OBSTETRICS

Rate of sonographic cervical shortening and biologic pathways of spontaneous preterm birth

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OBJECTIVE: The objective of the study was to estimate the relationship between midtrimester cervical length (CL) and maternal serum markers of systemic inflammation, activation of the maternal-fetal hypothalamic-pituitary axis, and alterations in thrombosis-hemostasis.

STUDY DESIGN: This is a secondary analysis of a prospective cohort study designed to predict preterm birth in the general obstetric population. Women had serial CL ultrasounds and assessment of maternal serum corticotrophin-releasing hormone, C-reactive protein, and thrombin-antithrombin III complexes between 20 and 33 weeks' gestation and were followed up until delivery.

RESULTS: Shortening of CL was associated with the rate of rise in corticotrophin-releasing hormone ($r^2 = 0.34$, $P = .014$) and C-reactive protein ($r^2 = 0.44$, $P = .001$) for women with CL less than 25 mm but not for the cohort overall. There was no association of change in CL with change in thrombin-antithrombin III concentration.

CONCLUSION: Among women with a midtrimester sonographically short cervix, changes in serum markers suggest that a shortening CL may be associated with systemic inflammation and activation of the maternal-fetal hypothalamic-pituitary axis but not systemic thrombosis-hemostasis.

Key words: cervical length, corticotrophin-releasing hormone, inflammation, preterm birth

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Sonographic cervical length (CL) measurement is the most useful tool available to assess risk for spontaneous preterm birth (SPTB) in asymptomatic women in midpregnancy. Among women in the general obstetric population, midtrimester short CL (<25 mm) is associated with an increased risk for SPTB.[1] More recently, analysis of serial measurements of sonographic CL has shown that risk assessment can be further refined; for women with a midtrimester short CL, the subsequent rate of cervical shortening is associated with SPTB.[2]

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There are several possible biological pathways implicated in the genesis of preterm birth: activation of the maternal-fetal hypothalamic-pituitary axis (HPA),[3-9] inflammation-infection,[10-12] and systemic thrombosis-hemostasis.[13-15] Levels of corticotrophin-releasing hormone (CRH) rise throughout pregnancy, leading many researchers to speculate that CRH may serve as a placental clock that contributes to the timing of parturition. The rate of rise in CRH has been shown to be higher for women who deliver preterm.[9,16] Elevations in C-reactive protein (CRP) may be associated with states of chronic inflammation or infection. Increased maternal CRP concentration has been associated with evidence of chorioamnionitis in patients with SPTB presenting either with symptoms of labor or ruptured membranes.[11,12] Concentrations of thrombin-antithrombin complexes have been associated with activation of systemic thrombosis-hemostasis pathways leading to preterm birth.[13-15]

A historical view of the cervix and its length as an anatomic or structural contributor, but not a biological contributor, to parturition has evolved recently into a view of CL as a physical manifestation of the biochemical and molecular process of activation of parturition. The relationship between CL, both cross-sectionally and over time, with activation of these pathways is not known.

The purpose of this study was to explore the relationship between pathways implicated in SPTB and change in sonographic CL. We hypothesized that, for women with a short cervix, shortening of CL on serial examinations is associated with an increase in systemic markers of inflammation, activation of the maternal-fetal HPA, and changes in systemic thrombosis-hemostasis.

Materials and Methods

This is a secondary analysis of data from the Preterm Prediction Study, a multicenter prospective observational cohort study conducted by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network between 1992 and 1994 to study the predictors of preterm birth.

Women with a singleton gestation from the general obstetric population

TABLE
Demographic characteristics of study population

Demographic	Number of subjects	%
Total	334	100
Age, y		
Median (range)	26 (18–44)	
BMI, kg/m^2		
Median (range)	23.2 (15.4–47.5)	
Race		
White	242	73.8
African American	84	25.6
Other	2	0.6
Parity		
Nulliparous	109	33.2
Multiparous	225	66.8
Marital status		
Married	161	49.1
Unmarried	173	50.9
Tobacco		
Yes	90	27.4
No	244	72.6
Prior PTB		
Yes	84	25.6
No	250	74.4
Gestational age, wks		
Visit 1 median (range)	23.9 (22.4–24.9)	
Visit 2 median (range)	28 (26.2–31.7)	
Time between visits, wks		
Median (range)	4 (2.6–7.9)	
CL, visit 1, mm		
<25	52	16
≥25	282	84

BMI, body mass index; *CL*, cervical length; *PTB*, preterm birth.

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with well-dated pregnancies less than 24 weeks' gestation were included. Women with multiple gestation, placenta previa, cerclage , and fetal anomalies were excluded. Women who had sonographic CL ultrasounds performed at a gestation at 24 weeks (range, 21–28 weeks) and at 28 weeks (range, 25–33 weeks) and had maternal blood samples collected at these visits were included in the secondary analysis.

The technique for sonographic measurement of CL has been described in detail in prior reports of this cohort.[1] Sonographic CL measurements were subjected to a quality assurance protocol. Each ultrasound visit included 3 transvaginal CL measurements, and the shortest measurement was recorded. Fundal pressure was not used to assess the shortest CL. When a cervical funnel was present, the CL below the funnel was recorded. Sonogram results were not reported to managing physicians unless fetal death, advanced cervical dilation, prolapsed membranes, oligo- or polyhydramnios, or regular uterine contractions were detected.

As part of the original study protocol for the Preterm Prediction Study, maternal serum samples for CRH, CRP, and thrombin-antithrombin III (TAT) were collected at the first study visit at 24 weeks and at a follow-up visit at 28 weeks. Serum samples were stored at −70°C until analysis. All serum assays were performed after 1 freeze-thaw cycle.

CRH concentrations were determined using an enzyme-linked immunosorbent assay from Peninsula Laboratories (San Carlos, CA). Free CRH, the biologically active form of CRH, was measured using a Sep Pak C18 column (Waters, Milford, MA). CRH levels reported in this secondary analysis refer to free CRH. CRP levels were obtained using an enzyme-linked immunosorbent assay from Kamiya Biomedical Co (Seattle, WA). An immunoassay for TAT was performed using a kit from American Diagnostica (Greenwich, CT), and absorbances were measured using a microtiter plate reader and software from Molecular Devices (Menlo Park, CA). Assays had been performed prior to this dataset, having been made available for the present secondary analysis.

The differences between maternal serum concentrations of CRH, CRP, and TAT at 24 weeks and 28 weeks were our primary outcome variables of interest. The bivariate relationships between the change in CL and plasma levels of these proteins were determined using simple linear regression. Covariate analyses used multiple linear regression and included age, race, unmarried status, tobacco use, and a history of prior preterm birth. A value of $P < .05$ was considered statistically significant. Statistical analyses were performed using Stata 10 (StataCorp, College Station, TX).