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The Impact of Routine Transvaginal Ultrasound Measurement of the Cervical Length on the Prediction of Preterm Birth: A Retrospective Study in a Tertiary Hospital

O impacto da medição por rotina do comprimento cervical por ecografia transvaginal na predição de parto pré-termo: Um estudo retrospetivo num hospital terciário

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Abstract

Preterm birth (PTB) is a major obstetric problem associated with high rates of neonatal morbidity and mortality. The prevalence of PTB has not changed in the last decade; thus, the establishment of a screening test and effective treatment are warranted. Transvaginal ultrasound measurement of the cervical length (TUCL) has been proposed as an effective method to screen pregnant women at a higher risk of experiencing PTB.

Objective To evaluate the applicability and usefulness of second-trimester TUCL to predict PTB in a cohort of Portuguese pregnant women.

Methods Retrospective cross-sectional cohort study including all singleton pregnant women who performed their second-trimester ultrasound (between weeks 18 and 22 + 6 days) from January 2013 to October 2017 at Centro Hospitalar Universitário São João.

Results Our cohort included 4,481 women. The prevalence of spontaneous PTB was of 4.0%, with 0.7% occurring before the 34th week of gestation. The mean TUCL was of 33.8 mm ,and percentiles 3, 5 and 10 corresponded to TUCLs of 25.0 mm, 27.0 mm and 29.0 mm respectively. The multiple logistic regression analysis, including maternal age, previous PTB and cervical surgery showed a significant negative association between TUCL and PTB, with an odds ratio (OR) of 0.92 (95% confidence interval [95%CI]: 0.90–0.95; $p < 0.001$). The use of a TUCL of 20 mm is the best cut-off, when compared with the 25-mm cut-off, improving the prediction of risk.

Keywords

- preterm birth
- preterm birth screening
- transvaginal ultrasound cervical length
- cervical length cut-off

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Conclusion The present study showed an inverse association between TUCL and PTB, and that the inclusion of other risk factors like maternal age, previous PTB and cervical surgery can improve the screening algorithm. Furthermore, it emphasizes that the TUCL cut-off that defines short cervix can differ according to the population.

Resumo

O parto pré-termo (PPT) é uma grande complicação obstétrica que se associa a elevadas taxas de morbimortalidade neonatal. A sua prevalência não tem alterado na última década, sendo esencial determinar uma forma de rastreio e tratamento eficaz. A medição ecográfica transvaginal do comprimento cervical tem sido proposta como um método eficaz de rastreio das grávidas com risco aumentado de PPT.

Objetivo Avaliar a aplicabilidade e utilidade da medição ecográfica transvaginal do comprimento cervical na previsão de PPT numa amostra de grávidas portuguesas.

Método Estudo de coorte retrospectivo incluindo todas as grávidas com gestação unifetal que realizaram ecografia do 2° trimestre (de 18 a 22semanas + 6 dias) no Centro Hospitalar Universitário de São João entre janeiro de 2013 e outubro de 2017.

Resultados A nossa amostra incluiu 4.481 mulheres. A prevalência de PPT espontâneo foi de 4,0%, sendo que 0,7% ocorreu antes das 34 semanas de gestação. A média do comprimento cervical por ecografia transvaginal foi 33,8 mm, e os percentis 3, 5 e 10 da amostra corresponderam a comprimentos cervicais de 25,0 mm, 27,0 mm e 29,0 mm, respetivamente. A regressão logística múltipla, que incluiu a idade materna, PPT anterior e antecedentes de conização, demonstrou uma associação estatisticamente significativa entre o comprimento cervical e o risco de PPT, com um risco relativo de 0,92 (intervalo de confiança de 95% [IC95%]: 0.90–0.95; $p < 0.001$). A utilização de um valor de referência de comprimento cervical de 20 mm, quando comparado com o valor de referência de 25 mm, melhora a previsão do risco de PPT.

Conclusão Este estudo demostra uma associação entre o comprimento cervical avaliado por ecografia tranasvaginal e o risco de PPT, e salienta que a inclusão de outros fatores de risco, como idade materna, PPT anterior e antecedentes de conização podem melhorar o algoritmo de rastreio. Realça ainda que o valor de comprimento cervical utilizado para definir "colo curto" varia de acordo com a população em estudo.

Palavras-chave
- parto pré-termo
- rastreio parto pré-termo
- comprimento cervical por ecografia transvaginal
- valor de referência do comprimento cervical

Introduction

The World Health Organization (WHO) defines preterm birth (PTB) as a delivery that occurs before the 37th week of gestation. It can occur spontaneously or due to medical induction (iatrogenic). Poorly understood to date, spontaneous PTB is a heterogeneous syndrome with multiple underlying pathophysiologic events and causes,.

Approximately 11% of infants worldwide are born too soon, corresponding to 15 million premature newborns every year.[1–3] The prevalence ranges from 5% in European developed countries to 18% in certain African countries, but these international differences may reflect variations in definitions rather than a true epidemiological difference. For example, the method to determine the gestational age and different viability limits can influence this rate. In Portugal, the prevalence of singleton live preterm newborns is of 7.4%.[4]

Despite all advances in medicine, PTB is still an important health problem, and the leading cause of neonatal mortality. Prematurity is associated with multiple neonatal complications and long-term morbidity.[5,6]

Fetal development is a continuum, and the risk of perinatal complications is inversely related to the gestational age at delivery. For this reason, some experts recommend a subclassification of PTB into early PTB (< 34 weeks) and late PTB (between 34 weeks and 36 weeks + 6 days), as the negative impact is different in the two groups.[7] Infants born before the 32th week of gestation represent less than 2% of all premature births, but they contribute to 50% of the overall perinatal mortality.[8]

Preterm birth is such a major economic and social burden that its reduction is one of the Millennium Development Goals established by the United Nations.[9] Unfortunately, despite all efforts, the rate of prematurity has not changed in the past 30 years, and, in 2016, the WHO included PTB as one of the top-10 priority research areas.[10,11]

During the last years, many risk scores have been proposed to predict PTB, but they all have a low sensitivity and poor positive predictive value (PPV).[12,13] The history of previous spontaneous PTB, for example, is the most significant risk factor known, but only 10% to 15% of PTBs occur after a previous event.[14,15]

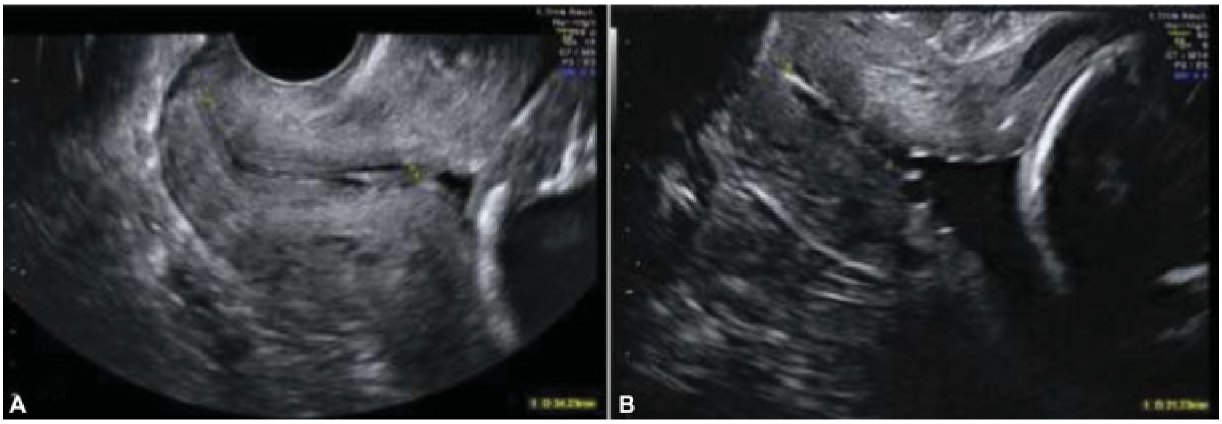

Fig. 1 Transvaginal ultrasound measurement of the cervical length (TUCL). (**A**) Normal cervix; (**B**) short cervix.

As the majority of spontaneous PTBs occur in low-risk pregnancies, Andersen et al.[16] (1990) proposed the use of transvaginal ultrasound measurement of the cervical length (TUCL) as a predictor of PTB. Since then, the technique has been well standardized, and its reproducibility, confirmed.[17,18]

The risk of experiencing PTB is inversely correlated to the cervical length, but the ideal cut-off for clinical use is still controversial.[16,19–23] By definition, a cervical length below the 10th centile for gestational age is considered "short." This value varies according to the gestational age, the populational distribution of TUCL, and the prevalence of PTB. In the initial trials, the 10th centile was of 25 mm; therefore, this cut-off has been widely used.[15,24–27] Since then, many cut-offs (from 15 mm to 30 mm) have been proposed, but none is consensual.

The main objective of the present study was to evaluate the applicability and usefulness of second-trimester TUCL to predict PTB in Portuguese pregnant women. We analyzed the distribution of TUCL in our cohort and determined the prevalence of short cervix using different cut-offs. Furthermore, we developed models to estimate the best TUCL cut-off in our cohort and improve its usefulness.

Methods

The present was an observational, retrospective cross-sectional cohort study carried out at the Obstetrics and Gynecology Department of Centro Hospitalar Universitário São João (CHUSJ), Portugal, after approval by the hospital's ethics committee (CES 81-17).

We included all singleton pregnant women who underwent the second-trimester ultrasound (the 18th week to the 22nd week + 6 days, determined by the crown-rump length before the 14th week) from January 2013 to October 2017 in this hospital. Delivery in the same institution and the existence of delivery data were also inclusion criteria. We excluded all women that had induced PTBs for medical reasons (including premature rupture of membranes), cervical cerclage performed prior to screening, diagnosis of chorioamnionitis, and deliveries before the 24th week.

The ultrasound exams at CHSJ are performed by obstetricians with accreditation from the Fetal Medicine Foundation (FMF) for cervical assessment. However, because the universal screening of TUCL is not mandatory, all ultrasound images available through the Astraia software (Astraia Software, GmbH, Munich, Germany) were reviewed in order to identify patients with an ultrasound image that complied with standard the rules of the FMF, which recommends the use of a transvaginal probe with the identification of the sagittal view of the cervix, occupying 75% of the image. Identification of the internal os, external os and cervical canal is essential. The measurement is performed in a straight line between the external and internal os. Care should be taken to distinguish between the cervical canal and the lower uterine segment (►**Fig. 1**).

At our hospital, all pregnant women with TUCLs ≤ 25 mm are considered to have a short cervix, and vaginal progesterone or the Arabin (Dr. Arabin GmbH & Co., Witten, Germany) pessary is suggested.

Maternal characteristics, medical history, obstetric history and delivery data were obtained from the database of the Obstetrics and Gynecology Department through the Obscare software. This data was compiled using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software, version 24, for the statistical analyses. The continuous variables were expressed as means ± standard deviations (SDs), and frequencies and percentages were used to describe the categorical variables.

The frequencies of PTB were calculated according to different groups of cervical length measurements. The diagnostic ability of different TUCL cut-offs was evaluated in terms of sensitivity, specificity, PPV, negative predictive value (NPV), and the area under the curve (AUC).

An exploratory univariate analysis of clinical and demographic global data was first performed to determine the variables that predicted PTB and those associated with TUCL. All of the hypothesis tests conducted were two-tailed, and they included the Student *t*-test, the Chi-squared (χ^2) test, and the Fisher exact test, as appropriate. Then, we developed a multivariate logistic regression model aiming to predict

PTB as the outcome, using the TUCL as the explanatory variable, and including the main effects of maternal age, previous PTB and cervical surgery. For all of these analyses, values of $p < 0.05$ were considered statistically significant.

To select an optimal TUCL cut-off, we used the maximum likelihood and a confidence interval based on a likelihood ratio test. The likelihoods were calculated for a series of our multivariate logistic regression model using all TUCL cuto-ffs between 8 mm and 50 mm. The 95% lower and upper confidence bounds were determined as parameter values that reduce the maximum likelihood by $\chi^2(0.05,1)/2 = 1.92$. Using this optimal TUCL cut-off, we then assessed the potential differential effects across subgroups of risk factors using a stratified analysis. The effect modification among strata was checked using a test of homogeneity. Adjusted estimates were calculated using the Cochran-Mantel-Haenszel method.

In Portugal, the most used cut-off is TUCL $\leq$ 25 mm. In order to compare our optimal cut-off with the 25-mm cut-off, we classified each woman into groups of predicted probabilities derived from corresponding multivariate models using each cut-off. We then cross-classified these groups and compared them to the observed proportions of events in each group.

Results

During the aforementioned period, 8,016 women underwent a routine second-trimester ultrasound and delivery at CHUSJ. In total, 3,476 women were excluded from this group for the following reasons: delivery before the 24th week (n = 5),; medically-induced PTB (n = 241); cervical cerclage prior to ultrasound (n = 19); diagnosis of chorioamnionitiss (n = 3); absence of cervical length measurement (n = 958); and images of the cervical length measurement that did not comply with FMF recommendations (n = 2,426). Within the latter group, the major reason for exclusion was a transabdominal measurement (n = 1,275), instead of the transvaginal approach preconized by the FMF. Some women presented more than one exclusion criteria.

Our final cohort consisted of 4,481 women with a mean age of 30.7 ± 5.5 years. Primigravidae represented 45.4% of the sample, and 56.2% had no previous delivery. Most of them had no medical (86.5%) or obstetric (96.7%) relevant background. Only 1.6% of these women had a previous spontaneous PTB, and 0.9% had history of cervical surgery, the 2 major known risk factors for PTB.

Spontaneous delivery occurred in 64.3% of the cases, and 76.4% of the women underwent vaginal delivery. The prevalence of spontaneous PTB prevalence of the original cohort (8,016 women) was of 6.9% (553), and, after applying the exclusion criteria (with the sample reduced to 4,481 women) the prevalence dropped to 4.0% (n = 179), mainly due to the exclusion of medically-induced PTB. In total, 96.0% (n = 149) of the cases of PTB occurred between the 34th and 37th weeks, and 0.7% (n = 30) occurred before 34th week of gestation. The maternal and clinical characteristics of our cohort are described in **table 1**.

The mean gestational age at the time of the ultrasound was 21 weeks + 3 days, with a distribution of 0.2% (8) at 18 weeks, 0.5% (22) at 19 weeks, 12.4% (555) at 20 weeks,

Table 1 Maternal and clinical characteristics of the study population

Maternal features	Medical background	Risk factors for Preterm birth
Age (years)	None: 86.5%	Spontaneous preterm birth: 1.6%
Mean ± standard deviation: 30.7 ± 5.5	Uterine malformations: 0.3%	Cervical surgery: 0.9%
Min: 14	Psychiatric disorders: 1.4%	Short cervical length ($\leq$25 mm)
Max: 50	Sexually-transmitted diseases: 1.0%	-» On 2nd-trismester ultrasound: 3.0%
Body mass index (kg/m^2)	Cardiac or renal disorders: 1.0%	Obstetric background
Mean ± standard deviation: 24.6 ± 4.9	Diabetes: 0.7%	None: 96.7%
Obesity (> 30): 8.0%	Hypertension: 2.6%	Preeclampsia: 0.9%
Years of schooling	Hypothyroidism: 5.2%	Fetal death: 0.6%
< 4th grade: 0.7%	Neoplasia: 0.8%	Fetal malformation: 0.4%
4th to 12th grades: 64.6%		2nd T abortion: 0.1%
> 12th grade: 34.7%		
Smokers: 12.9%		
Alcohol/drug users: 0.2%		
Obstetric intercurrences	**Actual obstetric data**	**Time of delivery**
Fetal growth restriction: 3.9%	Primigravida: 45.4%	Mean: 39.2 weeks
Fetal malformation: 1.6%	Nullipara: 56.2%	Minimum: 24.2 weeks
Urinary infection: 3.2%	Assisted reproduction: 2.7%	Maximum: 42 weeks
Other infections: 4.4%	Labor induction: 35.7%	Term delivery ($\geq$37 week): 96.0%
Hypertensive syndrome: 3.2%	Vaginal delivery: 76.4%	Preterm delivery (< 37 week): 4.0%
Gestational diabetes: 9.6%	Male newborn: 50.6%	Early preterm birth (< 34th week): 0.7%
Surgery on 1st/2nd trimesters: 0.2%		Late preterm birth ($\geq$ 34th week): 3.3%

Table 2 Distribution of preterm and term births across different cervical length intervals

Cervical length	Early preterm birth (< 34 weeks): n (%)	Preterm birth (< 37 weeks): n (%)	Term birth (≥37weeks): n (%)	Total: n (%)
< 15 mm	4 (13.3)	5 (2.8)	11 (0.3)	16 (0.4)
15.1 to 20 mm	3 (10.0)	4 (2.2)	11 (0.3)	15 (0.3)
20.1 to 25 mm	0 (0)	6 (3.4)	74 (1.7)	80 (1.8)
25.1 to 30 mm	3 (10.0)	30 (16.8)	506 (11.8)	536 (12.0)
≥ 30 mm	20 (66.7)	134 (74.9)	3,700 (96.5)	3,834 (85.6)

Table 3 Sensitivity and specificity of the cervical length measurement to predict preterm birth and cumulative incidence of the different cut-offs

Cut-off	Sensitivity	Specificity	Area under the curve	Positive predictive value	Negative predictive value
15 mm	2.8	99.7	0.51	10.9	0.97
20 mm	6.2	99.5	0.53	11.5	0.94
25 mm	10.6	97.3	0.54	3.9	0.91
30 mm	30.7	80.1	0.55	1.5	0.86

66.5% (2979) at 21 weeks, and 20.5% (917) at 22 weeks. The mean TUCL was of 33.8 mm ± 4.8 mm (range: 3.0 mm to 53.0 mm). Percentiles 3, 5 and 10 corresponded to TUCLs of 25.0 mm, 27.0 mm and 29.0 mm respectively. ►**Table 2** presents the frequency of term and preterm births across different TUCL intervals. Among pregnant women with PTB, the TUCL was significantly lower (mean: 31.6 mm; 95%CI: 30.7–32.5 mm) compared to the measurements of those with term birth (mean: 33.9 mm; 95%CI: 33.8–34.0 mm; $p < 0.001$).

Even though the TUCL alone showed a high specificity to predict PTB, its diagnostic ability was limited by a very low sensitivity, with an AUC close to 0.5 for all different cut-offs studied, as depicted in **table 3**.

The univariate analysis (►**Tables 4** and **5**) showed that maternal age ≥ 40 years, history of PTB, and cervical surgery were the main significant predictors of PTB. Additionally, history of PTB and previous cervical surgery were also associated with shorter TUCL, thus acting as confounders.

The multivariate logistic regression analysis, incorporating maternal age ≥ 40 years old, history of PTB, and previous cervical surgery, evaluated the impact of the TUCL as a predictor of PTB (►**Table 6**).

The estimated odds ratio (OR) for the effect of the TUCL on PTB, controlling for covariates, was of 0.92 (95%CI: 0.90–0.95; $p < 0.001$), which highlights the significant negative association between TUCL and PTB. The diagnostic ability of the multivariate model improved, showing an AUC of 0.65 (►**Fig. 2**).

As expected, in the univariate analysis, the treatment with progesterone/pessary was associated with shorter TUCL, and thus, also with PTB, when considering the total study cohort. Within the group of women with a diagnosis of short cervix, 68% (n = 93) underwent treatment, and 13% (n = 18) declined it. There was, however, no significant difference between the frequency of PTB among women who accepted or declined progesterone or the pessary (14% versus 22.2% of PTB respectively; $p = 0.472$); therefore, the treatment was not included in our multivariate model.

To select the optimal TUCL cut-off, we ran several multivariate logistic regression models using different cut-offs (from 8 mm and 50 mm) associated with other variables like maternal age ≥ 40 years, history of PTB, and previous cervical surgery. Plotting the log likelihood from these models against the TUCL showed that a cut-off of 20 mm (95%CI: 19.5-–22 mm) best discriminated 2 TUCL subgroups with differential odds for PTB (►**Fig. 3**). Women with a short cervix, defined by TUCL ≤ 20 mm, had an OR of 12.2 (95%CI: 5.8–25.4; $p < 0.001$) compared with those with TUCL > 20 mm.

Considering maternal age ≥ 40 years, history of PTB and previous cervical surgery as the main risk factors for PTB, a stratified analysis was performed by separately evaluating women with at least 1 of these factors (n = 297) versus women who did not presented any of them (n = 4,184 [93.4%]) (►**Table 7**). The significant association of a short cervix (TUCL ≤ 20 mm) with PTB was maintained in both groups, with an OR of 16.2 (95%CI: 2.7–97.1; $p < 0.001$) for women with risk factors, and an OR of 9.8 (95%CI: 4.1–23.7; $p < 0.001$) for women without them. There was no effect modification between the groups ($p = 0.614$, homogeneity test). Considering this stratification, the adjusted OR for women with short cervix (TUCL ≤ 20 mm) was of 11.4 (95%CI: 5.1–25.4; $p < 0.001$).

Table 4 Demographics comparing preterm and term births

		Preterm birth – n: 179 (4.0%)	Term birth – n: 4302 (96.0%)	*p*-value
Maternal age	Mean ± standard deviation	31.4 ± 6.0	30.7 ± 5.5	0.098[a]
	< 40 years old	161 (89.9%)	4122 (95.8%)	< 0.001[b]
	≥40 years old	18 (10.1%)	180 (4.2%)	
Body mass index	Mean (kg/m^2)	2397 ± 5.3	24.6 ± 4.9	0.055[a]
Schooling	≤ 12th grade	111 (62.4%)	2807 (65.4%)	0.404[b]
	> 12th grade	67 (37.6%)	1485 (34.6%)	
Addictions	Smoking	21 (11.7%)	556 (12.9%)	0.640[c]
	Drugs	0 (0%)	4 (0.1%)	1.000[c]
	Alcohol	1 (0.6%)	4 (0.1%)	0.184[c]
Gestational age at cervical length measurement	Mean ± standard deviation (weeks)	21.5 ± 0.5	21.5 ± 0.6	0.592[a]
Type of pregnancy	Spontaneous	165 (95.4%)	4,041 (97.2%)	0.150[b]
	Medical assisted	8 (4.6%)	115 (2.8%)	
Gravidity	Primigravida	83 (46.5%)	1,953 (45.4%)	0.789[b]
Parity	Nulliparous	101 (56.4%)	2,417 (56.2%)	0.949[b]
Obstetric history	Preterm birth	17 (9.5%)	55 (1.3%)	< 0.001[c]
	Second trimester miscarriage	1 (0.6%)	4 (0.1%)	0.184[c]
	Recurrent pregnancy loss	2 (1.1%)	16 (0.4%)	0.160[c]
Maternal background	Conization	10 (5.6%)	31 (0.7%)	< 0.001[b]
	Mullerian anomalies	3 (1.7%)	11 (0.3%)	0.016[c]
	Chronic hypertension	9 (5.0%)	100 (2.3%)	0.021[b]
	Diabetes	3 (1.7%)	28 (0.7%)	0.125[c]
	Hypothyroidism	7 (3.9%)	227 (5.2%)	0.429[b]
Obstetrical complications	Malformations and cromossomopathies	6 (3.4%)	64 (1.5%)	0.059[c]
	Fetal growth restriction	9 (5.0%)	167 (3.9%)	0.439[b]
	Hypertensive syndromes	0	143 (3.3%)	0.040[c]
	Gestational diabetes	24 (1.4%)	405 (9.4%)	0.751[b]
	Short interpregnancy intervals	1 (0.6%)	4 (0.1%)	0.184[c]
	Surgical procedure during pregnancy	0 (0%)	7 (0.2%)	1.000[c]
	Urinary infections or asymptomatic bacteriuria	8 (4.5%)	135 (3.1%)	0.321[b]
	Others infections during pregnancy	10 (5.9%)	188 (4.4%)	0.438[b]
Treatment with progesterone or Arabin pessary		25 (13.9%)	116 (2.7%)	0.000[b]

Notes: [a]*t*-test; [b]Chi-squared test; [c]Fisher test.

A simple comparison of the 20-mm and 25-mm cut-offs, based on AUCs of multivariate models, showed no statistical difference (20 mm: AUC = 0.59 [95%CI: 0.56–0.62] versus 25 mm: AUC = 0.60 [95%CI: 0.57–0.64]; $p = 0.157$). However, a better performance in the prediction of PTB of the 20-mm compared to the 25-mm cut-off was highlighted by comparing the distribution of women according to the prediction probabilities derived from the corresponding multivariate models. Globally, 15 (0.33%) women were reclassified to a different predicted-probability group when the multivariate model included the 20-mm instead of the 25-mm cut-off. As described in **table 6**, out of the 4 women upgraded to a higher probability (from 0.50-0.75 in the 25-mm model to > 0.75 in the 20-mm model), 75% (n = 3) experienced a PTB. On the other hand, out of the 8 women reclassified to a lower predicted probability (from 0.25-0.50 in the 25-mm model to < 0.25 in the 20-mm model), only 1 (12.5%) had PTB.

Table 5 Cervical length description according to demographics

			Cervical length (mean ± standard deviation)	*p*-value [a]
Maternal age	< 40 years old		33.8 ± 4.8	0.546
	≥ 40 years old		34.0 ± 5.0	
Schooling	≤ 12th grade		33.8 ± 4.8	0.568
	> 12th grade		33.9 ± 4.9	
Addictions	Smoking	No	33.9 ± 4.8	0.089
		Yes	33.5 ± 5.3	
	Drugs	No	33.8 ± 4.8	0.443
		Yes	35.5 ± 2.8	
	Alcohol	No	33.8 ± 4.8	0.170
		Yes	30.5 ± 3.1	
Type of pregnancy	Spontaneous		33.8 ± 4.8	0.664
	Medically-assisted		33.6 ± 6.4	
Gravidity	Primigravida		33.5 ± 4.8	0.000
	Multigravida		34.1 ± 4.9	
Parity	Nulliparous		33.4 ± 4.8	0.000
	Multiparous		34.3 ± 4.8	
Obstetric history	Preterm birth	No	33.9 ± 4.8	0.000
		Yes	31.8 ± 5.0	
	Second-trimester miscarriage	No	33.8 ± 4.8	0.001
		Yes	26.8 ± 8.4	
	Recurrent pregnancy loss	No	33.8 ± 4.8	0.412
		Yes	32.3 ± 7.9	
Maternal background	Conization	No	33.9 ± 4.8	0.000
		Yes	30.8 ± 5.6	
	Mullerian anomalies	No	33.8 ± 4.8	0.993
		Yes	33.9 ± 3.2	
	Chronic hypertension	No	33.8 ± 4.8	0.540
		Yes	34.1 ± 6.2	
	Diabetes	No	33.8 ± 4.8	0.120
		Yes	35.9 ± 4.6	
	Hypothyroidism	No	33.8 ± 4.9	0.659
		Yes	34.0 ± 4.5	
Obstetrical complications	Malformations and cromossomopathies	No	33.8 ± 4.8	0.821
		Yes	34.0 ± 4.9	
	Fetal growth restriction	No	33.9 ± 4.8	0.000
		Yes	32.4 ± 4.9	
	Hypertensive syndromes	No	33.8 ± 4.8	0.448
		Yes	33.5 ± 4.8	
	Gestational diabetes	No	33.8 ± 4.8	0.967
		Yes	33.8 ± 45.0	
	Short interpregnancy intervals	No	33.8 ± 4.8	0.871
		Yes	34.3 ± 2.4	
	Surgical procedure during pregnancy	No	33.8 ± 4.8	0.934
		Yes	34.0 ± 3.3	
	Urinary infections or asymptomatic bacteriuria	No	33.8 ± 4.8	0,112
		Yes	33.12 ± 4.8	
	Other infections during pregnancy	No	33.9 ± 4.9	0.880
		Yes	33.2 ± 4.6	
Treatment with progesterone or Arabin pessary		No	34.2 ± 4.3	0.000
		Yes	24.1 ± 7.2	

Note: [a]*t*-test.

Table 6 Multivariate logistic regression analysis to evaluate the impact of transvaginal ultrasound measurement of the cervical length as a predictor of preterm birth

Outcome	Odds ratio	95% confidence interval		*p*-value
Cervical length	0.925	0.90	0.95	0.000
Maternal age	2.265	1.32	3.90	0.003
Previous preterm birth	6.754	3.72	12.16	0.000
Cervical surgery	0.178	0.81	0.40	0.000
Constant	14.557	2.61	81.31	0.002

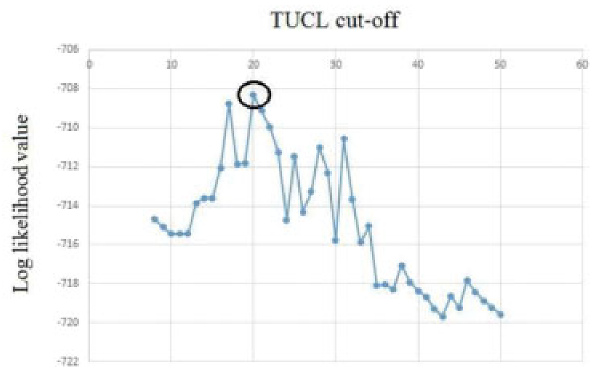

Fig. 3 Plotting to determine the best TUCL cut-off based on multiple log likelihood of the logistic regression model (including maternal age ≥ 40 years, history of PTB, and previous cervical surgery), using cut-offs between 8 mm and 50 mm. The circle represents the cut-off that best discriminated the risk of experiencing PTB.

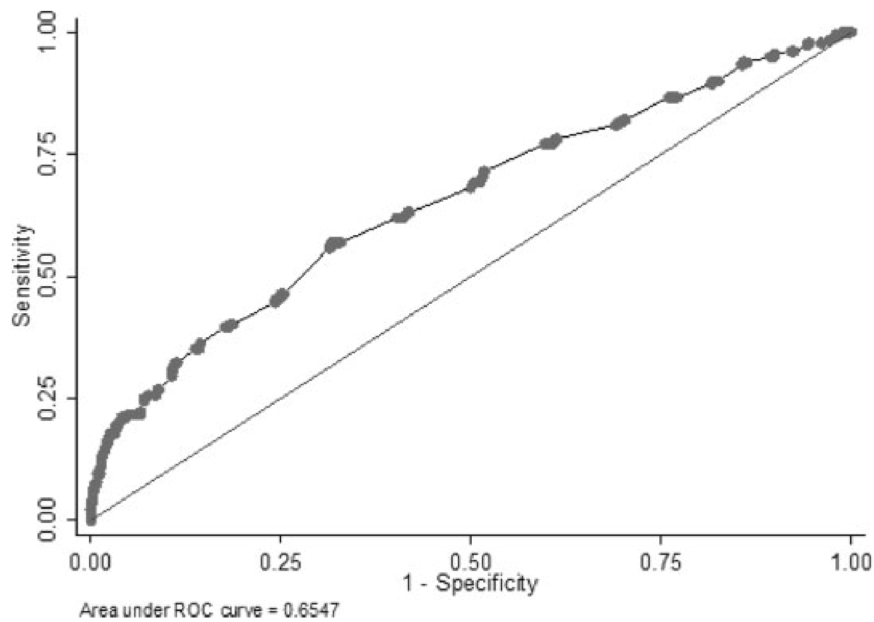

Fig. 2 Graphic representations of sensitivity, specificity and area under the curve (AUC) of the multivariate model.

Table 7 Distribution of the pregnant women according to group probability of preterm birth using transvaginal ultrasound measurement of the cervical length and presence/absence of risk factors (maternal age ≥ 40 years, previous PTB and cervical surgery). Cross-classification of the 25-mm cut-off group (most used cut-off) versus the 20-mm cut-off group (our best cut-off) and frequency of PTB in each subgroup

		Group probability – TUCL: 20 mm				
		< 0.25	0.25-0.50	0.50-0.75	≥ 0.75	Total reclassified
Group probability – TUCL: 25 mm	< 0.25	4,456	1	0	0	0.02%
	PTB% (n)	3.8% (168)	0%	0%	0%	
	0.25-0.50	8	8	2	0	55.6%
	PTB% (n)	12.5% (1)	50.0% (4)	50.0% (1)	0%	
	0.50-0.75	0	0	1	4	80.0%
	PTB% (n)	0%	0%	100% (1)	75.0% (n3)	
	≥ 0.75	0	0	0	1	0%
	PTB% (n)	0%	0%	0%	0%	

Abbreviations: PTB, preterm birth; TUCL, transvaginal ultrasound measurement of the cervical length.

Discussion

Good practice of disease screening recommends that the condition be an important health problem and facilities for diagnosis and treatment be available, as already published in 1968 by the WHO.[28]

Preterm birth fulfills the first prerequisite, as it represents a major obstetric complication. Our cohort presents 4% (179) of spontaneous PTB, and this prevalence is similar to that of other studies regarding screening and treatment.[27,29,30]

A second assumption needed to implement a screening process is the existence of a test able to detect the high-risk population, and the TUCL satisfies this requirement. An inverse association between the TUCL and PTB, which was also observed in our study, has been widely documented.[16,21,26,27,29–32] The TUCL in our cohort showed a high specificity to predict PTB, but low sensitivity and a poor AUC, results similar to those of other studies. Iams et al.[27] reported that TUCL $\leq$ 25 mm had a sensitivity of 37% and a specificity of 92%, but more recent studies obtained even lower sensitivities, such as 2.4% in the study by van der Ven et al.,[33] and 8.0% in the one by Esplin et al.[34]

Our multivariate model showed an improvement in the AUC value, highlighting that a combined screening including maternal age > 40 years, history of PTB and previous cervical surgery should be considered for screening, instead of the TUCL alone. The Society for Maternal-Fetal Medicine Publications Committee, in their 2012 guidelines, concluded that the most effective approach was to initiate treatment in low-risk women with a TUCL $\leq$ 20 mm, or high-risk pregnant women with a TUCL $\leq$ 25 mm, supporting that other risk factors should be included in the screening algorithm.[35]

Nowadays, there is no debate that second-trimester TUCL is the most powerful screening instrument available, but the best cut-off to separate normal from short cervixes is still controversial.[16,19–23] As most parameters in medicine, there is no biological TUCL cut-off, and defining "short" is not an easy task. Lower cut-offs present good specificity but low sensitivity, but higher values (like 29 mm) lead to an increase in the false-positive rate.[27,36] Most guidelines recommend a 25-mm cut-off, as it corresponds to the 10th percentile in the initial published trials.[7,15,16,27,36–40] However, more recent studies showed a lower prevalence of short cervices defined as TUCL $\leq$ 25 mm, averaging 2.5%.[14,33,34,41,42] Our results follow this new tendency, as the prevalence of TUCL $\leq$ 25 mm was of only 3% (134), and the 10th TUCL percentile in our cohort corresponded to 29.0 mm.

TUCL distribution can be influenced by many factors; therefore, the ideal cut-off can change in different populations. That said, we concluded that the best cut-off for our cohort was 20 mm (►**Fig. 3**). This value enabled us to improve the prediction of the risk of experiencing PTB mainly by reducing the false-positive rate (8 women were reclassified as low probability, and only 1 (15.5%) of them experienced a PTB).

In parallel to studies on the efficacy of TUCL screening, cost-analysis studies were also conducted, which concluded that TUCL screening is cost-effective even if we assume a low incidence of short cervical length and a modest impact of the treatment with progesterone.[25,31,43–45]

The Federation of Gynecology and Obstetrics Working Group on Best Practices in Maternal Fetal Medicine recommended universal transvaginal cervical length screening and vaginal progesterone when TUCL < 25 mm.[46] Subsequently, studies[41,42,47] using this recommendation showed a reduction in the PTB rate when universal screening was applied. Son et al.,[42] for example, obtained a 20% reduction in the rate of PTBs after implementing TUCL screening, even with a very low prevalence short cervixes (TUCL $\leq$ 25 mm: 0.89%). The negative impact of PTB is so huge that every approach able to reduce it has a positive impact and should be considered.

Conclusion

Preterm birth represents a major health problem, and strategies to prevent are important. The present study showed an inverse association between TUCL and PTB, and emphasized that other factors like maternal age, history PTB and previous cervical surgery can improve the screening algorithm. The value that defines a short cervix can differ in each population, and, for our cohort, the best cut-off was 20 mm. Even though TUCL has a low diagnostic performance, it is the best screening method available to predict PTB, and TUCL screening has been shown to reduce the PTB rate.

Contributors

All authors were involved in the design and interpretation of the analyses, contributed to the writing of the manuscript, and read and approved the final manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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