Original Article

Cervical Length Measurements in the Management of Threatened Preterm Labor: A Randomized Controlled Trial

Metha Songthamwat, MD, PhD[1], Jirada Promnimit, MD[1], Ueamporn Summart, PhD[1], Srisuda Songthamwat, MD[1]

[1] Department of Obstetrics and Gynecology, Udonthani Hospital, Udonthani, Thailand

Objective: To compare the obstetrics and neonatal outcome of a protocol using the cervical length (CL) measurement with a traditional protocol without CL measurement in the management of threatened preterm labor.

Materials and Methods: The present randomized controlled trial was carried out in Udonthani Hospital between November 2018 and August 2019. One hundred sixteen preterm pregnant women randomly allocated into either a CL group (n=58) or a non-CL group (n=58) were included in this study. CL of less than 3 cm and persistent contractions after one to two hours rest were indications for tocolytic treatment. The proportion of preterm births within 48 hours after treatment, the proportion of tocolytic using cases, and the obstetrics and neonatal outcomes were compared between the groups.

Results: Out of the 58 women in the CL group, 39.7% had a CL of less than 3 cm. Delivery within 48 hours occurred in 8.6% of the CL group compared with 15.5% in the non-CL group, which was not statistically significant. Tocolytic drug was given to 65.5% in the CL group compared with 94.8% in non-CL group ($p<0.01$). The participants were followed up until delivery and 55 women in the CL group and 57 women in the non-CL group completed the present study. Preterm delivery rate was 36.4% in the CL group compared with 36.8% in the non-CL group ($p>0.05$). There was no significant difference for the mean gestational age at delivery and neonatal complications for both groups.

Conclusion: CL measurement protocol did not improve the neonatal outcome of threatened preterm labor. However, it reduced unnecessary tocolytic treatment and its associated complication.

Keywords: Cervical length, Threatened preterm labor, Preterm labor, Tocolysis, Randomized trial

Received 16 December 2019 | Revised 20 February 2020 | Accepted 24 February 2020

J Med Assoc Thai 2020;103(10):964-70
Website: http://www.jmatonline.com

Preterm birth is the main cause of death and disability for infants. Globally, there are about 15 million premature babies born annually. Over the last two decades, the rate of preterm birth has increased in all countries with reliable data[1]. There are short-term and long-term complications for the survivors of this condition. These complications include the need for intensive care treatment, chronic lung disease, impaired vision and hearing, and long-term neurological and intellectual development issues[2,3].

There are many approaches for the treatment of preterm labor, which aim to extend the gestation period and reduce unnecessary treatment that are caused by false labor pain. One tool that is used to evaluate threatened preterm birth is cervical length (CL) measurement[4-6]. There are guidelines from many institutions, such as the American College of Obstetricians and Gynecologists (ACOG), which use CL to diagnose and provide care for preterm labor[7]. CL measurement requires the use of expensive equipment and trained staff, which is limited in low and middle-income countries. In Thailand, the Royal Thai College of Obstetricians and Gynecologists (RTCOG) has not added CL to the guidelines for the management of preterm labor[8]. The present study's goal was to evaluate the usefulness of CL in the management of preterm labor. This would be of

Correspondence to:

Songthamwat M.

Department of Obstetrics and Gynecology, Udonthani Hospital, Udonthani 41000, Thailand.

Phone: +66-81-5451499

Email: udonhome@yahoo.com

How to cite this article:

Songthamwat M, Promnimit J, Summart U, Songthamwat S. Cervical Length Measurements in the Management of Threatened Preterm Labor: A Randomized Controlled Trial. J Med Assoc Thai 2020;103: 964-70.

doi.org/10.35755/jmedassocthai.2020.10.10932

benefit for obstetricians and health care policy makers in low and middle-income country.

Materials and Methods

The present randomized controlled trial study was carried out in Udonthani Hospital between November 2018 and August 2019. The present study protocol was approved by the Ethical Research Committee of Udonthani Hospital (no.39/2561) and was registered in the Thailand Clinical Trial Registry (TCTR20190821001). Participants were eligible if they met the following criteria, 1) women with singleton live preterm (gestational age 25 to 36 weeks) pregnancies, 2) who have painful and regular uterine contraction of at least one time in every 10 minutes persisting for more than 30 minutes[9]. The ineligible criteria were women with placenta previa, abnormal vaginal bleeding, preterm premature rupture of membranes, cervix dilated more than 3 cm, dead fetus in utero, fetal anomaly, uncertain gestational age, those with a history of previous cervical or uterine surgery (such as previous cesarean section or cervical conization), and those unwilling to participate in the study.

The eligible participants were counseled and invited to participate in the present study. A written informed consent was obtained after the explanation of the study methods and adverse effects to the participants. All participants were then randomly allocated into either the study or control groups. The randomization was performed using a computer-generated number and sealed opaque envelopes.

All participants were examined by digital vaginal examination by experienced nurses who have worked in the labor room for at least five years. The cervical dilatation was assessed to rule out advance labor and evaluated baseline cervical condition. In the CL group, CL was measured transvaginally by trained obstetricians or residents, using a GE Voluson P6 ultrasound machine with a 7 to 10 MHz TVS probe. All patients were examined with an empty bladder. The CL was obtained by measuring from external to internal os in a longitudinal axis. Three measurements were taken, and the shortest values was taken as the final CL. Cut off value to decide for short cervix was a CL of less than 30 mm[7,10]. All staff and residents who participated in the present study were trained and assessed for standardization of CL measurement in a 1-day course.

In the CL group, the participants who had labor pain with the CL result from transvaginal ultrasound at less than 30 mm, were treated by tocolytic drug to inhibit uterine contraction and were given steroids to promote fetal lung maturity if indicated. In those participants who had labor pain with a CL of more than 30 mm, the treatment was observation. If the uterine contraction persisted after one to two hours rest or progressive cervical dilatation was detected, the tocolytics drugs or steroid were given. In the non-CL group, the participants were managed according to the clinical judgement of the in-service obstetricians in the labor room. The obstetrician followed the hospital protocol and the standard of treatment guidelines for preterm labor of the RTCOG[8].

The first line tocolytics agent in the present study was nifedipine 20 mg, four times every 30 minutes or until no regular uterine contraction was detected. It was then repeated every eight hours according to the World Health Organization (WHO) and RTCOG recommendations. Corticosteroid protocol was four doses of 6 mg intramuscular dexamethasone every 12 hours. Uterine contraction and fetal heart rate were recorded every 30 minutes in the first two hours. The cervical progression was assessed by digital examination after the first two hours observation, then every four hours in active labor cases, and when the mother felt an urge to push or the membrane ruptured. Fetal heart rate was monitored by both electronic fetal heart rate monitoring and periodic auscultation. The complications of tocolytics drugs were also recorded.

The primary outcomes were the comparison of the proportion of preterm birth within 48 hours after treatment and the proportion of tocolytic using cases in the study (CL) and the control (non-CL) group. The secondary outcomes were the comparison of gestational age at delivery, length of hospital stay, complications from tocolytics and steroids, duration of treatment, neonatal birth outcome, APGAR score, neonatal weight, treatment in the neonatal intensive care unit, and other complications.

Statistical analysis

The sample size was calculated using the formula for randomized controlled trial for binary data. The estimated proportion of successful labor inhibition in the control group was 0.35, and in the treatment group was 0.12, which were used for calculation[10]. An α was 0.01 and the power was 80%. The calculated sample size per group was 53 participants. The sample size was increased by 10% in case of missing data. Therefore, 116 participants, with 58 per group, were required.

The participants' characteristics were presented in number, percentage, range or mean ± standard

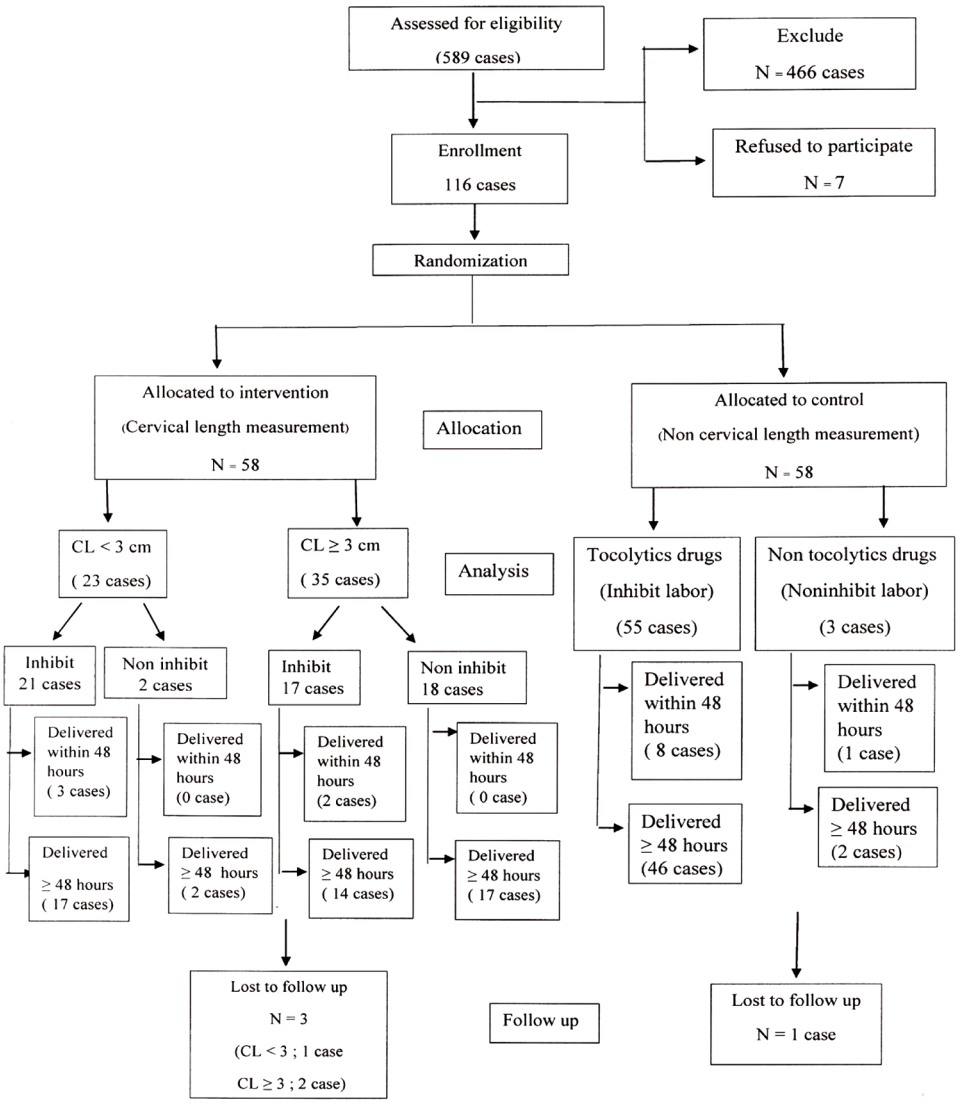

Figure 1. Study flow and Consort diagram.

deviation. Both groups were compared using an unpaired student's t-test for continuous variables. Chi-square and Fisher's exact tests were used for categorical variables. The risk ratio and mean difference with a 95% confidence interval (CI) were calculated for the magnitude of effect. Statistical analysis was performed using Stata Statistical Software, version 13 (StataCorp LP, College Station, TX, USA). A p-value of less than 0.05 was considered statistically significant.

Results

The present study included 116 participants, which were randomly allocated 58 into the CL group and 58 into the non-CL group. A consort diagram is presented in Figure 1. The comparison of baseline characteristics of participants in both groups is shown in Table 1. Both groups were comparable in terms of parity, gestational age at admission, history of previous term and preterm birth, infection, initial dilatation of cervix, and bishop score except for maternal age and body mass index (BMI). Most participants were between 20 to 34 years old, multipara, and only 7.8% had previous history of preterm birth. Half of the participants were late preterm and 61.2% of the participants had non-dilated cervical os with Bishop scores of less than 6.

All participants in the CL group had their CL

Table 1. Baseline characteristic of CL and non-CL groups

Characteristics	Total (n=116) n (%)	CL group (n=58) n (%)	Non-CL group (n=58) n (%)	p-value[β]
Maternal age (years)				
Mean±SD	26.0±7.0	27.5±7.0	24.5±6.6	0.017*
<20	27 (23.3)	10 (17.2)	17 (29.3)	0.041*
20 to 34	75 (64.7)	37 (63.8)	38 (65.5)	
≥35	14 (12.1)	11 (19.0)	3 (5.2)	
Gestational age (weeks)				
Mean±SD	33.2±2.5	33.3±2.4	33.1±2.5	0.598
<34	51 (44.0)	24 (41.4)	27 (46.6)	0.575
≥34	65 (56.0)	34 (58.6)	31 (53.5)	
Primigravida	48 (41.4)	22 (37.9)	26 (44.8)	0.451
Body mass index (kg/m^2)				
Mean±SD	25.5±4.0	26.4±4.1	24.6±3.7	0.015*
<18.5	4 (3.5)	1 (1.7)	3 (5.2)	0.338
18.5 to 22.9	27 (23.3)	11 (19.0)	16 (27.6)	
23 to 24.9	24 (20.7)	11 (19.0)	13 (22.4)	
25 to 29.9	45 (38.8)	24 (41.4)	21 (36.2)	
≥30	16 (13.8)	11 (19.0)	5 (8.6)	
Previous preterm birth	9 (7.8)	3 (5.2)	6 (10.3)	0.490
Previous term birth	48 (41.4)	27 (46.6)	21 (36.2)	0.258
Infection				
UTI	11 (9.4)	6 (10.3)	5 (8.6)	0.759
Vaginitis	5 (4.3)	1 (1.7)	4 (6.9)	0.175
Initial dilatation of cervix (cm)				0.849
Closed	71 (61.2)	36 (62.1)	35 (60.3)	
Dilate ≥1 cm	45 (38.8)	22 (37.9)	23 (39.7)	
Bishop score				
Mean±SD	3.7±2.5	3.5±2.3	3.9±2.6	0.407
<6	88 (75.9)	46 (79.3)	42 (72.4)	0.385
≥6	28 (24.1)	12 (20.7)	16 (27.6)	

CL=cervical length; SD=standard deviation; UTI=urinary tract infection

[β] p-value was calculated by Unpaired t-test in continuous data and by Pearson's chi-square or Fisher's exact test in categorical data, * Statistically significant (p<0.05)

measurement taken. The mean CL was 30.9±7.4 mm (range 13.4 to 47.2 mm). There were 23 (39.7%) participants in this group who had a CL of less than 30 mm. There were 35 (60.3%) participants with a CL greater than 30 mm observed for uterine contraction for one to two hours. Of these, 17 (48.6%) participants had persistent uterine contraction and received tocolytic drug for inhibiting uterine contraction. Thirty-eight (65.5%) participants in this group received tocolytic drug. In the non-CL group, the uterine contraction and cervical progression were observed for one to two hours. A tocolytic drug was used in 55 (94.8%) cases in this group, which was a statistically significant difference from the CL group.

In the CL group, five (8.6%) participants delivered within 48 hours after admission compared to nine (15.5%) participants in the non-CL group, which was not a significant difference (Table 2). The uterine contraction was stopped in the other participants. All participants were followed up until delivery. About two thirds of the participants in both groups continued their pregnancy until term. The mean gestational age

Table 2. Primary and secondary outcomes

Outcome	CL group (n=58) n (%)	Non-CL group (n=58) n (%)	Risk ratio (95% CI)	p-value[β]
Primary outcome				
Delivery ≤48 hours	5 (8.6)	9 (15.5)	0.56 (0.20 to 1.56)	0.264
Tocolytic drug use	38 (65.5)	55 (94.8)	0.69 (0.57 to 0.84)	<0.001*
Tocolytic side effect[µ]	10 (17.2)	22 (37.9)	0.46 (0.23 to 0.87)	0.018*
Secondary outcome				
Received corticosteroid	39 (67.2)	41 (70.7)	0.95 (0.74 to 1.21)	0.688
Delivery ≥37 weeks (n=112)	35/55 (63.6)	36/57 (63.2)	1.0 (0.76 to 1.33)	0.958
Gestational age at delivery; mean±SD	37.2±2.3	36.8±2.2	Mean difference 0.4 (–0.44 to 1.22)	0.353
Length of hospital stay (hours), mean±SD	79.7±122.5	84.5±100.6	Mean difference –4.8 (–36.6 to 46.3)	0.818
Mode of delivery (n=112)			1.2 (0.72 to 2.01)	0.465
• Vaginal delivery	34 (61.8)	39 (68.4)		
• Cesarean delivery	21 (38.2)	18 (31.6)		

CL=cervical length; SD=standard deviation; CI=confidence interval

[µ] Tocolytic side effect included tachycardia, headache, palpitation, [β] p-value was calculated by Unpaired t-test in continuous data and by Pearson's chi-square or Fisher's exact test in categorical data, * Statistically significant (p<0.05)

Table 3. Maternal and newborn outcomes

Outcome	Total (n=112) n	CL group (n=55) n (%)	Non-CL group (n=57) n (%)	p-value[β]
Mode of delivery				0.465
Vaginal delivery	73	34 (61.8)	39 (68.4)	
Cesarean delivery	39	21 (38.2)	18 (31.6)	
Neonatal birthweight (g); mean±SD	2933.3±596.8	3002.2±677.3	2866.8±504.5	0.232
Low birthweight (<2,500 g)	22	12 (21.8)	10 (17.5)	0.569
APGAR at 1 minute <7	4	2 (3.6)	2 (3.5)	0.971
Neonatal complication				0.377
RDS	4	2 (3.6)	2 (3.5)	
TTNB	11	8 (14.5)	3 (5.3)	
NICU admission	2	1 (1.8)	1 (1.8)	
Other	8	3 (5.5)	5 (8.8)	

CL=cervical length; SD=standard deviation; RDS=respiratory distress syndrome; TTNB=transient tachypnea of the newborn; NICU=neonatal intensive care unit

[β] p-value was calculated by Unpaired t-test in continuous data and by Pearson's chi-square or Fisher's exact test in categorical data

at delivery and proportion of term birth in both groups were not statistically significant different (Table 2).

The mode of delivery was mostly vaginally. Neonatal birthweight and proportion of low birthweight (less than 2,500 gram) were not significant different between the groups (Table 3). Neonatal APGAR score and proportion of neonatal asphyxia were also not significantly different between the groups. The most common neonatal complication was transient tachypnea of the newborn. The incidence of neonatal complication was not different between the groups.

Discussion

The use of CL measurement has been recommended, as a part of preterm labor diagnosis and management by many institutes and obstetric guidelines from developed countries[7,11,12]. An ultrasound with a transvaginal probe is needed to perform CL measurement. This is a problem in low and middle-income countries because the equipment

is expensive and requires trained personnel. Data from the present study demonstrated that CL measurement did not improve neonatal outcome in terms of delaying labor for more than 48 hours, gestational age at delivery, birthweight, and neonatal complications. The main benefit of CL measurement in the present study was the reduction of unnecessary tocolytic treatment and its associated complication.

The results presented are compatible with studies by Palacio et al[13], Alfirevic et al[14] and Sanin-Blair et al[15], which reported that the use of CL measurement reduced tocolytic drug use and the length of hospital stay. It also left unchanged the gestational age at delivery and the rate of preterm birth. Another study by Ness et al[10], which was a randomized controlled trial with 100 participants, found that knowledge of CL reduced the incidence of spontaneous preterm birth from 36.2% to 13.0% ($p<0.01$). A meta-analysis, which was derived from the three trials above[10,13,14], summarized that clinician knowledge of CL in threatened preterm patients reduced the rate of preterm birth (22% versus 35%) when compared with the absence of CL information[16,17].

Different cut-off lengths of CL were used in the previous studies. Alfirevic et al[14] study used a CL less than 1.5 cm, and Palacio et al study[18] suggested a cut-off point of 25 mm in gestational age less than 32 weeks and 15 mm for 32 weeks or later, and Ness et al study[10] used a cut-off point of 30 mm. In the present study, the 30 mm cut-off point was used in accordance with Ness et al study[10] and ACOG guideline[7].

Knowledge of CL is being used in preterm labor decision making for hospitalization, and administration of tocolytic and steroid treatment. It should be noted that tocolytic treatment's benefit has not been proven in the management of threatened preterm labor. Its use, especially nifedipine, is common in obstetric practice[19-21]. Side effect from tocolytic treatment is common and it can be fatal[21]. The authors' recommendation from the present study is to do CL measurement in medical centers that can do this procedure to avoid the unnecessary tocolytic side effect. In those centers where CL measurement is unaffordable, the treatment of threatened preterm birth can be done without negative effect to the obstetrics outcome.

There are some limitations with the presented. First, the diagnosis of threatened preterm labor was based on persistent uterine contraction after rest, even without cervical dilatation in many cases. This diagnosis was based on previous studies criteria[9,10]. Therefore, some cases of false labor might be included in the present study. Second, the sample size of the present study was calculated from the proportion of participants who delayed the onset of labor for more than 48 hours. Further study with a larger sample size is needed to determine the difference in neonatal morbidity and mortality between CL and non-CL treatment protocol. Third, although the present study used random allocation of participants to study groups, there was a significant difference in age and BMI between the groups.

Conclusion

The CL measurement protocol did not improve the obstetrics outcomes of threatened preterm labor. However, it reduced unnecessary tocolytic treatment and its associated complication.

What is already known on this topic?

CL measurement is suggested by many guidelines from developed countries for the diagnosis and management of suspected preterm labor. One study reported that CL measurement can improve the perinatal outcome while other studies reported no change of outcome from this measurement.

What this study adds?

The CL measurement protocol in this study did not improve the obstetrics and perinatal outcomes. However, it reduced unnecessary tocolytic treatment and its associated complication.

Acknowledgement

The authors gratefully acknowledge Dr. Narong Thadadech, Director of Udonthani Hospital for permission and grant support. Thanks for Udonthani Hospital staff and all participants who participated in this trial.

Funding disclosure

This study was supported by Udonthani Hospital. The study protocol was approved by the Udonthani Research Ethics Committee: No.39/2561.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Sharvit M, Weiss R, Ganor PY, Tzadikevitch GK, Danielli MN, Biron-Shental T. Vaginal examination vs. cervical length - which is superior in predicting preterm birth? J Perinat Med 2017;45:977-83.
2. Nirunsittirat A, Pitiphat W, McKinney CM, DeRouen

TA, Chansamak N, Angwaravong O, et al. Adverse birth outcomes and childhood caries: a cohort study. Community Dent Oral Epidemiol 2016;44:239-47.
3. McIntosh J, Feltovich H, Berghella V, Manuck T. The role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention. Am J Obstet Gynecol 2016;215:B2-7.
4. Sotiriadis A, Papatheodorou S, Kavvadias A, Makrydimas G. Transvaginal cervical length measurement for prediction of preterm birth in women with threatened preterm labor: a meta-analysis. Ultrasound Obstet Gynecol 2010;35:54-64.
5. Tsoi E, Fuchs IB, Rane S, Geerts L, Nicolaides KH. Sonographic measurement of cervical length in threatened preterm labor in singleton pregnancies with intact membranes. Ultrasound Obstet Gynecol 2005;25:353-6.
6. Tsoi E, Akmal S, Rane S, Otigbah C, Nicolaides KH. Ultrasound assessment of cervical length in threatened preterm labor. Ultrasound Obstet Gynecol 2003;21:552-5.
7. The American College of Obstetricins and Gynecologists. Practice bulletin No. 159: Management of preterm labor. Obstet Gynecol 2016;127:e29-e38.
8. The Royal Thai College of the Obstetricians and Gynaecologists. OB014: The management of preterm labour and premature rupture of membranes. In: RTCOG Clinical practice guideline. Bangkok: RTCOG; 2015. p. 15-41.
9. Chawanpaiboon S, Pimol K, Sirisomboon R. Comparison of success rate of nifedipine, progesterone, and bed rest for inhibiting uterine contraction in threatened preterm labor. J Obstet Gynaecol Res 2011;37:787-91.
10. Ness A, Visintine J, Ricci E, Berghella V. Does knowledge of cervical length and fetal fibronectin affect management of women with threatened preterm labor? A randomized trial. Am J Obstet Gynecol 2007;197:426-7.
11. National Institute for Health and Care Excellence. Preterm labour and birth [Internet]. 2018 [cited 2019 Sep 15]. Available from: https://www.nice.org.uk/guidance/ng25/chapter/Recommendations#diagnosing-preterm-labour-for-women-with-intact-membranes.
12. Lockwood CJ. Diagnosis of preterm labor. UpToDate [Internet]. Waltham, MA: UpTodate; 2018 [cited 2019 Sep 15]. Available from: https://www.uptodate.com/contents/diagnosis-of-preterm-labor.
13. Palacio M, Caradeux J, Sanchez M, Cobo T, Figueras F, Coll O, et al. uterine cervical length measurement to reduce length of stay in patients admitted for threatened preterm labor: A randomized trial. Fetal Diagn Ther 2018;43:184-90.
14. Alfirevic Z, Allen-Coward H, Molina F, Vinuesa CP, Nicolaides K. Targeted therapy for threatened preterm labor based on sonographic measurement of the cervical length: a randomized controlled trial. Ultrasound Obstet Gynecol 2007;29:47-50.
15. Sanin-Blair J, Palacio M, Delgado J, Figueras F, Coll O, Cabero L, et al. Impact of ultrasound cervical length assessment on duration of hospital stay in the clinical management of threatened preterm labor. Ultrasound Obstet Gynecol 2004;24:756-60.
16. Berghella V, Palacio M, Ness A, Alfirevic Z, Nicolaides KH, Saccone G. Cervical length screening for prevention of preterm birth in singleton pregnancy with threatened preterm labor: systematic review and meta-analysis of randomized controlled trials using individual patient-level data. Ultrasound Obstet Gynecol 2017;49:322-9.
17. Lockwood CJ. Preterm labor: clinical findings, diagnostic evaluation, and initial treatment. UpToDate [Internet]. Waltham, MA: UpTodate; 2019 [cited 2019 Sep 15]. Available from: https://www.uptodate.com/contents/preterm-labor-clinical-findings-diagnostic-evaluation-and-initial-treatment.
18. Palacio M, Sanin-Blair J, Sanchez M, Crispi F, Gomez O, Carreras E, et al. The use of a variable cut-off value of cervical length in women admitted for preterm labor before and after 32 weeks. Ultrasound Obstet Gynecol 2007;29:421-6.
19. World Health Organization. WHO recommendations on interventions to improve preterm birth outcomes. WHO guidelines approved by the guidelines review committee. Geneva: WHO; 2015.
20. Songthamwat S, Na Nan C, Songthamwat M. Effectiveness of nifedipine in threatened preterm labor: a randomized trial. Int J Womens Health 2018;10:317-23.
21. Flenady V, Wojcieszek AM, Papatsonis DN, Stock OM, Murray L, Jardine LA, et al. Calcium channel blockers for inhibiting preterm labour and birth. Cochrane Database Syst Rev 2014;(6):CD002255.