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Serial cervical-length measurements after first episode of threatened preterm labor improve prediction of spontaneous delivery prior to 37 weeks' gestation

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KEYWORDS: cervical length; spontaneous preterm birth; threatened preterm labor

CONTRIBUTION

What are the novel findings of this work?

Women undelivered after their first episode of threatened preterm labor are at high risk of spontaneous delivery < 37 weeks' gestation if their cervical length, measured using transvaginal ultrasound, is below 10 mm at the time of hospital discharge or in the following 4 weeks.

What are the clinical implications of this work?

Transvaginal cervical-length assessment could be included in the antenatal care of women discharged from hospital after their first episode of threatened preterm labor in order to stratify their risk of preterm birth, rationalize resource utilization and improve pregnancy outcome.

ABSTRACT

Objective To assess whether repeat cervical-length (CL) measurement in women discharged from hospital after their first episode of threatened preterm labor can predict their risk of spontaneous preterm birth.

Methods This was a secondary analysis of a randomized controlled trial of maintenance tocolysis, in which CL was measured on transvaginal ultrasound at the time of hospital discharge and after 2, 4, 8 and 12 weeks, in women who remained undelivered after their first episode of threatened preterm labor. After univariate analysis,

multivariate logistic regression analysis was used to assess whether CL < 10 mm at the time of hospital discharge or at any follow-up evaluation could predict spontaneous delivery prior to 37 weeks of gestation.

Results Of 226 women discharged after a diagnosis of threatened preterm labor, 57 (25.2%) delivered spontaneously prior to 37 weeks' gestation. The risk of spontaneous preterm birth was higher among women with CL < 10 mm at hospital discharge compared to those with CL ≥ 10 mm (adjusted odds ratio (aOR), 3.3; 95% CI, 1.2–9.2). Moreover, spontaneous preterm delivery was more common when CL < 10 mm was detected up to 2 weeks (aOR, 2.9; 95% CI, 1.1–7.3) or up to 4 weeks (aOR, 7.3; 95% CI, 2.3–22.8) post discharge, as compared with when CL was persistently ≥ 10 mm. The association was not significant when considering CL measurements at 8 weeks, and there was insufficient information to assess the effect of measurements obtained at 12 weeks.

Conclusions Women who remain undelivered after their first episode of threatened preterm labor continue to be at high risk of spontaneous preterm birth if their CL is below 10 mm at the time of hospital discharge or at any follow-up visit up to 4 weeks later. CL measurement could be included in the antenatal care of these women in order to stratify their risk of preterm birth, rationalize resource utilization and help clinicians improve pregnancy outcome. © 2020 International Society of Ultrasound in Obstetrics and Gynecology.

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INTRODUCTION

Spontaneous preterm birth occurs in 8–12% of all pregnancies in developed countries¹, accounting for 80% of cases of perinatal morbidity and 50% of childhood neurodevelopmental disorders². Although approximately 75% of women presenting with threatened preterm labor remain undelivered after a 48-h course of tocolytics, their risk of preterm delivery remains high, with approximately 30% delivering before 37 weeks' gestation³. Cervical length (CL) measured by transvaginal sonography has been shown to be an accurate predictor of spontaneous preterm birth among women presenting with painful uterine contractions^{4,5}. However, studies have focused mainly on the role of a single CL measurement recorded at the time of the initial evaluation for threatened preterm labor. As the potential advantages of repeat CL assessments in identifying women at risk of spontaneous preterm birth remain speculative, we aimed to evaluate whether serial CL measurements, obtained at hospital discharge and during follow-up, can predict spontaneous preterm birth among women who did not deliver after their first episode of threatened preterm labor.

METHODS

This was a secondary analysis of a multicenter randomized controlled trial on the efficacy of progestogens for maintenance tocolysis in reducing the rate of preterm birth among women who did not deliver after their first episode of threatened preterm labor. Detailed methodology for the trial is reported elsewhere⁶. Briefly, singleton pregnancies hospitalized at 22 + 0 to 31 + 6 weeks' gestation with painful contractions (≥ 6 in 30 min) and cervical changes (i.e. shortening, softening or dilation on manual examination), who did not experience preterm delivery prior to hospital discharge, were approached to participate in the trial if their transvaginal CL measurement at discharge was ≤ 25 mm. Women who consented to participate were assigned randomly to receive either a weekly 341 mg intramuscular injection of 17-alpha-hydroxyprogesterone caproate, a daily 200 mg dose of vaginal micronized progesterone or no treatment until 36 weeks or delivery. Exclusion criteria were previous spontaneous preterm delivery (at 20 + 0 to 36 + 6 weeks' gestation), multiple pregnancy, preterm prelabor rupture of membranes (PPROM) at presentation, fetal or maternal indication for preterm delivery, Müllerian malformation, prior cervical surgery, cerclage placement in a prior or in the current pregnancy and persistence of regular contractions at the time of hospital discharge. Tocolysis and antenatal corticosteroids were administered according to the patient's gestational age and national guidelines⁷. CL was measured at the time of discharge with a 7–9-MHz transvaginal probe by trained obstetricians–gynecologists following the same standardized approach⁸. The original study protocol was approved by the institutional review board of the five tertiary care university hospitals at which enrolment took

place. The current secondary analysis was considered exempt from institutional review board approval.

According to the study protocol, follow-up appointments were scheduled at 2, 4, 8 and 12 weeks after hospital discharge, to inquire about side effects from the study medications, hospital admissions that might have followed the initial hospitalization and changes in the patient's medical history. At each visit, the obstetrician–gynecologist performed transvaginal CL measurement. If the patient had delivered since the previous clinical encounter, the obstetrician–gynecologist collected delivery data. Patients who remained undelivered at the last scheduled follow-up visit were contacted approximately 2 weeks after their due date, to acquire delivery data.

Our primary objective was to investigate whether information on CL measured at the time of hospital discharge and at subsequent follow-up appointments is useful to predict delivery, before 37 + 0 weeks' gestation, due to spontaneous onset of labor or PPRM. We chose to categorize CL measurements as $<$ or ≥ 10 mm for the following reasons. First, although midpregnancy CL length ≤ 25 mm has a strong association with preterm delivery among asymptomatic patients⁹, sensitivity in predicting birth before 37 weeks' gestation among women presenting with uterine contractions is only 70%, with a high false-positive rate of 30%⁴. As fewer than 10% of women with a clinical diagnosis of preterm labor actually give birth within 7 days of presentation¹⁰, we used a lower CL cut off to increase specificity. Second, despite contrasting opinions, midgestation CL < 10 mm has been used by some researchers to identify a population at even higher risk of preterm labor, that may benefit from cerclage placement, rather than vaginal progesterone supplementation^{11,12}.

Using a transvaginal CL threshold of 10 mm, we estimated the risk of preterm delivery at hospital discharge and at scheduled follow-up appointments; each risk assessment was based on CL measurements from hospital discharge up to that time. At hospital discharge, patients were classified as being at low-risk of preterm delivery if their CL measured ≥ 10 mm, while high-risk subjects had CL < 10 mm. The risk of preterm birth was then assessed in all women who remained undelivered 2 weeks later (first follow-up visit); pregnancies with CL measurement ≥ 10 mm both at the 2-week follow-up and at the time of hospital discharge were considered low-risk, while those with CL < 10 mm on at least one of the two assessments were classified as high risk. If delivery had not occurred after 4 weeks (second follow-up visit), pregnancies that had CL measurement ≥ 10 mm at hospital discharge, as well as at the following two visits, were classified as low-risk, while high-risk women had CL < 10 mm on at least one of the three assessments. Risk was assessed in a similar fashion in women who were still pregnant at 8 and 12 weeks after hospital discharge (third and fourth follow-up visits, respectively). In cases of missing CL data at follow-up visits, the most recent observation was used.

Descriptive statistics were used to characterize the sociodemographic and obstetric characteristics of women who delivered before, compared with at or after, 37 weeks' gestation. Categorical variables were presented as absolute frequency and percentage and were tested using chi-square test or Fisher's exact test, as appropriate. Continuous variables were summarized as mean \pm SD and were compared using Student's *t*-test. The level of statistical significance was set at $P \leq 0.05$.

To control for confounding, multivariate logistic regression models were built to describe the association between spontaneous delivery < 37 weeks' gestation and CL < 10 mm at hospital discharge or during follow-up. Sociodemographic variables, such as maternal age, body mass index at entry to care, ethnicity (Caucasian *vs* non-Caucasian), smoking (non-smoking or smoking stopped prior to conception *vs* smoking during pregnancy) and time in education (≤ 8 *vs* > 8 years) were considered as potential confounders, as they are known risk factors for spontaneous preterm birth. Similarly, obstetric features, such as parity (nulliparous *vs* parous), tocolysis at initial hospitalization or at any subsequent hospital admission, urine culture collected at initial hospitalization and gestational age at enrolment (≤ 28 *vs* > 28 weeks' gestation) were also taken into account. The area under the receiver-operating-characteristics curve was used to measure discrimination and calibration of the models. The Kaplan–Meier estimator was used with log rank test to compare how gestational age at delivery varied according to CL risk category (high *vs* low risk).

RESULTS

In this analysis, we included 226 of the 235 women with threatened preterm labor and CL ≤ 25 mm who participated in the original trial; we excluded two participants with medically indicated preterm delivery (due to cholestasis and pre-eclampsia) and seven with incomplete information on CL at enrolment (the exact measurements were unavailable, with records indicating only whether CL was $<$ or ≥ 15 mm). Spontaneous preterm birth affected 1 in 4 (57/226) patients in our study population.

The baseline sociodemographic and obstetric characteristics of the women who delivered prior to 37 weeks' gestation due to spontaneous onset of labor or PPRM were similar to those of women who delivered at or after 37 weeks (Table 1). Gestational age at hospital discharge and at all follow-up visits was similar between the two groups. Women who delivered preterm had significantly shorter CL measurements from hospital discharge to the third follow-up visit ($P < 0.01$ for all), were more likely to develop PROM ($P < 0.01$) and more frequently received tocolysis and had a positive urine culture at initial hospitalization ($P = 0.02$ for both). Vaginal progesterone was more commonly administered in those who delivered prematurely ($P = 0.03$). Approximately one in five deliveries ≥ 37 weeks' gestation was indicated medically,

while indicated preterm deliveries were excluded from the study population.

Figure 1 shows the cohort of patients followed after hospital discharge, according to their risk of preterm delivery based on serial CL measurements. In our population, CL < 10 mm at the time of hospital discharge had specificity of 88% and sensitivity of 28% in the prediction of spontaneous birth before 37 weeks' gestation.

Table 2 summarizes the multivariate logistic regression models investigating, at each assessment, the association between the risk of spontaneous preterm delivery and categorization as high risk based on at least one CL measurement < 10 mm. At hospital discharge and at the first and second follow-up visits, pregnancies with at least one CL measurement < 10 mm had a statistically significant 2.9–7.3-fold higher odds of spontaneous preterm delivery, when compared to women whose CL was persistently ≥ 10 mm. The association between spontaneous preterm delivery and at least one CL measurement < 10 mm was also confirmed by Kaplan–Meier analysis (Figure 2). Positive urine culture at initial hospitalization, smoking and treatment with vaginal progesterone were also associated independently with spontaneous preterm delivery (Table 2). Although the same trends were confirmed, statistical significance was not reached when analyzing women still pregnant at the third follow-up visit, while insufficient information was available to build a model that could summarize the effects of CL measurements obtained from hospital discharge to the fourth follow-up visit.

Although CL values measured at the time of discharge were available for all 226 patients, values were missing for 27/214 (12.6%), 13/148 (8.8%) and 2/64 (3.1%) cases at the first, second and third follow-up visits, respectively. The most recent observation was used to deal with missing CL measurements; however, similar results were obtained when missing values were replaced by the subsequently recorded observation or by the mean value of the previous and the following measurements. The results were also similar when the analysis was conducted using only available measurements, omitting cases with missing CL data.

The association between CL and spontaneous preterm delivery was confirmed when the analysis was restricted to women experiencing spontaneous labor or PROM (i.e. excluding those with medically indicated delivery).

DISCUSSION

Measurement of CL in women presenting with painful uterine contractions prior to 34 weeks' gestation has been shown to predict the majority of those who deliver within 1 week⁴ or 2 weeks¹³. Amongst symptomatic patients, CL measurement at the time of initial presentation may be helpful in terms of short-term management but, if the pregnancy continues, further CL evaluations could be useful to determine whether the patient remains at risk

Table 1 Baseline characteristics of study population of 226 women who remained undelivered after first episode of threatened preterm labor (PTL), according to delivery ≥ 37 weeks or delivery < 37 weeks due to spontaneous onset of labor or preterm prelabor rupture of membranes

Characteristic	Spontaneous delivery < 37 weeks (n = 57)		Delivery ≥ 37 weeks (n = 169)		P
	N	Value	N	Value	
Maternal age (years)	56	32.6 \pm 6.6	169	31.8 \pm 5.7	0.3*
BMI at booking (kg/m ²)	56	22.9 \pm 4.8	165	22.7 \pm 4.5	0.7*
Non-Caucasian	56	10 (17.9)	169	28 (16.6)	0.8†
Education ≤ 8 years	55	17 (30.9)	162	41 (25.3)	0.4†
Smoking during pregnancy	56	6 (10.7)	168	8 (4.8)	0.1†
Nulliparous	54	34 (63.0)	167	102 (61.1)	0.8†
Gestational age (weeks) at:					
Hospital discharge	57	28.9 \pm 2.4	169	28.6 \pm 2.3	0.5*
First follow-up visit	57	30.7 \pm 2.6	163	30.9 \pm 2.6	0.5*
Second follow-up visit	57	32.5 \pm 2.8	118	33.4 \pm 2.8	0.1*
Third follow-up visit	57	32.1 \pm 1.7	38	32.7 \pm 2.2	0.5*
Fourth follow-up visit	1	32.8	3	36.3 \pm 0.3	—
Delivery	57	34.1 \pm 2.4	169	39.2 \pm 1.2	$< 0.01^*$
Cervical length (mm) at:					
Hospital discharge	57	16.3 \pm 5.8	169	18.2 \pm 5.0	$< 0.01^*$
First follow-up visit	51	15.4 \pm 6.0	163	17.5 \pm 5.2	$< 0.01^*$
Second follow-up visit	27	13.7 \pm 6.8	121	16.7 \pm 5.4	$< 0.01^*$
Third follow-up visit	7	14.5 \pm 7.7	56	17.2 \pm 5.5	$< 0.01^*$
Fourth follow-up visit	1	23.0	12	17.2 \pm 5.3	—
Tocolysis at initial hospitalization	56	31 (55.4)	169	64 (37.9)	0.02†
Positive urine culture at initial hospitalization	52	13 (25.0)	158	19 (12.0)	0.02†
Subsequent admissions due to threatened PTL requiring tocolysis					0.1‡
1	57	8 (14.0)	169	11 (6.5)	
2	57	1 (1.8)	169	1 (0.6)	
Prelabor rupture of membranes	57	39 (68.4)	168	35 (20.8)	$< 0.01^{\dagger}$
Courses of antenatal corticosteroids					0.5†
0	57	7 (12.3)	169	32 (18.9)	
1	57	44 (77.2)	169	119 (70.4)	
2	57	6 (10.5)	169	18 (10.7)	
Type of labor					0.3‡
Spontaneous	57	48 (84.2)	169	124 (73.4)	
Induced	57	6 (10.5)	169	30 (17.8)	
No labor	57	3 (5.3)	169	15 (8.9)	
Mode of delivery					0.1‡
Vaginal delivery	57	38 (66.7)	169	123 (72.8)	
Operative vaginal delivery	57	3 (5.2)	169	17 (10.1)	
Cesarean delivery	57	16 (28.1)	169	29 (17.2)	
Medically indicated delivery	57	—	169	35 (20.7)	—
Treatment arm					0.03†
Control	57	15 (26.3)	169	60 (35.5)	
17-alpha-hydroxyprogesterone caproate	57	15 (26.3)	169	62 (36.7)	
Vaginal micronized progesterone	57	27 (47.4)	169	47 (27.8)	

Data are given as mean \pm SD, n (%) or mean. *Student's *t*-test. †Chi-square test. ‡Fisher's exact test. BMI, body mass index.

of spontaneous preterm birth. Pregnant women who have had an episode of threatened preterm labor comprise a subgroup at high risk for spontaneous preterm birth, as 45% of them are readmitted with a subsequent episode of threatened preterm labor, and 25–30% deliver preterm³. Identification of this subgroup of patients is pivotal in order to optimize their pregnancy outcome and rationalize their management. Therefore, we sought to determine if serial CL evaluations in women who remain undelivered after their first episode of threatened preterm labor can help identify those who will deliver prior to 37 weeks' gestation.

Our findings demonstrate that, when CL is below 10 mm on at least one occasion up to 4 weeks after cessation of regular uterine contractions, the odds of spontaneous preterm birth are 3–7-fold higher than when CL is persistently at or above 10 mm.

Serial transvaginal CL measurements have been studied among asymptomatic women¹⁴, while only CL changes from the time of initial presentation have been investigated in symptomatic women. To the best of our knowledge, this is the first attempt to investigate the predictive role of serial CL evaluations after the first episode of threatened preterm labor. Wagner *et al.*¹⁵ conducted a retrospective

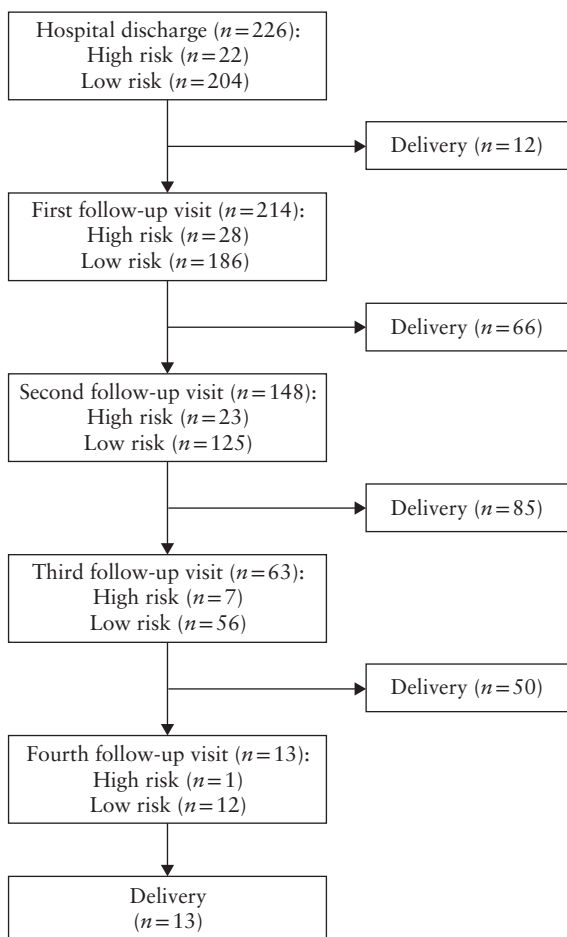


Figure 1 Flowchart summarizing assessments of risk for delivery < 37 weeks based on serial cervical-length measurements, at discharge and during follow-up, in women who remained undelivered after hospitalization for threatened preterm labor. Women were classified, at each evaluation, as high risk if at least one serial cervical-length measurement was < 10 mm and as low risk if cervical length was ≥ 10 mm at all assessments.

study in 310 singleton pregnancies presenting with preterm contractions at 24 + 0 to 33 + 6 weeks of gestation; CL was measured at the time of presentation and on average 3.6 days later. Combination of the first or second CL measurement with the difference between the two was better than a single assessment alone in predicting delivery within 14 days. Sotiriadis *et al.*¹⁶ examined 122 women with preterm contractions and measured the cervix at presentation and after 24 h. They found similarly that the positive predictive value of the first CL assessment for delivery within 7 days increased with the addition of the difference between the two measurements. Conversely, Rozenberg *et al.*¹⁷ examined 109 patients with threatened preterm labor at presentation and 48 h

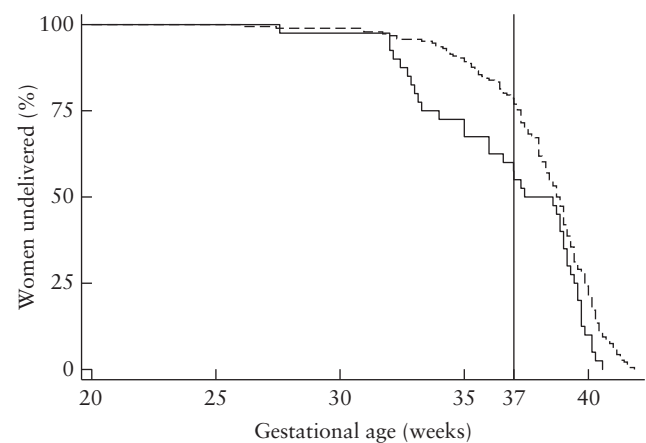


Figure 2 Kaplan-Meier plot showing proportion of women who remained undelivered after first episode of threatened preterm labor, according to categorization as high (—) or low (---) risk based on serial cervical-length measurements. Women were classified, at each evaluation, as high risk if at least one serial cervical-length measurement was < 10 mm and as low risk if cervical length was ≥ 10 mm at all assessments. Log-rank test, $P = 0.01$.

Table 2 Multivariate logistic regression analysis of risk of delivery < 37 weeks due to spontaneous preterm labor or preterm prelabor rupture of membranes, at different timepoints following first episode of threatened preterm labor

Prognostic factor	Hospital discharge		First follow-up visit		Second follow-up visit		Third follow-up visit	
	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
CL-based risk*								
Low risk†	—		—		—		—	
High risk	3.3 (1.2–9.2)	0.02	2.9 (1.1–7.3)	0.02	7.3 (2.3–22.8)	< 0.01	3.2 (0.3–38.0)	0.4
Urine culture at hospitalization								
Negative†	—		—		—		—	
Positive	3.0 (1.3–7.0)	0.01	3.1 (1.2–7.6)	0.01	3.9 (1.2–12.6)	0.02	5.7 (0.6–50.0)	0.1
Smoking during pregnancy								
No†	—		—		—		—	
Yes	3.6 (1.1–12.0)	0.03	3.9 (1.2–13.0)	0.02	5.5 (1.0–30.6)	0.049	3.7 (0.3–51.0)	0.3
Treatment arm								
Control†	—		—		—		—	
17-P	0.9 (0.3–2.1)	0.7	1.2 (0.5–3.1)	0.6	1.4 (0.3–5.3)	0.6	0.5 (0.3–6.0)	0.5
Vaginal micronized progesterone	2.7 (1.2–6.1)	0.01	2.9 (1.2–6.7)	0.02	4.5 (1.3–15.5)	0.002	1.0 (0.2–7.0)	0.9

*Women were classified, at each evaluation, as high risk if at least one serial cervical-length (CL) measurement was < 10 mm and as low risk if CL was ≥ 10 mm at all assessments. Areas under the receiver-operating-characteristics curves were 0.69, 0.69, 0.76 and 0.69 for models based on CL measurement at hospital discharge and those based on serial CL measurements from hospital discharge to first, second and third follow-up visits, respectively. †Reference. 17-P, 17-alpha-hydroxyprogesterone caproate; aOR, adjusted odds ratio.

later and observed no benefit from adding the difference between the two measurements to the risk calculation for delivery <37 weeks, based on the first assessment alone. As we followed women with serial cervical evaluations, we identified patients with CL ≥ 10 mm at the time of hospital discharge who experienced cervical shortening in the following weeks and delivered preterm. Therefore, CL changes monitored over time may provide better assessment of the risk of spontaneous preterm birth, compared with a single CL evaluation, optimizing interventions such as maternal hospitalization, transfer to centers with level III and IV neonatal intensive care units, antenatal rescue corticosteroids, neuroprotection with magnesium sulfate and screening for concurrent infections.

The well-described shortening of CL as pregnancy advances suggests that the predictive accuracy of sonographic CL in women with threatened preterm labor depends on gestational age at presentation, and that cut-off values predictive of preterm labor should be gestational-age specific¹⁸. Instead, we showed that 10 mm is the cut-off value that better identifies women at risk of delivery prior to 37 weeks, independently of gestational age. Our findings are supported indirectly by previous reports showing that gestational-age specific CL values had only modest predictive accuracy for spontaneous preterm birth among women with threatened preterm labor¹⁸. Moreover, among asymptomatic women, midtrimester CL of 10 mm seems to identify a group at particularly high risk of spontaneous preterm birth. An exploratory subgroup analysis of a systematic review on cerclage placement showed that the intervention prevented spontaneous preterm delivery only when CL was < 10 mm among women without a prior spontaneous preterm birth¹². Moreover, in a recent systematic review, treatment with vaginal progesterone accounted for a dramatic drop in the rate of preterm birth in women with a short cervix and no prior preterm delivery; however, the intervention did not appear to be as beneficial when CL was < 10 mm⁹.

The main strengths of this study include its prospective design, the use of a standard methodology for CL measurement, identification of a population at risk with a high number of spontaneous preterm births (57/226; 25.2%), recruitment of patients from five tertiary care hospitals and the multivariate approach accounting for confounding. However, our study is not without limitations. First, as we did not record CL at presentation, some patients may have had a short cervix prior to the onset of painful uterine contractions. Second, enrollment was based on CL criteria; therefore, our analysis did not account for the role of cervical dilatation in the risk of spontaneous preterm birth. Third, fetal fibronectin was not evaluated systematically upon presentation; detection of such glycoprotein could better define the risk of preterm labor among symptomatic patients. Fourth, patients were treated according to national guidelines (i.e. for tocolysis and antibiotic treatment), which could limit the generalizability of our findings.

The findings of our study confirm the importance of risk factors for preterm birth, such as smoking and urinary tract infections, and corroborate that maintenance tocolysis with progestogens does not lower the rate of preterm delivery. Furthermore, we also showed that vaginal progesterone increases the risk of spontaneous preterm birth when administered after the first episode of threatened preterm labor, as also indicated in the primary analysis of the trial⁶. Given the association of inflammation and infection with preterm delivery¹⁹, we speculate that suppositories inserted daily into the vagina may favor ascending infections and promote cervicovaginal inflammation in women likely to have a proinflammatory vaginal milieu related to the recent threatened preterm labor episode.

In conclusion, women who remain undelivered after their first episode of threatened preterm labor continue to be at high risk of spontaneous preterm delivery if their CL is below 10 mm at the time of hospital discharge or at any follow-up visit up to 4 weeks later, with odds ratios ranging from 2.9 to 7.3. This means that, in a population of women who remain undelivered after their first episode of threatened preterm labor, the risk of spontaneous preterm birth in those with CL < 10 mm will be 13% to 35% higher than the 10% risk in those with CL ≥ 10 mm. Therefore, information on CL measurements could become part of antenatal care in order to stratify the risk of preterm delivery in this population and help clinicians utilize resources to improve pregnancy outcomes. Moreover, CL assessment could also reassure mothers of their low risk of preterm delivery when measurements remain above 10 mm, despite a previous hospitalization from threatened preterm labor. Adequately powered prospective studies are necessary to confirm the utility of serial CL assessments in symptomatic patients not receiving additional treatments after their first episode of threatened preterm labor, and to determine the feasibility and cost effectiveness of such a monitoring program.

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