Archives of Gynecology and Obstetrics (2019) 299:1275–1282
https://doi.org/10.1007/s00404-019-05109-9

MATERNAL-FETAL MEDICINE

Can myometrial thickness/cervical length ratio predict preterm delivery in singleton pregnancies with threatened preterm labor? A prospective study

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Received: 15 October 2018 / Accepted: 4 March 2019 / Published online: 14 March 2019

Abstract

Objective To investigate whether myometrial thickness (MT) to cervical length (CL) ratio could be used in the prediction of preterm birth (PTB) in singleton pregnancies presented with threatened preterm labor (TPL).

Methods After 48 h of successful tocolysis, MT was measured transabdominally from the fundal, mid-anterior walls and the lower uterine segment (LUS) in 46 pregnancies presented with TPL. MT measurements were divided into CL, individually. The main outcome was PTB before 37 weeks of gestation.

Results The patients were divided into two groups as women delivered ≥ 37 weeks (38.68 ± 1.01 weeks) ($n = 25$) and those delivered < 37 weeks (34.28 ± 2.53 weeks) ($n = 21$). The mean ± SD CL in the preterm delivery group was significantly shorter than the term delivery group (23.77 ± 9.23 vs 29.91 ± 7.03 mm, $p < 0.05$). Fundal, mid-anterior or LUS MT values were similar in both groups. However, in those who delivered preterm, the ratios of fundal MT-to-CL ($p = 0.026$) and mid-anterior MT-to-CL ($p = 0.0085$) were significantly different compared to those delivered at term. The optimal cutoff values for CL, fundal MT-to-CL and mid-anterior MT-to-CL ratios in predicting PTB were calculated as 31.1 mm, 0.19 and 0.20, respectively. Fundal MT-to-CL ratio predicted preterm delivery with 71% sensitivity, 72% specificity, 68% positive and 75% negative predictive values. For mid-anterior MT-to-CL ratio, respective values were 76, 76, 73 and 79%.

Conclusion Measurement of MT along with CL may offer a promising method in the management of women presented with TPL.

Keywords Threatened preterm labor · Preterm delivery · Cervical length · Myometrial thickness

Introduction

In developed countries, preterm birth (PTB) affects approximately 12.5% of all deliveries whereas 50% of PTB generally occur following threatened preterm labor (TPL). TPL is characterized by regular uterine contractions accompanied

The study was presented in part as a poster presentation at the 16th World Congress in Fetal Medicine, 25–29 June 2017, Slovenia.

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by cervical effacement or dilation or both before 37 weeks of gestation. Although majority of PTBs occur after TPL, most patients admitted with TPL do not deliver preterm, but only < 10% deliver within the next 7 days or before 35 weeks of gestation [1, 2]. Treat-all strategy increases unnecessary hospitalizations, referrals to tertiary centers, maternal anxiety and financial cost [3]. On this account, various predictive methodologies are being developed to distinguish who are truly at risk for PTB. Although short cervical length (CL) by transvaginal ultrasound, positive fetal fibronectin and placental alpha microglobulin-1 testing in cervicovaginal fluid, or ruptured membranes, vaginal bleeding and cervical dilation are highly predictive, there is not a precise test for identifying women with TPL who will end up with PTB [4–9].

The upper uterine segment acts in concert with the lower segment and cervix during the normal process of labor. As the cervix undergoes concrete changes, namely effacement and dilation, which are required in the diagnosis of TPL, dynamic changes take place in the myometrium concurrently [10]. From this standpoint, we investigated whether the myometrial thickness (MT) to CL ratio could be used in the prediction of PTB in singleton pregnancies presented with TPL after successful tocolysis.

Methods

This prospective study was conducted between January 2016 and February 2017 at the Perinatology Unit of Trakya University, Faculty of Medicine. Inclusion criteria were as follows: (1) singleton pregnancies; (2) nonsmoker; (3) gestational age between 24^{+0} and 36^{+0} weeks; (4) admitted with TPL (accepted as at least two regular, painful contractions within 10 min persisting against 1 h of bed rest accompanying with cervical changes, dilatation less than 3 cm and effacement of less than 80%); (5) intact membranes; (6) no vaginal bleeding or non-reassuring fetal status. Patients with multiple pregnancies, intrauterine growth restriction, preeclampsia, major fetal abnormalities, prior history of PTB, preterm premature rupture of membranes (PPROM), uterine anomalies, myomas, placental abnormalities (placenta previa, accreta, placental abruption), history of cervical surgery, polyhydramnios, indicated preterm births with medical disorders, chorioamnionitis, persistent uterine contractions, those in active labor or delivered within 48 h after admission were excluded. The study was approved by Ethics Committee of Trakya University (Protocol number: 2014/183) and was also prospectively registered by Thai Clinical Trials Registry (TCTR20190129001). Signed informed consent was received from all patients. Thirteen patients were excluded from the study because of sustained uterine contractions ($n = 1$) and PPROM ($n = 12$) during the course of the study. Twelve women refused to participate in the study, whereas 13 were lost follow-up. MT was measured prospectively from three different points of the uterus, with a full bladder in 46 pregnant women presented with TPL (Figs. 1, 2). MT was measured transabdominally from the lower uterine segment (LUS), mid-anterior and fundal walls, perpendicular to the myometrium. LUS MT was calculated as described below: the first caliper arranged at the interface between the amniotic fluid and the decidua and the second caliper between the myometrium and the bladder wall (C in Fig. 1). The MT was measured as echogenic homogenous layer between the serosa and the decidua twice with the scan 1 cm above and 1 cm below the maternal umbilicus and the mid-anterior MT was calculated by taking the average of these two points (B in Fig. 1). If placenta was situated on these points, then we took the measurement till the basal plate of the placental tissue. Fundal MT was obtained from the most convex area of the uterine curvature by placing the probe above the fundal area (A in Fig. 1). At least three measurements were obtained at each site and the average value was estimated. CL was measured by transvaginal ultrasound with an empty bladder (D in Fig. 1), as previously described by Kagan et al. [12]. All measurements were carried out in the absence of uterine contractions, 48 h after admission and successful tocolysis, by a single operator (S.G.E.), with Voluson E6 (GE Electrical Systems, Zipf, Austria) with 4D convex (RAB-6) and vaginal (IC5-9) probes. MT measurements were divided into CL, individually. All women received tocolysis with nifedipine (Nidilat®, Sanofi Aventis, Istanbul, Turkey). Initially, an oral loading dose of 10 mg nifedipine was administered. If contractions persist, repeat doses were administered every 15 min. The maximum dose that was administered in the first hour was 40 mg. The therapy was continued with 10 mg every 6 h for 48 h. All women were also given betamethasone (12 mg intramuscular, repeated after 24 h) (Celestone Chronodose®, Schering-Plough, Istanbul, Turkey) for accelerating fetal lung maturation. Magnesium sulfate was administered for fetal neuroprotection if the gestational age was ≤ 32 weeks. Antibiotics (ampicillin plus sulbactam, or cefazoline) were

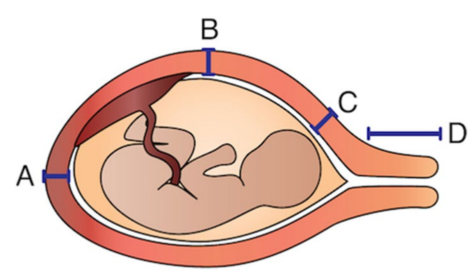

Fig. 1 Illustration of different points of uterus from where measurements were obtained. *A* fundal myometrial thickness, *B* mid-anterior myometrial thickness, *C* lower uterine segment myometrial thickness, *D* cervical length

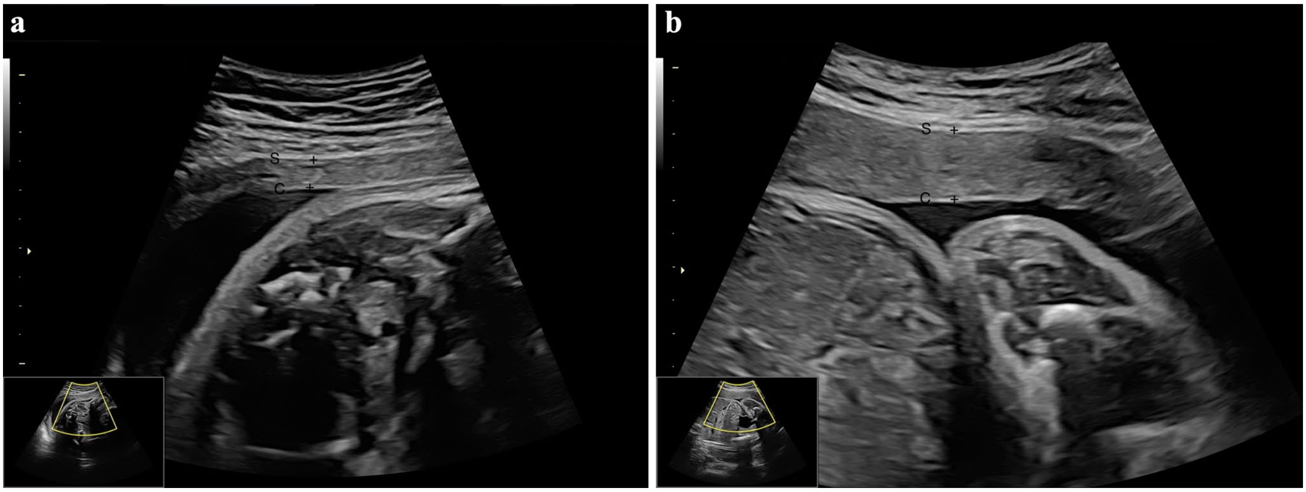

Fig. 2 Transabdominal sonographic scans from upper (**a**) and lower (**b**) parts of uterus for measurement of myometrial thickness. *S* serosa, *C* chorion or decidua

also administered in the presence of urinary tract or vaginal infections. The patients were followed up till delivery. The patients were not given any maintenance tocolysis after the episode of TPL. At every visit, fetal growth and fetal well-being tests such as fetal measurements, nonstress test, amniotic fluid, Doppler ultrasound of the umbilical artery were assessed clinically. According to the gestational age at delivery, patients were divided into two groups: Group 1 (term delivery group) comprised 25 women who delivered after ≥ 37 weeks of gestation and Group 2 (preterm delivery group) consisted of 21 women who delivered < 37 weeks of gestation following TPL.

Statistical analysis

Normal distribution for the variables was assessed using Shapiro–Wilk's test for continuous variables. Student's *t* test was used for two independent group comparisons. Pearson Chi-square test was employed to investigate relationships between two categorical variables. Receiver operative curve (ROC) analysis and Youden's index were used to determine optimal cutoff values. Univariate and multivariate logistic regression analyses were applied to investigate risk factors for PTB. Descriptive statistics were represented as mean and standard deviation for continuous variables, and as frequency and percentage for categorical variables. The relations between variables and the ratios were analyzed by Spearman's rank-order correlation coefficient. Multiple comparisons performed for area under curve (AUC) values and a Bonferroni correction was applied to control the type 1 error. A 0.05 significance level was used for all statistical analyses. All statistical analyses were performed using IBM SPSS Statistics 20.0 (SPSS Inc., Armonk, NY, USA).

Results

Table 1 represents the demographic and ultrasonographic variables at recruitment. The study population included 46 singleton pregnancies. No significant difference was detected between the two groups in terms of maternal age, parity, gestational age at assessment, previous cesarean section, body mass index (BMI), placental location, cesarean section rate and fetal sex ($p > 0.05$). In the preterm delivery group, the mean ± SD time of the delivery ($p < 0.001$), latency interval ($p = 0.0002$), CL ($p = 0.014$), neonatal birthweight ($p < 0.001$) were significantly lower compared to the term group. Fundal MT, mid-anterior MT and LUS MT values were similar in both groups ($p > 0.05$). However, fundal MT-to-CL ($p = 0.026$), and mid-anterior MT-to-CL ratios ($p = 0.008$) were significantly higher in the preterm delivery group than those delivered at term, but similar measurements were obtained in the LUS MT-to-CL ratio ($p = 0.09$).

There were significant negative correlations between CL and fundal MT-to-CL ($r = -0.8$, $p < 0.001$), CL and LUS MT-to-CL ($r = -0.747$, $p < 0.001$), and CL and mid-anterior MT-to-CL ratios ($r = -0.783$, $p < 0.001$) in whole 46 patients. Significant positive relationships between LUS MT-to-CL and fundal MT-to-CL ($r = 0.787$, $p < 0.001$), between LUS MT-to-CL and mid-anterior MT-to-CL ($r = 0.829$, $p < 0.001$), and between fundal MT-to-CL and mid-anterior MT-to-CL ratios ($r = 0.806$, $p < 0.001$) were also observed.

The predictive performances of CL, fundal MT-to-CL ratio and mid-anterior MT-to-CL ratio for the prediction of PTB are given in Table 2. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) for fundal MT-to-CL and mid-anterior MT-to-CL ratios were higher than the values found for CL alone.

Table 1 Demographic and ultrasonographic variables measured at recruitment

	Group 1 (term delivery, $n=25$)	Group 2 (preterm delivery, $n=21$)	p
Age (year)	26.32 ± 6.8	27.714 ± 8.79	0.547
Gravidity	1 (1–2)	2 (1–3)	0.074
Nulliparity	60% (15)	38% (8)	0.139
Antibiotic treatment	32% (8)	57.14% (12)	0.14
Previous cesarean section	72% (17)	66.7% (16)	0.695
Body mass index	27.30 ± 4.22	25.46 ± 4.07	0.140
Placenta	44% anterior 28% posterior 28% fundus	28.6% anterior 19% posterior 52.4% fundus	0.240
CL (mm)	29.91 ± 7.03	23.77 ± 9.23	**0.014**
Fundal MT (mm)	5.61 ± 1.24	5.80 ± 1.79	0.680
Fundal MT/CL	0.21 ± 0.10	0.28 ± 0.12	**0.0261**
Mid-anterior MT (mm)	5.63 ± 1.81	6.09 ± 1.52	0.359
Mid-anterior MT/CL	0.20 ± 0.09	0.31 ± 0.16	**0.0085**
LUS MT (mm)	5.35 ± 2.06	5.45 ± 2.35	0.870
LUS MT/CL	0.20 ± 0.13	0.28 ± 0.20	0.090
Gestational age at MT measurement (weeks ± days)	32.87 ± 2.92	32.12 ± 2.89	0.388
Gestational age at delivery (weeks ± days)	38.68 ± 1.01	34.28 ± 2.53	**< 0.001**
Latency interval (days)	40.36 ± 22.55	16.14 ± 17.11	**0.0002**
Birthweight (grams)	3197.8 ± 454.04	2275 ± 550.18	**< 0.001**

Bold values indicate statistically significant differences ($p < 0.05$)

Descriptive are represented as mean ± SD, median (25th percentile–75th percentile) and frequency (percent)

CL cervical length, *MT* myometrial thickness

$p < 0.05$ was considered to be statistically significant

Table 2 The predictive performances of cervical length (CL), fundal myometrial thickness (MT)-to-CL ratio and mid-anterior MT-to-CL ratio for the prediction of preterm birth

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CL	76	43	61	60
Fundal MT-to-CL ratio	84	48	66	71
Mid-anterior MT-to-CL ratio	84	48	66	71

CL cervical length, *MT* myometrial thickness, *NPV* negative predictive value, *PPV* positive predictive value

ROC analysis (Fig. 3) revealed that CL (AUC: 0.71, 95% CI 0.55–0.83, $p=0.009$), fundal MT-to-CL (AUC: 0.72, 95% CI 0.56–0.84, $p=0.006$) and mid-anterior-to-CL ratios (AUC: 0.74, 95% CI 0.59–0.86, $p=0.002$) have predictive effects on the occurrence of PTB after 48 h following an episode of TPL (Table 3). A cutoff value of 0.19 was calculated for the prediction of preterm birth for fundal MT-to-CL ratio (sensitivity: 71%, specificity: 72%, PPV: 68%, NPV: 75%). For the mid-anterior MT-to-CL ratio, the optimal cutoff was found as 0.20 (sensitivity: 76%, specificity: 76%, PPV: 73%, NPV: 79%) (Table 3). According to the univariate logistic regression analyses, PTB risk increases as fundal MT-to-CL ratio and mid-anterior MT-to-CL ratio increase (Table 4).

We also investigated possible effects of maternal age, nulliparity, gravidity, BMI, previous cesarean section, placental localization, gender and birthweight on PTB using multivariate logistic regression model. Since there were high correlations between fundal MT-to-CL ratio and mid-anterior MT-to-CL ratio, we have built two separate prediction models. Both models revealed that only gravidity and BMI were significant independent factors for PTB (Table 5). When fundal MT-to-CL ratio and mid-anterior MT-to-CL ratio were added to the logistic regression model separately, PTB risk increases as the number of gravidity increases (b value = 1.137, $p=0.030$, and b value = 1.176, $p=0.014$, respectively), or as BMI decreases (b value = −0.269, $p=0.020$, and b value = −0.255, $p=0.030$, respectively) in both models. No variables were found to have a significant relationship with the latency interval. When logistic regression analysis of CL, fundal MT-to-CL and mid-anterior MT-to-CL ratios were modeled together, no variable was found to contribute significantly to distinction of preterm or term delivery (Table 6).

Discussion

In our study, we have analyzed the combined use of MT and CL measurements as a ratio to differentiate and identify the women truly at risk for PTB after an episode of TPL. After the arrest of preterm labor, fundal MT-to-CL and mid-anterior MT-to-CL ratios can predict PTB, but the combination of these two ratios with CL measurement did not provide a higher predictive performance. We found the optimal respective cutoff values for fundal MT-to-CL and mid-anterior MT-to-CL ratios were 0.19 and 0.2; with similar specificity and sensitivity as the sole CL measurement.

Serial sonographic measurement of MT has been studied throughout gestation, in twin pregnancies, after PPROM, during labor and the postpartum period [10, 13–17]. To our knowledge, ours is the first study evaluating MT values with CL measurement after successful tocolysis in patients presented with TPL. Although we found similar

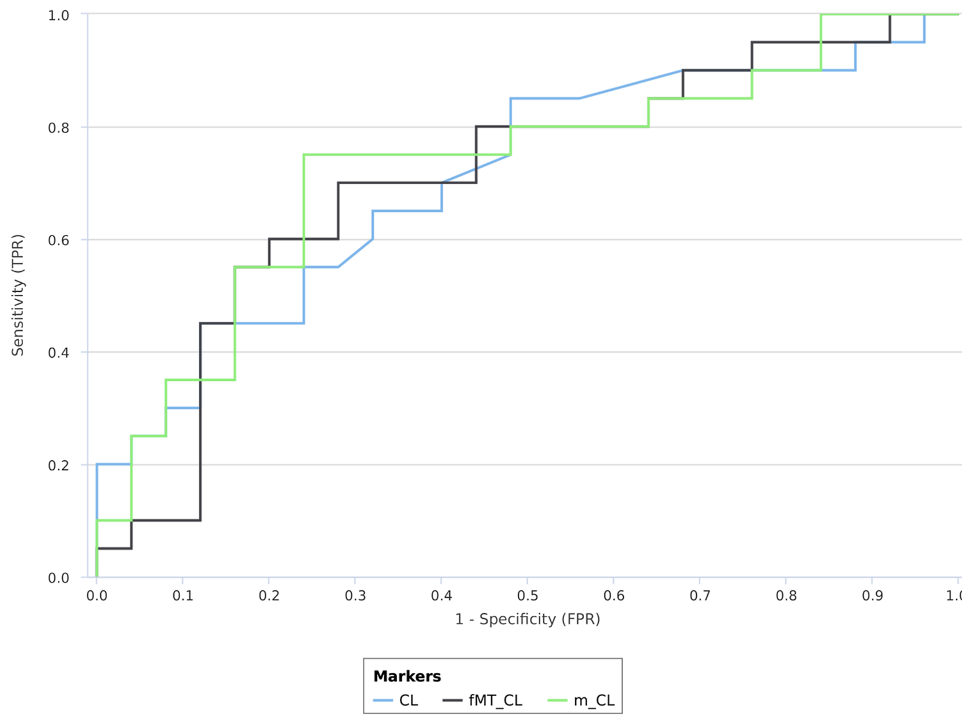

Fig. 3 Receiver operative curve analysis of cervical length (CL), f_MT–CL (fundal myometrial thickness-to-cervical length), and m_MT–CL (mid-anterior myometrial thickness-to-cervical length) ratios

Table 3 Cervical length (CL), fundal myometrial thickness (MT)-to-CL ratio and mid-anterior MT-to-CL ratios in patients delivered < 37 weeks of gestation after an episode of TPL by ROC analysis which is represented as Fig. 3

	Cutoff	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
CL (mm)	< 31.1	0.71 (0.55–0.82)	0.86 (0.64–0.97)	0.52 (0.31–0.72)	0.60 (0.39–0.89)	0.81 (0.56–0.91)
Fundal MT-to-CL ratio	> 0.19	0.72 (0.56–0.84)	0.71 (0.48–0.89)	0.72 (0.51–0.88)	0.68 (0.46–0.87)	0.75 (0.52–0.90)
Mid-anterior MT-to-CL ratio	> 0.20	0.74 (0.59–0.86)	0.76 (0.53–0.92)	0.76 (0.55–0.91)	0.73 (0.51–0.90)	0.79 (0.57–0.92)

ROC receiver operative curve, *AUC* area under curve, *CL* cervical length, *MT* myometrial thickness, *NPV* negative predictive value, *PPV* positive predictive value

Table 4 Univariate logistic regression analysis results for fundal myometrial thickness (MT)-to-cervical length (CL) ratio and mid-anterior MT-to-CL ratio in patients delivered < 37 weeks of gestation

Variable	Coefficient (*b* value)	Standard error	*p*
Model 1			
Constant	− 1.710	0.782	0.029
Fundal MT-to-CL ratio	6.504	3.118	0.037
Model 2			
Constant	− 1.907	0.792	0.016
Mid-anterior MT-to-CL ratio	7.179	3.181	0.024

$p < 0.05$ was considered to be statistically significant

MT measurements at the three uterine segments in women delivered term or preterm; CL, fundal MT-to-CL and mid-anterior MT-to-CL ratios were different in these groups, independent of gestational age at assessment. In the prediction of PTB, the eminent sonographic variable by far

Table 5 Multivariate logistic regression analysis results for preterm birth according to two different models

Variable	Coefficient (*b* value)	Standard error	*p*
Model 1			
Constant	3.296	2.874	0.252
Gravidity	1.137	0.480	0.018
BMI	− 0.255	0.118	0.030
Mid-anterior-to-CL ratio	6.940	3.899	0.007
Model 2			
Constant	3.697	2.750	0.179
Gravidity	1.176	0.481	0.014
BMI	− 0.269	0.116	0.020
Fundal MT-to-CL	7.289	3.875	0.006

CL cervical length, *BMI* body mass index (kg/m^2), *MT* myometrial thickness

$p < 0.05$ was considered to be statistically significant

Table 6 Combination of CL, fundal MT-to-CL and mid-anterior MT-to-CL ratios

Variable	Estimate	Standard error	*z* value	*p* value
Intercept	0.19	2.951	0.065	0.949
CL	0.042	0.068	0.613	**0.54**
Fundal MT-to-CL ratio	1.048	5.445	0.192	**0.847**
Mid-anterior MT-to-CL ratio	−5.797	4.955	−1.17	**0.242**

Bold values indicate statistically significant differences ($p < 0.05$)

is the CL since short cervix has been proved to be closely associated with an increased risk of PTB [1, 2, 10, 18–20]. Although the methodology used for CL measurement is the same in most studies, substantial differences were present, i.e., definition and criterion of TPL show great variability between studies. Second, most of the CL measurements were performed at admission, not after tocolysis. In our study, all measurements were recorded 48 h after the diagnosis of TPL, and most importantly while the patients were clinically stable after TPL episodes were subsided. In line with our study, Crane et al. [21] examined patients after contractions had arrested and found that a CL < 30 mm had a sensitivity of 81%, specificity of 65%, PPV of 46% and NPV of 90%, for the prediction of PTB. Similar to our study design, another study evaluated CL 24–48 h after admission once the contractions had ceased and concluded that knowing CL may reduce the length of hospital stays, without affecting gestational age at delivery or PTB rate [11]. Also, repeat CL measurements obtained some days after the episode of TPL were interpreted as useful in the prediction of the subsequent risk of preterm delivery [19]. On the contrary, two other studies measured CL in symptomatic women on admission and 24 or 48 h after tocolysis, but found lack of conclusive result with repeat measuring on subsequent PTB prediction [22, 23]. Third, the predictive performance of CL in women with TPL varies greatly in different studies depending on the different cutoff values used (shorter than 15, 20, 25, or 30 mm). Different management protocols (tocolysis or no tocolysis) have also been applied according to the different cutoff values. In a meta-analysis, respective sensitivity, specificity and NPV values for predicting PTB before 34 weeks of gestation for CL < 25 mm were 64.3, 68.4 and 95.8%, while for CL < 15 mm were 46.2, 93.7 and 94.8%. They concluded that a CL of 15 mm is satisfactory to rule out PTB within the following week with a 95% probability accentuating that higher cutoff level will not increase the NPV [2]. Another systemic review and meta-analysis conducted by Berghella et al. [20] showed that the management protocol based on the knowledge of CL reduces the incidence of PTB by 36% and postpone gestational age at delivery in pregnancies admitted with TPL. They recommended intervention in women with TPL for those with CL < 20 mm and for whom CL was 20–29 mm together with a positive fetal fibronectin testing and discharge women with CL ≥ 30 mm. These two meta-analyses included the studies evaluating the combined use of CL and several biochemical testing. It might be thought that the addition of biochemical marker screening tests to sonography can improve the identification of patients who are truly at risk for PTB; however, our study was based solely on sonography.

In our study, we found significantly shorter CL in patients presented with TPL and delivered preterm, as can be expected. The optimal cutoff value for CL was calculated as 31.1 mm with a high sensitivity. Consistent with the previous data, for women with arrested preterm labor with a CL above this limit, we can suggest to follow-up them in an outpatient setting [2, 7, 20, 24, 25].

Durnwald et al. [14] described the reference ranges of MT in different sites of the uterus for all three trimesters of pregnancy, showing a significant myometrial thinning mainly between the first and second trimesters, without further thinning thereafter. They emphasized this significant thinning takes place especially in the uterine fundus and LUS, with a 1/3 diminution at the second trimester in comparison to the first trimester. They observed that the respective mean ± SD thicknesses of fundal, mid-anterior walls and LUS were 6.1 ± 1.9, 7.1 ± 2.1 and 5.4 ± 1.7 mm, in the third trimester. The upper and lower segments of the uterus act differently during labor; the upper uterine segment contracts and the myometrium thickens whereas the lower segment relaxes and thins concurrently. This coordination between upper and lower segments of the uterus does not work properly in preterm delivery [10]. Akins et al. [26] also denoted that PTB is not an accelerated form of physiologic labor. Degani et al. [13] evaluated MT of upper and lower uterine segments in the second and third trimesters in low-risk pregnancies, excluding preterm delivery, and observed no difference in MT measurements of the upper uterine segment throughout gestation, but a significant inverse relation between LUS thickness and gestational age. They found thicker mean ± SD values for fundal, mid-anterior wall and LUS thicknesses (9.48 ± 1.5, 9.13 ± 1.6 and 7.4 ± 1.8 mm, respectively) compared to our measurements, suggesting that the myometrium thins after an episode of TPL. In another study, it was noted that only active myometrial contractility leads to global thinning of the myometrium with the least at the fundal area [17]. Guo et al. [27] investigated the relationship between preterm delivery and anterior MT in the second trimester. They found significantly thinner anterior MT in the spontaneous preterm delivery group compared to those who delivered at term. However, Guo et al. measured anterior MT in patients during routine antenatal visits at 20–$27^{6/7}$ weeks of gestation. They also have included patients with PROM and did not evaluate CL.

Our measurements were thinner in comparison to the previous studies giving reference ranges of MT [13, 14], but our study group consisted of patients after an episode of TPL without active uterine contractions at the time of the recordings, taken 48 h after the acute episode.

In our study, the optimal cutoff value for fundal MT-to-CL ratio was calculated as 0.19, and for mid-anterior MT-to-CL ratio as 0.20 with high sensitivity and specificity. The specificities of both ratios were found higher than that of universal CL measurement. We can suggest that these measurements can be useful than sole evaluation of the cervix for the prediction of PTB after an episode of TPL. Also, we have demonstrated in our study that as the CL decreases and fundal MT-to-CL ratio and mid-anterior MT-to-CL ratio increase without an effect on LUS MT-to-CL ratio, the risk of PTB increases.

Although no significant contribution was demonstrated when all these three variables were evaluated together, it can be suggested that in addition to CL measurement, a woman after an episode of TPL, with a fundal MT-to-CL ratio < 0.19 or mid-anterior MT-to-CL ratio < 0.20 can be followed as an outpatient setting.

The main limitation of our study was the small sample size. Besides, measurements were taken from different uterine segments, all of which are soft tissues and one can think that taking these measurements are hard to reproduce in clinical setting. Also, the mean gestational age at assessment was 32.53 ± 2.90 weeks, meaning that mostly late preterm patients were included and those actually troubled < 28 weeks were not. However, the strength of our study is that our population was consisted of patients after the first TPL episode was subsided.

In conclusion, to our knowledge, this is the first preliminary study evaluating the MT for the prediction of PTB in women presenting with TPL, along with CL. We believe that besides the universally adopted screening method—CL, MT measurements might be used in the management of these patients as an in- or outpatient setting who admitted with TPL. However, further studies on this field are needed to validate our results.

Acknowledgements We thank Ahsen Ozturk for her medical illustration.

Author contributions SGE project development, data collection, data analysis, manuscript writing. NCS project development, data analysis, manuscript writing, and critical comments. SK statistical analysis. HS data collection. CI data collection. IUC data collection. FGV data collection.

Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

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