervals, and the percentiles of CL.

Results: The mean gestational age (GA) at delivery was 36.7 weeks' gestation. Forty-two percent of women had spontaneous late PTD. The significant negative correlation between CL and GA was demonstrated ($r=-0.549$) at $p<0.01$. The mean CL of 579 measurements was 33.2±9.2 mm, while the mean CL captured at 18 to 24 weeks' gestation was 38.3±5.8 mm. The reference ranges of CL of each GA were established.

Conclusion: The mean CL at mid-trimester of twin pregnancies was 38.3 mm The reference range for CL in twin pregnancies between 16- and 34-weeks' gestation was constructed.

Keywords: Cervical length (CL); Transvaginal ultrasound (TVS); Twin pregnancies

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In 2019, twin pregnancy accounted for 3% of total delivery at the authors' center and approximate 63% of those had preterm delivery (PTD). The most common obstetric complication of twin pregnancies is PTD causing neonatal morbidity and higher mortality risk than that of singleton pregnancies[1]. The pathophysiology underlying spontaneous PTD in twin pregnancy has been widely investigated[2-4]. However, further investigations are required to understand the mechanism of spontaneous PTD and develop potential targeted interventions[5]. Nevertheless, many studies have been reported that risk of spontaneous PTD in pregnant women has been increased with short cervical length (CL) measured by transvaginal ultrasound (TVS)[6,7] and CL has provided a better predictor of spontaneous PTD in twin pregnancies than in singleton pregnancy[8]. The cut-offs value of CL in mid-trimester varied by the gestational age (GA) performed and the GA of PTD referred in the studies. Most studies have been published using the threshold of CL at 20 to 25 mm as increased risk for PTD[8-12].

The CL screening in mid-trimester has been implemented by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[13]. Although some societies did not recommend routine CL screening because of the conflicting data of an effective intervention for PTD prevention[14,15], they still supported the use of CL measurements to predict PTD in twin pregnancy. In addition, serial CL measured in asymptomatic twin pregnancies can detect the women at risk of PTD[16,17] and recognize the different CL shortening patterns over time that some specific patterns can confer the risk of PTD[18].

Accordingly, the serial CL measurements might be the reasonable option for PTD surveillance in

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asymptomatic twin pregnancies but insufficient evidence of serial CL and normal range of CL beyond mid-trimester have been provided. Therefore, the authors had constructed the reference range of CL based on the retrospective longitudinal data of serial CL measurements to provide the baseline information for further investigation regarding PTD surveillance by using CL measurement.

Materials and Methods

The present retrospective study was conducted at Ramathibodi Hospital, Mahidol University, Thailand by reviewing the electronic medical record of twin pregnancies at 16- to 34-weeks' gestation attending the Twin clinic between February 22, 2016 and March 26, 2019. The study protocol was approved by the Institutional Review Boards of Faculty of Medicine, Ramathibodi Hospital, Mahidol University (COA MURA2019/1060). All pregnancies dating were assigned by the crown to rump length (CRL) measurement in the first trimester or date of conception in IVF pregnancies and the larger head circumference will be used in the woman presenting after the first trimester[13]. According to the authors' institution protocol, the obstetricians performed the serial CL measurements using transvaginal ultrasound (TVS CL) in all visits of twin pregnancies at 16- to 34-weeks' gestation. Therefore, there was no missing data of TVS CL in the present study cohort. The TVS CL measurements were obtained by maternal fetal medicine specialists or maternal fetal medicine fellows under direct supervision after giving verbal informed consent from twin pregnant women and were measured strictly based on the technique proposed by Iams et al[6].The shortest CL chosen of three measurements of each visit was noted in the medical record. All CL data were obtained from 123 uncomplicated twin pregnancies delivered beyond 34-weeks' gestation after excluding the women who had an abortion, history of previous PTD, monoamniotic twins, single twin demised, history of cervical insufficiency, history of cervical surgery, cervical cerclage, cervical pessary placement, fetal anomaly, fetal chromosome abnormality, fetoscopic surgery, or unknown pregnancy outcome (Figure 1). The median of visits was five and the range of visits was one to ten visits per participant. Therefore, 579 TVS CL examinations were analyzed for establishing the mean CL and the CL percentile throughout 16- to 34-weeks' gestation. The maternal characteristics, maternal outcomes, and neonatal outcomes were also provided.

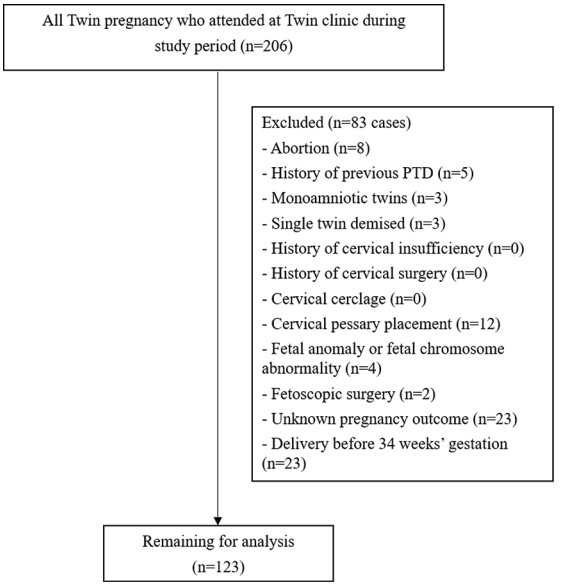

Figure 1. Study flow diagram.

Statistical analyses and the reference percentiles were calculated by using IBM SPSS Statistics, version 19.0 (IBM Corp., Armonk, NY, USA). The TVS CL data of 20 twin pregnancies as mean ± standard deviation (SD) at 35.57±6.24 was used for sample size calculation. The sample size was 33 calculated by using the one population mean formula at the significant level of 0.05 and power of 90%. Normality of all data were examined, and the continuous data were described as mean, range, and standard deviation. The correlation between GA and CL was identified by the Pearson correlation coefficient. A p-value of less than 0.05 was considered statistically significant.

Results

Five hundred seventy-nine CL measurements were obtained from 123 twin pregnancies consisting of monochorionic and dichorionic twins in an equal amount. The mean maternal age of participants was 32.6 years and about 37% of them were multiparity. One-fifth of participants had a history of abortion, while 17% conceived by using assisted reproductive technology. In terms of delivery outcomes, the mean GA of delivery was 256.7 days and 47.2% of the participants were preterm delivery as shown in Table 1.

The normality of all CL data was tested and it revealed normal distribution pattern. The mean CL of all measurements and during mid-trimester at 18- to 24-weeks' gestation were 33.2±9.2 mm and

Table 1. Maternal characteristics and outcomes (n=123)

Characteristics	
Maternal age (year); mean±SD	32.6±5.2
Prepregnant BMI (kg/m^2); mean±SD	21.7±3.7
Parity; n (%)	
Nulliparous	77 (62.6)
Multiparous	46 (37.4)
Previous cesarean section; n (%)	26 (21.1)
Previous abortion; n (%)	25 (20.3)
Chorionicity; n (%)	
Dichorionic twins	61 (49.6)
Monochorionic twins	62 (50.4)
Conceived by using ART; n (%)	21 (17.0)
Gestational age at delivery (day); mean±SD	256.7±8.7
Preterm delivery; n (%)	58 (47.2)

SD=standard deviation; BMI=body mass index; ART=assisted reproductive technology

38.3±5.8 mm, respectively. The TVS CL at the fifth, tenth, fiftieth, ninetieth, and ninety-fifth percentiles various by GA are shown in Table 2. Unfortunately, the ninety-fifth percentile of TVS CL at 16-, 17-, 18-, and 34-weeks' gestation could not be demonstrated due to the small number of measurements obtained from those twin pregnancies at 16-, 17-, 18-, and 34-weeks' gestation. Nevertheless, these finding were unlikely to affect the clinical application since the authors focused on the occurrence of short cervix for PTD prognostication. In addition, the significant inverse relationship between CL and GA was found by using Pearson correlation (r=–0.549) at $p<0.01$ and the 95% confidence intervals (CI) of CL measured at different gestations are shown in Figure 2. The regression line between CL and GA is presented in Figure 3 at r^2 =0.302.

Discussion

According to racial disparities in CL for prediction of preterm birth proposed by previous reports[19-21], the CL might vary from population to population. Therefore, the authors have studied the CL in twin pregnancies of the present study population. To the extent of the authors knowledge, this is the first study providing the reference range for TVS CL in twin pregnancy of Thai. The present study showed that the mean CL at 18- to 24-weeks' gestation was comparable with that of Thai singleton

Table 2. TVS CL demonstrated as mean±SD, minimum, maximum, and percentiles

GA (week)	Number of measurements	TVS CL (mm)			Percentiles				
		Mean±SD	Min	Max	5th	10th	50th	90th	95th
16	14	39.3±5.5	30.0	49.0	30.0	32.0	37.5	48.4	NA
17	11	41.8±7.1	33.2	57.0	33.2	33.6	41.0	55.6	NA
18	17	39.5±7.3	25.0	56.0	25.0	31.4	38.0	50.2	NA
19	25	38.6±6.2	27.0	55.0	27.3	29.8	39.0	44.5	52.3
20	29	40.1±6.1	27.0	50.0	29.0	33.0	39.8	49.0	49.5
21	28	39.0±4.0	30.1	47.0	31.4	33.0	39.3	44.1	46.1
22	24	37.6±6.1	25.0	48.0	25.5	28.0	39.5	45.0	47.5
23	41	37.0±5.3	29.0	59.0	29.1	30.2	37.0	43.6	45.8
24	32	37.1±5.9	27.0	46.4	27.7	29.1	37.0	45.4	46.1
25	31	35.3±5.6	26.5	48.0	26.8	27.0	36.0	42.8	46.2
26	36	34.2±6.3	19.7	45.8	23.0	25.4	36.5	41.3	44.3
27	36	35.0±8.6	14.1	52.0	15.7	22.0	36.1	46.2	52.0
28	33	32.2±6.9	16.9	46.0	19.5	22.7	34.0	40.2	42.8
29	46	30.7±8.6	11.0	52.0	11.8	14.3	32.0	40.0	41.3
30	43	28.9±9.6	8.0	59.0	13.8	17.0	29.2	40.0	46.6
31	36	28.8±9.9	9.0	53.0	9.9	17.9	28.5	43.0	47.1
32	45	24.6±9.9	8.3	43.0	9.3	11.0	25.0	37.4	40.7
33	40	25.4±9.8	5.0	49.0	7.8	10.2	26.1	37.1	38.0
34	12	20.5±7.7	8.0	28.0	8.0	8.3	24.0	28.0	NA
Total	579	33.2±9.2	5.0	59.0	14.1	20.1	34.8	44.0	46.0
18 to 24	196	38.3±5.8	25.0	59.0	29.0	31.0	38.0	45.9	47.7

GA=gestational age; TVS CL=cervical length measurements using transvaginal ultrasound; SD=standard deviation; NA=not available

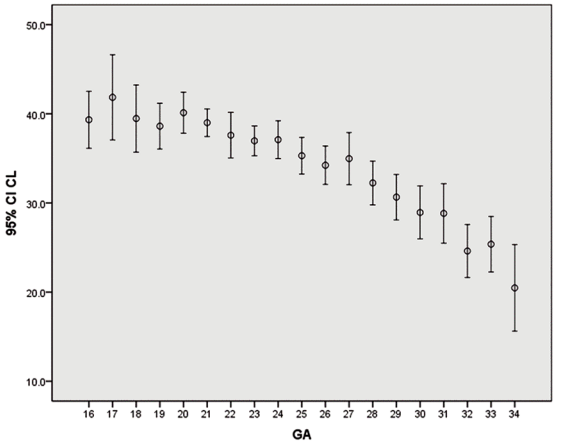

Figure 2. A graph of 95% confident intervals of cervical length (mm) for the different gestational age (week).

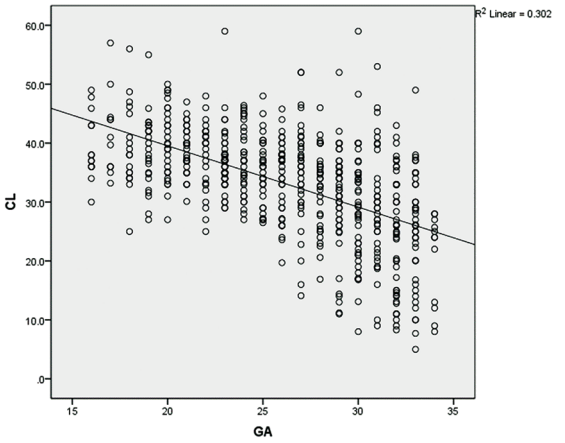

Figure 3. The relationship between cervical length and gestational age shown as the regression line.

pregnancies described in the previous studies[22-23]. Studies have broadly reported that the mid-trimester CL may provide the risk for PTD in twin pregnancy. Despite that different cut-offs have been utilized for preterm risk stratification in twin pregnancy, the most commonly use is 25 mm[13]. However, studies have outlined the failure of PTD prediction by using the receiver operating characteristic (ROC) curve analysis in asymptomatic twin pregnancy[24,25]. Interestingly, Pasquini et al found a significant predictive value of CL for PTD prediction by using a priori cutoff, the fifth percentile. Both ROC curve and a priori cutoff, are justify in terms of a statistical analysis, but the fifth percentile is useful in a clinical setting[26]. Based on the present study cohort, the authors found that the TVS CL at 25 mm is less than the fifth percentile in mid-trimester. Therefore, it is reasonable to consider 25 mm of CL as a cut-off value for defining short CL in twin pregnancy.

Furthermore, the present study has demonstrated the negative correlation of CL and GA. Linear regression analysis presented a correlation between CL and GA (r^2=0.302, p<0.01), which substantially differs from a correlation of serial CL studied in Thai singleton pregnancy (r^2=0.12, p<0.01)[27]. Interestingly, the CL did not show the significant change in mid-trimester period, but it sharply decreased beyond late second trimester. This observation was described as the late CL shortening pattern proposed by Melamed et al[18]. Most of twins with this changing pattern gave birth after 34 weeks' gestation. Unsurprisingly, the present study solely recruited the participants who delivered beyond 34 weeks' gestation.

The major strengths of the present study are the TVS CL measurement beyond mid-trimester and exclusion of the complicated twin pregnancies such as monoamniotic twins, complicated monochorionic twins treated with fetoscopic surgery, and single twin demised. Those complicated twin pregnancies are well known cause of indicated PTD. In addition, the authors provided the data of CL in twin pregnancies of the present study population.

There are limitations in the present study. Firstly, since the study was conducted retrospectively, the authors could not control the confounding factors including the intervention for preterm prevention such as treating with tocolytic drugs or bed rest. Secondly, the inter-observer reliability could not be evaluated because of the retrospective study design. However, in the present study, it was overcome by using the standard protocols for TVS CL measurement[6]. Unfortunately, around 10% of twin pregnancy in the present study was excluded due to unknown pregnancy outcome. Additionally, the authors exclusively collected the data of those who delivered beyond 34 weeks' gestation due to low sensitivity and positive likelihood ratio of TVS CL in predicting spontaneous PTD in twin pregnancies[8]. In addition, no proven benefit of preterm management schemes such as antenatal corticosteroid and tocolytic drug were suggested for those twins who presenting with preterm birth after 34 weeks' gestation.

In summary, the authors have established the reference range of TVS CL for twin pregnancies serially measured from 16- to 34-weeks' gestation and the mid-trimester TVS CL was presented. Negative correlation between TVS CL and GA was demonstrated. These data might be applied for further

studies in terms of preterm prediction and prevention in twin pregnancies.

Conclusion

The mean CL at mid-trimester of twin pregnancies was 38.3 mm. The reference range for CL in twin pregnancies between 16- and 34-weeks' gestation was constructed.

What is already known on this topic?

TVS CL is a widely accepted option for screening the risk of PTD in twin pregnancies. However, contradictory evidence about serial CL measurement and TVS CL's shortening overtime for predicting preterm birth in twin pregnancy has been reported.

What this study adds?

This study provided the reference range of serial TVS CL for twin pregnancies in Thai women. Accordingly, it might be useful for further studies regarding preterm prediction and prevention in twin pregnancies.

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Conflicts of interest

The authors declare no conflicts of interest.

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