Predictors of Early Preterm Birth Despite Vaginal Progesterone Therapy in Singletons with Short Cervix

Rupsa C. Boelig, MD, MS[1] Mackenzie N. Naert, MD[2] Nathan S. Fox, MD[2,3]
Sean Hennessy, Pharm D, PhD[4] Inna Chervoneva, PhD[4] Vincenzo Berghella, MD[1] Amanda Roman, MD[1]

[1] Division of Maternal Fetal Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania
[2] Department of Obstetrics Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, New York
[3] Mount Sinai School of Medicine—Obstetrics and Gynecology, Maternal Fetal Medicine Associates, PLLC, New York, New York
[4] Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania
[5] Division of Biostatistics, Thomas Jefferson University, Philadelphia, Pennsylvania

Address for correspondence Rupsa C. Boelig, MD, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Thomas Jefferson University Hospital, 833 Chestnut St 1st floor, Philadelphia, PA 19107 (e-mail: Rupsa.boelig@jefferson.edu).

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Abstract

Objective Identify the incidence of and risk factors for early preterm birth (PTB) (delivery <34 weeks) in women without prior PTB and current short cervix (≤20 mm) prescribed vaginal progesterone.

Study Design Retrospective cohort study of singletons without prior PTB diagnosed with short cervix (≤20 mm) between $18^{0/7}$ and $23^{6/7}$ weeks. Women who accepted vaginal progesterone and had delivery outcomes available were included. Demographic/obstetric history, cervical length, and pregnancy characteristics compared between women with early PTB versus delivery ≥34 weeks. Multiple logistic regression analysis used to identify predictors; odds ratio for significant factors used to generate a risk score. Risk score and risk of early PTB assessed with receiver operating characteristic curve (ROCC). Perinatal outcomes compared by risk score.

Results Among 109 patients included, 29 (27%) had a spontaneous PTB <34 weeks. In univariate analysis, only gestational age at ultrasound, presence funneling, and mean cervical length were significantly different between those with and without early sPTB. With multiple logistic regression analysis, only gestational age at diagnosis (odds ratio [OR]: 0.66; 95% confidence interval [CI]: 0.46–0.96; $p = 0.028$) and index cervical length (OR: 0.84; 95% CI: 0.76–0.93; $p = 0.001$) remained significantly associated with early PTB. ROCC for the risk score incorporating cervical length and gestational age was predictive of early PTB with an AUC of 0.76 (95% CI: 0.67–0.86; $p < 0.001$). A high-risk score was predictive of early PTB with a sensitivity of 79%, specificity of 75%, positive predictive value of 54%, and negative predictive value of 91%. Women with a high-risk score had worse perinatal outcomes compared with those with low-risk score.

Conclusion A total of 27% of patients with short cervix prescribed vaginal progesterone will have a sPTB < 34 weeks. Patients at high risk for early PTB despite vaginal progesterone therapy may be identified using gestational age and cervical length at diagnosis of short cervix. Given the narrow window for intervention after diagnosis of short cervix, this has important implications for clinical care.

Keywords
- preterm birth
- progesterone
- short cervix

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Early preterm delivery is a leading cause of neonatal morbidity and mortality.[1] Early preterm birth (PTB) (<34 weeks) accounts for >75% of neonatal morbidity and mortality, increasing as gestational age decreases.[1] Unfortunately, our ability to predict preterm delivery is limited. A cervical length ≤20 mm prior to 24 weeks has been associated with an increased risk of preterm birth.[2–4] Among PTBs, those preceded by a short cervix tend to have a periviable delivery compared with those with normal cervical length.[5] Vaginal progesterone is effective in reducing the risk of PTB in women with short cervix.[4,6,7] Although the incidence of short cervix is only approximately 1%,[8–10] it is a significant risk factor for early PTB. A recent meta-analysis of vaginal progesterone therapy for women with short cervix (≤25 mm) concluded the risk of PTB <34 weeks reduced from approximately 27 to 18%.[11] However, more recent studies have demonstrated that even with vaginal progesterone therapy, approximately 25% of women will still go on to have an early PTB.[12,13] This increased incidence compared with earlier trials may be due to the fact that clinical trials often excluded those at higher risk such as those with a cervical length <10 mm, or any history of vaginal bleeding, or medical comorbidities, thus limiting the external validity of the data.[6,11]

The objective of this study is to identify the incidence of and risk factors for early PTB (delivery <34 weeks) in women without prior PTB and current short cervix (≤20 mm) prescribed vaginal progesterone.

Materials and Methods

This is a retrospective cohort study from January 2012 to December 2018 of pregnant women undergoing ultrasound at Thomas Jefferson University Antenatal Testing Unit (Philadelphia, PA) and Mount Sinai Hospital (New York, NY). The cohort was constructed by doing an electronic search of ultrasound reports for singleton pregnancies, gestational age $18^{0/7}$ to $23^{6/7}$ weeks and diagnosis of short cervix (cervical length ≤20 mm) and without a diagnosis of prior PTB (prior delivery $20^{0/7}$–$36^{6/7}$ weeks). Exclusion criteria included prior use of progesterone therapy, delivery data unavailable, not being recommended or starting vaginal progesterone, iatrogenic preterm delivery, or major chromosomal/congenital anomaly. Use of cerclage or pessary in addition to progesterone was not an exclusion. During this time period, both institutions routinely screened for short cervix with transvaginal ultrasound during anatomy scan. Patients with a short cervix ≤20 mm were recommended vaginal progesterone therapy (200 mg micronized progesterone or 8% vaginal progesterone gel daily until 36 weeks). Patients at Mount Sinai routinely had follow-up cervical length screening 1 to 2 weeks after diagnosis of short cervix, while Thomas Jefferson University did not have a standard protocol for follow-up cervical length screening after diagnosis of short cervix. During the course of the cohort study period, cerclage use was on a case by case basis taking into consideration history, cervical dilation, ultrasound findings per provider discretion; additionally, there was an ongoing clinical trial on cerclage in addition to vaginal progesterone for women with cervical length ≤25 mm.

Women with a singleton gestation and without a history of spontaneous PTB who were found to have a short cervix (cervical length ≤20 mm) $18^{0/7}$ to $23^{6/7}$ weeks' gestation, and were treated with vaginal progesterone were included. Index cervical length was defined as the first cervical length that was ≤20 mm. Treatment with vaginal progesterone was determined by documentation of prescription of vaginal progesterone and prenatal note indicating that the patient-initiated therapy. Specific adherence to progesterone therapy for the duration of pregnancy was not able to be assessed. Progesterone formulation varied depending on insurance coverage but was either micronized progesterone 200 mg or 8% vaginal progesterone gel. Women with prenatal care at another institution, delivery outcomes not available, major congenital anomaly, placenta previa or accreta, elective termination of pregnancy, and fetal demise were excluded. Comprehensive obstetric history, medical history, demographic data, and delivery information were collected from the prenatal and delivery records.

Demographic and obstetric history were compared with identify risk factors for early PTB <34 weeks. Demographic/obstetric history, cervical length, and pregnancy outcomes compared between women with early PTB versus delivery ≥34 weeks. Continuous variables compared with Mann–Whitney U test, categorical with Chi-square/Fisher's exact as appropriate. Multiple logistic regression analysis with backward selection was used to identify factors predictive of spontaneous early PTB with $p < 0.05$. A weighted risk score was developed using odds ratio from multiple logistic regression analysis. Perinatal outcomes were compared by risk score. A value of $p < 0.05$ was considered significant. A post hoc analysis was conducted to compare AUC of risk score versus cervical length alone given this is easily accessible clinical information. This comparison was done using R package[14,15] and previously developed permutation test to compare ROCC.[16] This study was approved by both the Thomas Jefferson Institutional Review Board and Mount Sinai Institutional Review Board. SPSS v25 was used for all statistical analyses except ROCC comparison as described above.

Results

During the study period, 121 women met inclusion criteria; after 13 exclusions (►Fig. 1), there were 108 patients included in the final cohort and 29 (27%) had a spontaneous preterm birth (sPTB) <34 weeks. In comparing demographic, medical, and pregnancy characteristics with univariate analysis, only gestational age at ultrasound, presence funneling, and mean cervical length were significantly different between those with and without early sPTB (►Table 1). There was use of other interventions including pessary and cerclage, but these did not differ significantly between those with and without an early sPTB. There were 23 cerclages placed total, 12 were placed due to cervical dilation on exam, 9 were placed based on ultrasound indications by provider discretion, and 2 were placed for short cervix <25 mm in the setting of clinical trial.

With multiple logistic regression analysis, only gestational age at diagnosis (OR: 0.66; 95% confidence interval [CI]:

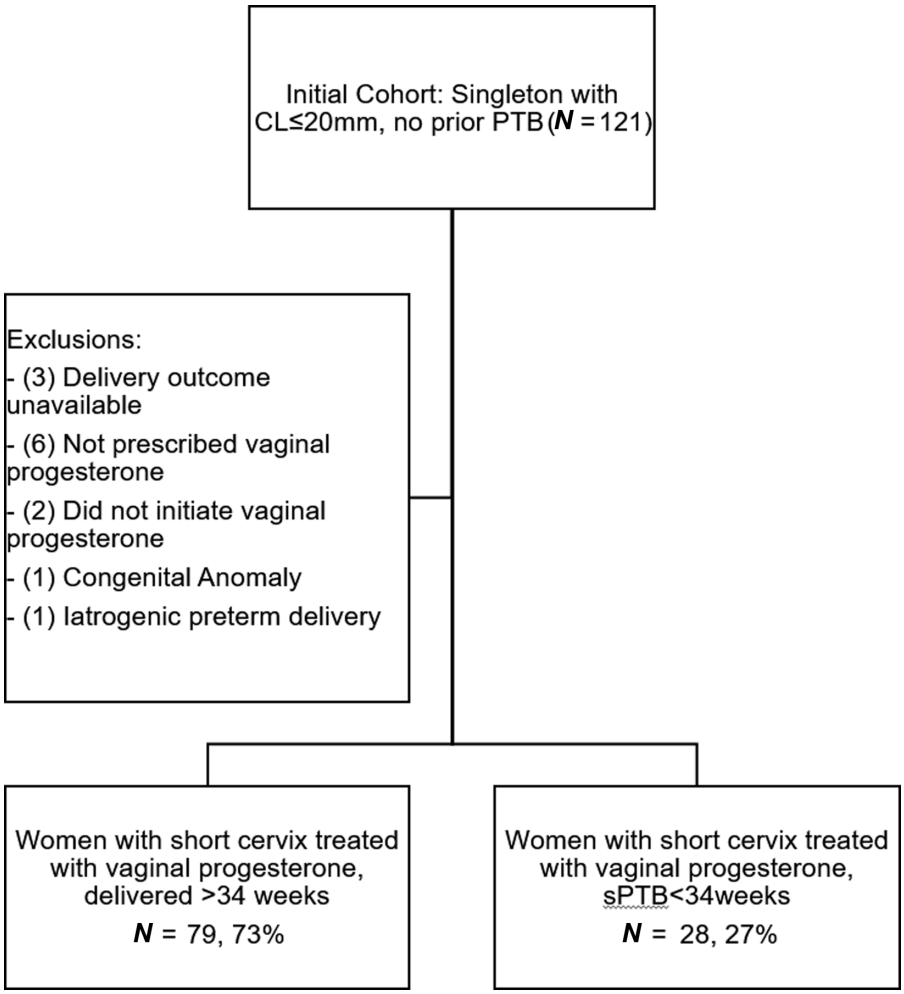

Fig. 1 Cohort Flow Diagram.

0.46–0.96; $p = 0.029$) and index cervical length (OR: 0.84; 95% CI: 0.76–0.94; $p = 0.001$) remained significantly associated with early PTB. A *post hoc* multiple logistic regression analysis including nulliparity and pessary use along with gestational age, cervical length, and funneling still found that only gestational age at diagnosis and index cervical length were significant. Index cervical length and gestational age were not correlated ($p = 0.12$), while index cervical length was correlated with presence of funneling ($r = -0.325$, $p < 0.001$). Risk score for early PTB was developed using the OR from multiple logistic regression analysis (risk score = 0.84 × cervical length [mm]) + (0.66 × gestational age [wk]). A lower score indicated higher risk. In evaluating ROC curves, the risk score incorporating cervical length and gestational age had an AUC of 0.76 (95% CI: 0.67–0.86; $p < 0.001$). In using Youden's index to select a cut point (25.3), a high-risk score was predictive of early PTB with a sensitivity of 79%, specificity of 75%, positive predictive value of 54%, and negative predictive value of 91% (Youden's index = 0.54). Women with a high-risk score had a significantly reduced latency to delivery compared with those with a low-risk score (►**Fig. 2**) and had worse neonatal outcomes (►**Table 2**).

In *post hoc* analysis looking at the individual components of the risk score, gestational age at diagnosis had an AUC of 0.65 (95% CI: 0.54–0.76; $p = 0.018$), while cervical length alone had an AUC of 0.74 (95% CI: 0.64–0.84; $p < .001$; ►**Fig. 3**). There was no improvement in AUC when using risk score compared with cervical length alone using a paired comparison ($p = 1.0$). Using cervical length alone with a cut point of <15 mm (Youden's index = 0.50), there was an 79% sensitivity, specificity of 71%, a positive predictive value of 50%, and a negative predictive value of 90% for early PTB. Total 75 patients had a follow-up cervical length after initial cervical length. Of those, 14 (18%) had an early spontaneous PTB. Mean follow-up time was 1.15 ± 0.80 weeks and median change in cervical length was 0 (95% CI: –3.0 to 5.0) mm. In multiple logistic regression analysis incorporating index cervical length, follow-up cervical length, and change in cervical length, only index cervical length remained associated with early PTB (OR: 0.84 (95% CI: 0.73–0.96; $p = 0.009$). When evaluating for interaction between follow-up cervical length and initial risk score, the interaction term was not significant in multiple logistic regression analysis ($p = 0.31$).

Discussion

We have demonstrated that a significant percentage of women with a short cervix will go on to have an early PTB

Table 1 Comparison of baseline characteristics

	Delivery ≥34 wk ($n = 79$)	Early preterm birth (<34 wk) ($n = 29$)	*p*-Value
Demographics			
Maternal age (y)	29.1 ± 6.9	30.0 ± 6.6	0.50
Race			0.49
African American	40 (51)	17 (59)	
Caucasian	30 (39)	8 (28)	
Asian	4 (5)	3 (10)	
Latino	3 (4)	0 (0)	
Other	1 (1)	1 (3)	
BMI (kg/m^2)	26.2 ± 6.2	28.4 ± 7.5	0.17
Tobacco use	8 (10)	1 (3)	0.44
Medical history			
Methadone therapy	3 (4)	2 (7)	0.48
Hypertensive disorder	6 (8)	3 (10)	0.70
Diabetic disorder	2 (3)	1 (3)	1.0
Depression/anxiety	6 (8)	6 (21)	0.079
Obstetric history			
Nulliparous	43 (54)	21 (72)	0.09
Prior cervical surgery	8 (10)	1 (3)	0.44
Current pregnancy			
Pessary	15 (19)	9 (31)	0.20
Cerclage	17 (21)	6 (21)	0.92
Gestational age at ultrasound	21.2 ± 1.4	20.5 ± 1.3	0.018
Funneling	34 (44)	20 (71)	0.01
Mean CL (mm)	15.7 ± 4.4	11.9 ± 4.1	<0.001
CL< 15 mm	23 (29)	23 (79)	<0.001
High-risk score	20 (25)	23 (79)	<0.001

Abbreviations: BMI: body mass index, CL: index cervical length.
Note: Comparison of demographic, social, obstetric, and ultrasound characteristics in patients with short cervix prescribed vaginal progesterone with spontaneous early preterm birth (<34 weeks) versus not.

(<34 weeks) in clinical practice. This rate is significantly higher than previously reported in clinical trials on vaginal progesterone for PTB prevention in short cervix,[6,11] but is consistent with what was reported in a recent multicenter study on pessary for PTB prevention that included treatment with vaginal progesterone in both the control and pessary groups.[17] A recent commentary highlighted that there are no data to suggest vaginal progesterone is not effective at <10 mm.[18] Our results, however, do suggest an association between shorter cervical length (and specifically <15 mm) and a high rate of early PTB despite therapy. There are a few potential reasons for this higher than previously reported rate of early PTB in women treated with vaginal progesterone for short cervix. First, our study is based on an urban, largely African American population, which is inherently at higher risk for PTB.[19] Additionally, randomized trials have several exclusion criteria, such as medical comorbidities and very short cervical length (<10 mm) that do not preclude use of vaginal progesterone in the clinical setting.[6,7] Our finding of a higher early PTB rate in women with short cervix (<15 mm) treated with vaginal progesterone highlights the importance of exploring what may be associated with failure of vaginal progesterone therapy so these women may be identified and targeted for studies on adjunctive therapies. A secondary analysis of a recent randomized trial identified that cervical length ≤11 mm was associated with cervical dilation, and this may explain the association with early PTB identified in this study.[20]

The exact mechanism by which vaginal progesterone may prevent preterm delivery is not fully known.[21] The exact mechanism of action of progesterone in PTB prevention is not well understood, but it is thought to involve antiinflammatory affects and cervical remodeling, and most likely acts locally.[22–24] Given the multifactorial nature of PTB as well as

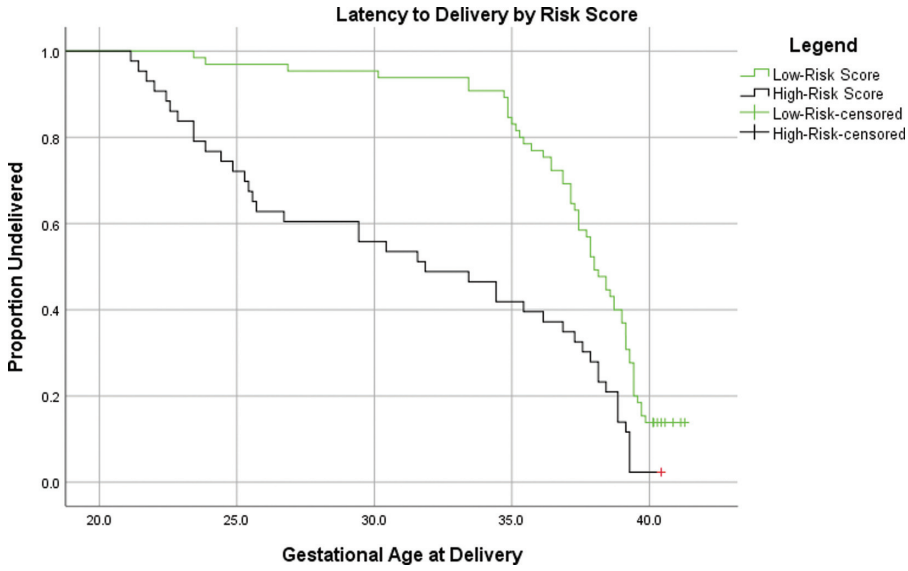

Fig. 2 Kaplan–Meier survival curve for latency to delivery by risk score stratification comparison of latency to delivery for high (black) versus low (green) risk score in patients with short cervix treated with vaginal progesterone, Mantel–Cox log rank $p < 0.001$.

Table 2 Risk score and perinatal outcomes

	Low risk ($n = 64$)	High risk ($n = 43$)	*p*-Value
Gestational age (wk)	37.2 ± 3.6	31.3 ± 6.8	<0.001
Birthweight (g)	2,932 ± 721	1,966 ± 1,156	<0.001
NICU admission	12 (19)	18 (45)	0.004
Perinatal death	1 (2)	10 (26)	<0.001

Abbreviation: NICU, neonatal intensive care unit.
Note: Comparison of perinatal outcomes based on high- or low-risk score calculated from index cervical length and gestational age of diagnosis. Neonatal information available for 104 of 109 patients. Data presented as mean ± standard deviation or *n* (%).

the multifaceted effect of vaginal progesterone, it stands to bear that this one therapy would not uniformly benefit all patients with a short cervix. There is increasingly an emphasis on the importance of personalizing medical therapy rather than treating all at risk women the same.[25,26] The significant percentage of women, who do not respond to vaginal progesterone therapy, are at increased risk of suffering the devastating consequences of an early PTB. Manuck et al addressed this issue in women with a prior PTB treated with intramuscular progesterone.[27] As we strive to improve the personalization of medicine, it is critical to identify individual factors that may impact response to therapy and allow us to target a subgroup of women that may benefit from studies on adjunctive interventions.

We examined a large number of potential factors that may influence the efficacy of vaginal progesterone and identified shorter cervical length and earlier gestational age to be the strongest predictors for early PTB despite progesterone therapy. Our results suggest that the ability of vaginal progesterone to affect cervical remodeling may be limited in very short cervical length. Currently, national guidelines do not recommend any therapies for short cervix in women without a prior PTB beyond vaginal progesterone.[28] Our study highlights the need for further research into adjunctive interventions in women found to have a very short cervix (<15 mm) as they may be at high risk of early PTB despite vaginal progesterone therapy. The risk score developed here should be validated in an external population before further use, but our results are consistent with other studies on the pathology of short cervix. It should be noted that gestational age of diagnosis was incidental depending on timing of anatomical survey, but nonetheless was associated with PTB.

Although we did not identify additional utility to follow-up cervical length screening, other studies have suggested change in cervical length may add to early PTB prediction,[29] and certainly the limited number of patients who had follow-up cervical length limits our ability to detect a weaker association.

There are several strengths to this paper. There are few studies published on the effectiveness of vaginal progesterone outside the setting of a trial. Our study provides an exploration into the real world application and limitations of vaginal progesterone therapy for PTB prevention in women with a short cervix and exposes some of the limitations in the external validity of randomized trials on vaginal progesterone for PTB prevention in women with a short cervix. We were able to assess a wide range of risk factors for PTB and identify that a risk score incorporating cervical length and gestational age, and even just cervical length alone, may be used to identify a subgroup of women at high risk for early PTB despite vaginal progesterone therapy for short cervix. Finally, we focused on the clinically significant end point of early PTB, as that is the source of most neonatal morbidity and mortality.[1]

There are a few weaknesses in this study. Although even with a limited sample size we were able to identify both index cervical length and gestational age as significant predictors of early PTB and poor perinatal outcomes, we may not be powered to detect other weaker—although still statistically

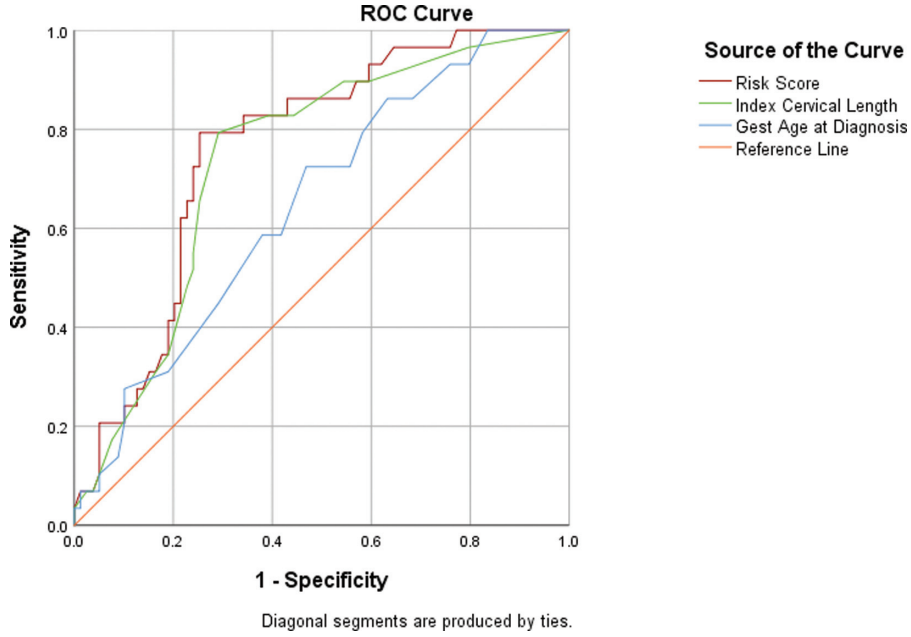

Fig. 3 Receiver operating characteristic curve comparison of receiver operating characteristic curve of gestational age at diagnosis (blue, AUC of 0.65 [95% CI: 0.54–0.76, $p = 0.018$]), index cervical length (green, AUC: 0.74 [95% CI: 0.64–0.84, $p < .001$), and risk score incorporating cervical length and gestational age (red AUC: 0.76 (95% CI: 0.67–0.86), $p < .001$) in predicting early spontaneous preterm birth <34 weeks.

significant—predictors of early PTB in women with short cervix treated with vaginal progesterone. Other interventions, such as pessary and cerclage were used per provider discretion and in some cases as part of concurrent randomized trial; however, these were not significantly associated with early PTB (►**Table 2**). The risk score developed was tested internally which is inherently biased, and thus, our results should be validated in an external cohort. This is a retrospective study thus can only describe association and not causation. There is always a risk of bias from variation in provider practices, institutional differences, and although we tried to assess relevant confounders, there remains the risk of unmeasured bias. Although we have patient reported confirmation that vaginal progesterone was started, there is no way for us to retrospectively ascertain degree of adherence.

Our findings suggest baseline ultrasound findings may be used to identify patients at high risk for early PTB despite vaginal progesterone therapy. Given the potentially narrow window for intervention after diagnosis of short cervix (i.e., initiation of therapy prior to 24 weeks), this could have important implications for clinical care. Our risk score should be validated in an external cohort and further randomized trials on adjunctive interventions for PTB prevention are necessary in this subgroup of women.

Note

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Conflict of Interest

None declared.

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