Reviewing short cervix in singleton pregnancies: a multicentric prospective cohort study in the Brazilian population

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Abstract

Objective: To identify the association between cervical length (CL) and gestational age at birth. Design: Prospective cohort study. Setting: Seventeen Brazilian reference hospitals. Population: A cohort of 3139 asymptomatic singleton pregnant women who participated in the screening phase of a Brazilian multicenter randomized controlled trial (P5 trial). Methods: Transvaginal ultrasound (TVU) to measure CL was performed from 18 to 22+6 weeks. Women with CL [?] 30 mm received vaginal progesterone (200 mg/day) until 36 weeks' gestation. Main Outcome Measures: Area under receive operating characteristic curve (AUC), sensitivity, specificity, Kaplan-Meier curves for preterm birth (PTB), number needed to screen (NNS). Results: CL [?]25mm was associated with extremely severe, severe, moderate and late PTB, whereas a CL 25–30mm was directly associated with late sPTB. The AUC to predict sPTB<28 weeks was 0.82 and for sPTB<34 weeks was 0.67. Almost half of the sPTB occurred in nulliparous women and CL [?]30mm was associated with sPTB <37 weeks (OR = 7.84; 95%CI = 5.5–11.1). The NNS to detect one sPTB <34 weeks in women with CL [?]25mm is 121 and 248 screening tests are necessary to prevent one sPTB <34 weeks using vaginal progesterone prophylaxis. Conclusions: CL measured by TVU is associated with sPTB <34 weeks. Women with CL [?]30mm are at increased risk for late sPTB. Funding: Bill & Melinda Gates Foundation [OPP1107597], the Brazilian Ministry of Health, and the Brazilian National Council for Scientific and Technological Development (CNPq) [401615/20138]. Keywords: cervical length; number needed to screen; preterm birth; short cervix.

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Short Title - Reviewing short cervix for Brazilian population

Abstract

Objective: To identify the association between cervical length (CL) and gestational age at birth.

Design: Prospective cohort study.

Setting: Seventeen Brazilian reference hospitals.

Population: A cohort of 3139 asymptomatic singleton pregnant women who participated in the screening phase of a Brazilian multicenter randomized controlled trial (P5 trial).

Methods: Transvaginal ultrasound (TVU) to measure CL was performed from 18 to 22+6 weeks. Women with CL [?] 30 mm received vaginal progesterone (200 mg/day) until 36 weeks' gestation.

Main Outcome Measures : Area under receive operating characteristic curve (AUC), sensitivity, specificity, Kaplan-Meier curves for preterm birth (PTB), number needed to screen (NNS).

Results: CL [?]25mm was associated with extremely severe, severe, moderate and late PTB, whereas a CL 25–30mm was directly associated with late sPTB. The AUC to predict sPTB<28 weeks was 0.82 and for sPTB<34 weeks was 0.67. Almost half of the sPTB occurred in nulliparous women and CL [?]30mm was associated with sPTB <37 weeks (OR = 7.84; 95%CI = 5.5–11.1). The NNS to detect one sPTB <34 weeks

in women with CL [?]25mm is 121 and 248 screening tests are necessary to prevent one sPTB <34 weeks using vaginal progesterone prophylaxis.

Conclusions: CL measured by TVU is associated with sPTB <34 weeks. Women with CL [?]30mm are at increased risk for late sPTB.

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Keywords : cervical length; number needed to screen; preterm birth; short cervix.

Tweetable abstract

Cervical length(CL) measured by transvaginal ultrasound(TVU) has good performance to predict spontaneous preterm birth(sPTB) <28 weeks and it should be recommended as a mid-trimester screening test. The number needed to screen to predict one sPTB <34 weeks in women with CL [?]25mm is 121 and 248 screening tests are necessary to prevent one sPTB <34 weeks using vaginal progesterone prophylaxis. We suggest that women with CL[?] 25mm are at risk of sPTB <34 weeks and should receive treatment to prevent sPTB, but also those with CL between 25-30mm are at risk for late sPTB and should receive optimum antenatal care.

Introduction

Prematurity is the leading cause of neonatal morbidity and mortality[1], with severe emotional sequelae and high economic costs. Nowadays, the Preterm Birth (PTB) rate is 10.6% worldwide and 11.2% in Brazil, higher than suggested by the World Health Organization[2,3]. There are 15 million PTBs each year and the burden is directly associated with gestational age at birth.

To prevent PTB bad outcomes, studies have focused on identifiable risk factors such as having a short cervix. Early uterine cervical shortening in the second trimester is an important risk factor for prematurity[4] and is associated with spontaneous preterm birth (sPTB). Thus, cervical length (CL) measurement during the second trimester could be used as a tool to identify women at risk of premature delivery [5].

Transvaginal ultrasound (TVU) performed during the second trimester can evaluate cervical shortening before labor and then a universal screening test has been proposed [6]. Nevertheless, the CL cutoff point related to PTB is still in debate. Most studies consider CL [?]25mm as a risk factor, whereas others consider higher or lower cutoff points[7–9].

Predicting PTB among pregnant women is the key to preventive interventions[10]. Thus, the aim of this study is to identify the association between CL at 18–22(+6) weeks of pregnancy and gestational age at birth in asymptomatic Brazilian women with singleton pregnancy and to assess the performance of TVU as a screening test to predict PTB.

Methods

This is a prospective multicenter cohort study involving singleton pregnant women screened during a multicenter randomized controlled trial entitled "Pessary plus Progesterone for Preventing Preterm Birth" (P5 trial; Registration no. RBR-3t8prz, approved by the Brazilian National Review Board/CONEP - number 1.055.555) [11]. The P5 trial was conducted by the University of Campinas (UNICAMP) and involved 17 centers in nine states of Brazil from July 2015 to March 2019. Women between 18 and 22(+6/7) gestational weeks were invited to participate in the P5 screening phase. A consent form was signed and TVU was performed to measure the CL.

The standard technique followed the P5 study protocol and the Fetal Medicine Foundation orientation for CL measurement. Briefly, with the woman in dorsal lithotomy position and empty bladder, a TVU probe was introduced inside the vagina until the anterior fornix avoiding pressure. A sagittal view of the cervix, including the edge, identified the internal and external ostium. Calipers were used to measure the linear distance (in mm) between the external and internal ostium. Funneling and Sludge were described. All data

from the screening phase were included in the online database Gsdoctor. Every participating center stored their ultrasound images with the CL measurements to confirm that all centers were correctly applying the TVU technique.

All women with a CL [?]30mm who did not have exclusion criteria and who accepted to participate in the trial were randomized into two groups: 200 mg/day vaginal progesterone or 200 mg/day vaginal progesterone + cervical pessary. Randomized women have delivery information in the P5 database. Women with CL >30 mm had their childbirth and postnatal information collected from hospital medical registers and added to the P5 database.

The sample for this analysis considered all women with CL [?]30mm receiving only progesterone and a random selection of women with CL >30mm, keeping the populational distribution of cervical length. Women using cervical pessary were excluded since we did not have clear information of how it could influence the gestational age at birth and this treatment is not routine for preventing PTB. Considering that progesterone is an established evidence-based treatment for preventing PTB and women are encouraged to use it if they have a short CL identified in the mid-trimester, we included the P5 trial progesterone group in our cohort sample. The P5 trial total sample screened 13.7% women with CL[?]30mm and 86.3% of CL>30mm. To maintain the same CL distribution, we projected the progesterone group to correspond to 13.7% of CL [?]30mm for our analysis. To complete our final sample and reach the complementary 86.3% of CL >30mm, we selected singleton women with CL >30 mm using a random model. We excluded women who had received a cervical pessary, multiple gestations and those with incomplete gestational outcome data. We kept very similar baseline characteristics percentages found in the total of singleton pregnant that participated in the P5 trial screening, maintaining homogeneity and avoiding any possible selection bias (Table S1). The primary outcome was PTB at <37 weeks' gestation and secondary outcomes were sPTB at <37, <34, <32 and <28 weeks' gestation.

Descriptive statistical analysis was performed for demographic characteristics, expressed as means and percentages. Logistic regression was used to estimate odds ratios for baseline characteristics, gestational age and CL at measurement. A multivariate logistic regression analysis was performed to estimate adjusted odds ratio for different gestational ages.

For our primary outcome, receiver operating characteristic (ROC) curve analysis was performed to identify the most effective cutoff point to predict a PTB (<37 weeks). Our secondary outcomes were ROC curve analysis to identify the most effective cutoff points to predict sPTB at different gestational ages (<37, <34, <32 and <28 weeks). Kaplan-Meyer survival curves were used to analyze time to delivery, considering CL intervals ([?]10mm, 10-15mm, 15-20mm, 20-25mm, 25-30mm, 30-35mm, 35-40mm and >40mm). We calculated the number needed to screen (NNS) to detect one true positive sPTB<34 in women with CL [?]25mm. Considering a recent IPD-metanalysis that included RCTs involving women with CL [?]25mm treated with vaginal progesterone, the number needed to treat (NNT) with vaginal progesterone to prevent one sPTB <34 weeks is 18[12]. Therefore, we estimated the number of TVU necessary to identify 18 women with CL [?]25mm. $P<0.05$ was considered as statistically significant. All statistical analyses were performed using R version 3.6.2 software.

This study was funded by Bill & Melinda Gates Foundation [OPP1107597], the Brazilian Ministry of Health, and the Brazilian National Council for Scientific and Technological Development (CNPq) [401615/20138]. The funders had no role in the design, development of the study, analysis, interpretation of data, writing the manuscript and in the decision to submit the article for publication.

Results

The P5 trial screened 8168 women, of whom 7857 were singleton and 1081 had CL [?]30mm. In a CL distribution curve including only singleton pregnancies, 1081 women corresponds to 13.7% of total. For this study, we excluded 310 twins, 14 women without CL data and 3 women in progesterone group without gestational age at birth. We included 430 singleton women with CL [?]30 mm randomized to progesterone alone and we projected this group to correspond to 13.7% of CL [?]30mm for our analysis. To complete

our final sample and reach the complementary 86.3% of CL >30mm, we randomly selected 2709 singleton women with CL >30 mm, comprising a total of 3139 women (Figure S1).

Among women with CL [?]30mm receiving progesterone, compliance was 82%. Regarding obstetric history, 46.2% (1449) of our sample were nulliparous, 10.1% (318) had at least one previous PTB and 24.4% had a previous abortion. The prevalence of PTB at <37 weeks was 14.43%: sPTB at <37 weeks was found in 7.1% (223/3139); and sPTB at <37 weeks in women with CL [?]30mm receiving progesterone was 16.7% (72/430). Of all 223 women who had a sPTB, 32.3% (72/223) had a CL [?]30mm. Sociodemographic information is listed in Table 1.

Logistic univariate regression analysis for PTB at <37 weeks identified the following risk factors: low body mass index (BMI [?] 18.5) (OR = 1.95, 95%CI = 1.05–3.43,); hypertension (OR 2.15, 1.5–3.02); endocrinopathies (OR = 1.73, 1.27–2.33); previous PTB (OR = 2.51, 1.88–3.32); previous abortion (OR = 1.43, 1.15–1.78); cervical length [?]30mm (CL 25-[?] 30mm OR 2.10, 1.47 - 2.95; CL 20-25mm OR 2.55, 1.71 - 3.72; CL 15-20mm OR 3.33, 1.74 - 6.11; CL 10-15 mm OR = 6.40, 2.53–5.99, and CL [?]10mm OR 11.17, 4.37–30.55); funneling at measurement (OR = 5.03, 3.36–7.49); and sludge at measurement (OR = 3.50, 2.24–5.39). Considering only sPTB at <37 weeks, these factors presented an even higher association except for comorbidities and low BMI. A comparison between sPTB at < 34 weeks and [?] 34 weeks illustrates that there is a robust association among risk factors and sPTB<34 weeks, highlighting CL[?]10mm (OR 44.9, 15.45–125.87) and 10–15mm (OR13.32, 2.98–43.09), funneling at measurement (OR 10.22, 5.57–17.95) and sludge at measurement (OR = 5.61, 2.63–10.86) (Table 2).

A multivariate logistic regression analysis also identified an association between CL [?]30mm and PTB (CL 25-[?]30mm ORa 1.80, 1.23-2.63; CL 20-25mm ORa 1.93, 1.22-3.06; CL 10-20mm ORa 3.04, 1.54-5.71, and CL [?]10mm ORa 3.82, 1.12-13.06). The ORa for cervical length <30mm increased when considered only sPTB <37 (CL 25-[?]30mm ORa 2.2, 1.35-3.57; CL 20-25mm ORa 2.07, 1.14-3.76; CL 10-20mm ORa 4.59, 2.12-9.94, and CL[?]10mm ORa 6.71, 1.79-25.27). For sPTB<34, there was an association with CL [?]25 mm (Table S2). We also performed a multivariate analysis for cervical length and PTB <37, sPTB <37 and sPTB<34 weeks with adjusted odds ratios for BMI, comorbidities, obstetrical history, funneling and sludge and the association between CL<30mm and PTB and sPTB<37 was also significant. Again, moderate sPTB (sPTB<34) where associated with CL [?]25mm (Table S3).

We identified an inverse association between CL and sPTB at <37 weeks (OR = 7.84, 5.5–11.1). The ROC curve analysis to predict PTB at < 37 weeks and sPTB at <37 weeks showed low performance, with area under the curve (AUC) of 0.598 (0.57–0.63) and 0.643 (0.60–0.68), respectively. For sPTB at <34 weeks and sPTB at <32 weeks the ROC curve presented a moderate performance with AUC of 0.665 (0.59–0.74) and 0.718 (0.62–0.81), respectively; and for sPTB at <28 weeks the ROC curve demonstrated good performance, with AUC of 0.820 (0.63–0.95) (Table S4 and Figure 1).

The best cutoff point to predict PTB at <37 weeks was 31.75 mm, with 31.3% sensitivity and 84.4% specificity. To predict sPTB at <37 weeks the best cutoff point was 31.75mm, with 37.2% sensitivity and 84.3% specificity. TVU provided good prognostic results combining: AUC (0.82), high sensitivity (73.7%) and acceptable specificity (91.3%) rates for sPTB at <28 weeks' gestation (Table S4). The best cutoff points to predict sPTB at <34, <32 and <28 weeks were 28.05, 28.05 and 26.55 mm, respectively.

Kaplan-Meyer survival analysis demonstrated an association between extremely severe, severe, moderate and late PTB and CL [?]25 mm, and an association between CL of 25–30mm and late PTB (p<0.001) (Figure 2). The number needed to screen (NNS) to detect one true positive sPTB <34 weeks in women with CL [?]25mm is 121. To prevent one sPTB <34 weeks among women with CL [?]25mm, the number needed to treat (NNT) with vaginal progesterone prophylaxis is 18^{12}. Assuming that all women with CL [?]25mm are treated with vaginal progesterone, we estimated that the number of TVU necessary to identify 18 women with CL [?]25mm and prevent one sPTB <34 weeks is 248.

Discussion

Main Findings

Our study identified a negative association between CL measured during the second trimester of pregnancy and the rate of sPTB. CL [?]31.7mm is an important risk factor for PTB at [?]37 weeks and CL [?]25mm is associated with extremely severe, severe, moderate and late PTB whereas CL of 25–30mm is associated with late PTB. This study also confirms previous observational studies that found low BMI, previous abortion, previous PTB, CL [?]30mm, funneling and sludge as predictors for PTB[13–15].

The most relevant risk factor for PTB in a singleton pregnancy is a previous history of PTB; however, in nulliparous women this does not apply. We had almost half of the sPTB in nulliparous women and TVU is an important mean to identify nulliparous women at risk of PTB. In those women, except for BMI, the other important risk factors are directly connected to the second trimester TVU results. Thus, considering the higher incidence of sPTB in Brazil and globally [16], TVU is an important tool to routinely identify these women.

As a screening test for PTB, TVU did not present good performance to predict PTB at <37 weeks. This result agrees with previous studies that did not find high sensitivity or acceptable specificity to consider TVU as a screening test to predict late PTB[17,18]. Nevertheless, we can consider that TVU has a moderate prognostic performance to predict sPTB at <34 weeks and, moreover, has a good performance for predicting sPTB at <28 weeks, with a high sensitivity and acceptable specificity. The extremely severe and severe PTB correspond to only 5% of all premature deliveries but are responsible for most deaths associated with PTB [3].

There is an inverse correlation between long-term morbidity and adverse neurodevelopmental outcomes with gestational age at birth, which incurs higher medical costs and extrapolates this health problem to the economic sphere, generating a huge financial impact on the health system. The suggested NNS to identify a woman under real risk for an early preterm birth is very acceptable for a screening test. Thus, offering TVU as a screening test for women at risk of moderate and extreme sPTB would increase the reaching of optimal timing for antenatal corticosteroid administration [19] and allow preventive treatments for reducing sPTB as progesterone, cervical pessary or cerclage[8,20].

Interpretation

Recently, a multicenter Swedish cohort study involving 11,465 asymptomatic singleton pregnant women found that TVU ability to predict sPTB at <37 weeks was poor: AUC of 0.63 (0.59–0.67) for measurement at 21–23 (+6) weeks with best cutoff point 35mm; and the number needed to screen (NNS) to detect one true positive test result for sPTB at <34 weeks considering CL [?]25mm was 524. TVU demonstrated good performance (AUC >0.75) for predicting sPTB at <31 weeks' gestation [21]. Despite the considerable differences between our population and theirs, including the fact that our patients used progesterone if CL [?]30mm and the difference between sPTB rates (7.1% our study versus 3.6% Swedish study), both studies illustrate that 25 mm does not seem to be the best cutoff point to identify women at PTB risk; moreover, TVU has moderate or good accuracy when different gestational ages are considered in both analyses. In addition, our NNS to identify one true positive sPTB<34 weeks when patients with CL [?]25mm is considerably lower than previous studies that considered populations with lower PTB rate [21,22], what is an alert to correctly define the applicability and cost-utility of TVU-CL measurement as a screening test for PTB in different countries.

Strengths and Limitations

The main strength of this study is that we have a considerably large sample of Brazilian women from 17 centers in three regions, thus covering possible internal population differences. In Brazil, previous TVU performance analyses to predict PTB were from single-center studies[18,23] with smaller samples. All cervical measurements were performed by expert medical sonographers in tertiary reference centers, along with checking of the ultrasound images to correct and reinforce the pattern technique. We analyzed TVU using different accuracy tests, different cutoff points and specific PTB subgroups for gestational age.

The vaginal progesterone used for women with CL [?]30mm is a limitation in our study because progesterone

reduces the occurrence of PTB. Nevertheless, in our prenatal clinical assistance, women with CL [?]25mm are encouraged to use progesterone, so maintaining this intervention in our sample allows the possibility to pragmatically infer the results to medical practice. Unfortunately, we cannot identify if progesterone has caused any reduction in PTB between women with CL 25-[?]30mm, which could have underestimated PTB incidence in this subgroup. Another limitation is that some participating centers did not perform universal TVU screening, which could introduce some selection bias in our sample and the tendency to have a shorter CL. However, the mean CL identified was very similar to other previous Brazilian studies[16,24,25].

Conclusion

Women with CL[?]25mm had a significant association with sPTB <34 weeks, which is an important clinical goal for preterm birth. Additionally, we found that the best cutoff points for all gestational ages outcomes (<37, <34, <32 and <28 weeks) are over 25mm. Considering the feasibility to perform CL measurement following a standard technique and the capability to detect almost one third of all sPTB <37 weeks, we suggest to use CL [?]30mm as the cutoff for cervical length to identify women at risk of sPTB. This is easier to remember and is very similar to the best cutoff point identified in our study. Thus, women with CL[?]30mm should be recognized as at higher risk for PTB and those with CL[?]25mm should be recognized and treated properly to reduce PTB<34 weeks.

It is important to highlight that although women with CL[?]30mm are at higher risk for PTB, effective treatment for preventing PTB in women with 25–30mm CL are not available [26]. These women should not be treated with progesterone, cervical pessaries, or cerclage because these treatments did not show clear benefits in reducing sPTB but should, however, receive a close antenatal care follow-up.

Considering the cutoff point where vaginal progesterone has demonstrated efficacy (25mm), the NNS of 248 to detect 18 women with CL [?]25mm is an acceptable number, which suggests the feasibility of implementing TVU for pregnant women in mid-trimester in settings like Brazil.

As most PTBs worldwide are concentrated in low- and middle-income countries, this analysis is important to describe specific results for our population and stimulate new studies in other similar settings focused on strategies to reduce PTB. In such countries, where economical resources are considerably limited, it is important to define with precision the best strategies to reduce costs while improving health care. Nowadays, the national antenatal care for Brazil has not adopted routine TVU at mid-trimester screening based on studies developed in high-income countries with lower rates of sPTB. The NNS estimated in our study creates an opportunity to review the Brazilian and other countries' protocols to deal with the PTB prevention. The estimated NNS is considered low and acceptable and should underpin the implementation of the TVU as a mid-trimester screening test.

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Disclosure of interests

The authors report no conflict of interest.

Contribution to authorship

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ABC: Data curation, Funding acquisition, Investigation, Writing - review & editing

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Ethics approval

This study was approved by the Brazilian National Review Board/CONEP - number 1.055.555

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Tables

Table1- Sociodemographic and baseline characteristics x gestational age at birth

Characteristics		Overall PTB<37 (n=453)		Overall [?]37w (n=2686)			Spontaneous (sPTB) <37 (n=223)		Spontaneous (sPTB) <37 (n=223)	Spontaneous [?]37w (n=2686)			Spontaneous (sPTB) <34 (n=78)		Spontaneous (sPTB)
		n or Mean	% or ±SD	n or Mean	% or ±SD		n or Mean	% or ±SD	n or Mean	n or Mean	% or ±SD		n or Mean	% or ±SD	n or M
Maternal age at measurement (years)	Maternal age at measurement (years)	28.7	±7	27.8	±7		27.4	±6.9	27.8	27.8	±7		27.1	±7.2	27
	[?]19	56	12.4	405	15.1		36	16.2	405	405	15.1		15	19.2	43
	20-[?]34	307	67.9	1794	67.1	1.24 (0.92 - 1.69)	152	68.5	1794	1794	67.1	0.95 (0.66 - 1.41)	49	62.8	20
	>35	89	19.7	476	17.8	1.35 (0.95 - 1.95)	34	15.3	476	476	17.8	0.80 (0.49 - 1.31)	14	17.9	52
Body-mass index (kg/m^2)	Body-mass index (kg/m^2)														
	[?]18.5	16	3.5	52	1.9	1.95 (1.05 - 3.43)	10	4.5	52	52	1.9	2.07 (0.96 - 4.06)	6	7.7	62
	18.5-25	148	32.7	937	34.9		87	39.0	937	937	34.9		33	42.3	10
	25-30	157	34.7	913	34.0	1.09 (0.85 - 1.39)	72	32.3	913	913	34.0	0.85 (0.61 - 1.17)	23	29.5	10

Characteristics	Characteristics	Overall PTB<37 (n=453)	Overall PTB<37 (n=453)	[?]37w (n=2686)	[?]37w (n=2686)	OR (95%CI)	Spontaneous (sPTB)<37 (n=223)	Spontaneous (sPTB)<37 (n=223)	Spontaneous (sPTB)<37 (n=223)	[?]37w (n=2686)	[?]37w (n=2686)	OR (95%CI)	Spontaneous (sPTB)<34 (n=78)	Spontaneous (sPTB)<34 (n=78)	[?] (n
	>30	132	29.1	784	29.2	1.07 (0.83 - 1.37)	54	24.2	784	784	29.2	0.74 (0.52 - 1.05)	16	20.5	86
Ethnic origin (self-reported)	Ethnic origin (self-reported)														
	Non-white	289	63.8	1680	62.5		143	64.1	1680	1680	62.5		46	59.0	18
	White	164	36.2	1006	37.5	0.95 (0.77 - 1.16)	80	35.9	1006	1006	37.5	0.93 (0.70 - 1.24)	32	41.0	11
Schooling	Schooling														
	Preschool/Elementary	116	25.8	711	26.6		55	24.9	711	711	26.6		18	23.1	78
	Middle School	275	61.2	1666	62.3	1.01 (0.80 - 1.28)	140	63.3	1666	1666	62.3	1.09 (0.79 - 1.51)	50	64.1	18
	High School and Higher Education	58	12.9	298	11.1	1.19 (0.84 - 1.67)	26	11.8	298	298	11.1	1.13 (0.68 - 1.81)	10	12.8	33
Comorbidities	Comorbidities														
	No comorbidities	285	62.9	1992	74.2		163	73.1	1992	1992	74.2		50	64.1	21
	Hypertension	47	10.4	153	5.7	2.15 (1.50 - 3.02)	8	3.6	153	153	5.7	0.64 (0.28 - 1.24)	3	3.8	18
	Endocrinopathies*	63	13.9	254	9.5	1.73 (1.27 - 2.33)	28	12.6	254	254	9.5	1.35 (0.87 - 2.02)	12	15.4	29
	Cardiovascular disease	2	0.4	18	0.7	0.78 (0.12 - 2.71)	1	0.45	18	18	0.7	0.68 (0.04 - 3.32)	0	0.0	20
	Others**	56	12.4	269	10.0	1.46 (1.06 - 1.98)	23	10.3	269	269	10.0	1.04 (0.65 - 1.61)	13	16.7	30

Characteristics		Overall PTB<37 (n=453)	Overall PTB<37 (%)	[?]37w (n=2686)	[?]37w (%)	OR (95%CI)	Spontaneous (sPTB)<37 (n=223)	Spontaneous (sPTB)<37 (%)	Spontaneous (sPTB)<37 (n=223)	[?]37w (n=2686)	[?]37w (%)	OR (95%CI)	Spontaneous (sPTB)<34 (n=78)	Spontaneous (sPTB)<34 (%)	Spontane (sPTB) [?] (n
Previous Conization (yes)	Previous Conization (yes)	9	1.9	36	1.3	1.33 (0.57 - 2.73)	3	1.3	36	36	1.3	1.00 (0.24 - 2.81)	2	2.6	41
Uterine Anomaly (yes)	Uterine Anomaly (yes)	9	1.9	36	1.3	1.50 (0.67 - 2.99)	3	1.3	36	36	1.3	1.00 (0.24 - 2.81)	1	1.3	38
Obstetrical history	Obstetrical history														
	Nulliparous	205	45.4	1244	46.3		109	48.9	1244	1244	46.3		44	56.4	13
	Parous with no previous PTB	154	34.1	1217	45.3	0.77 (0.61 - 0.96)	69	30.9	1217	1217	45.3	0.65 (0.47 - 0.88)	17	21.8	13
	Parous with at least one previous PTB	93	20.6	225	8.4	2.51 (1.88 - 3.32)	45	20.2	225	225	8.4	2.28 (1.56 - 3.30)	17	21.8	28
	Previous abortion (yes)	138	30.5	629	23.4	1.43 (1.15 - 1.78)	69	30.9	629	629	23.4	1.47 (1.08 - 1.97)	27	34.6	70

Data are number (%) or mean (±SD). OR values in bold mean that they are significant at a *P*- value <0.05. BMI was calculated at CL measurement.

* Diabetes Mellitus, gestational diabetes, thyroidopathy. **Asthma, autoimmune diseases, anemia, obesity, hepatitis

Table 2 – Cervical length measurement and gestational age at birth

		Overall PTB<37	Overall PTB<37
		n or Mean	% or ±SD
GA at measurement (days)	**GA at measurement (days)**	145.9	±8.8
CL at measurement (mm)	**CL at measurement (mm)**		
	[?]10mm	11	2.4
	10 - [?]15mm	9	1.9
	15 - [?]20mm	15	3.3

		Overall PTB<37	Overall PTB<37
	20 - [?]25mm	38	8.4
	25 - [?]30mm	46	10.2
	> 30mm	334	73.7
Funneling at measurement (yes)	**Funneling at measurement (yes)**	46	10.2
Sludge at measurement (yes)	**Sludge at measurement (yes)**	33	7.3

Data are number (%) or mean (±SD). OR values in bold mean that they are significant at a *P*- value <0.05.

GA = gestational age. CL = cervical length

Table legends

Table1- Sociodemographic and baseline characteristics x gestational age at birth

Table 2 – Cervical length measurement and gestational age at birth

Figure legends

Figure 1 – ROC curve analysis of PTB and sPTB at different gestational ages

Figure 2 – Kaplan-Meyer survival analysis for PTB considering different ranges of CL

Supporting information

Table S1 – Comparison of socio-demographics and obstetrics characteristics between the cohort and P5 trial screening phase (only singleton pregnancies)

Table S2 - Multivariate logistic regression analysis for total and sPTB at different gestational ages

Table S3 – Cervical length x PTB with adjusted OR for BMI, comorbidities, obstetrical history, funneling and sludge (tables S3.1, S3.2 and S3.3)

Table S4 – TVU measurement of CL performance for predicting preterm birth

Figure S1 – Patient enrolment flowchart

Figure S2– Kaplan-Meyer survival analysis for sPTB considering different ranges of CL

Supplementary information

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