Title: Cervicovaginal Fluid (CVF) Cytokine Profiles vary by Obstetrical History

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Objective: An association has repeatedly been demonstrated between pro-inflammatory cervicovaginal cytokines and preterm birth. Our objective was to evaluate the cervicovaginal milieu of women categorized by their obstetric history to determine whether subpopulations carried different risks.

Study Design: This was a secondary analysis of a longitudinal multicenter study of women with singleton gestations. Maternal cervicovaginal fluid (CVF) specimens were collected in the first and second trimesters. Cytokines (IL-1α, IL-1β, IL-6, IL-8, IL-10, TNF-α, MMP-8, CRP) were measured using a multiplex beadlyte assay on a luminex IS-100. Women were stratified by obstetrical history into three groups: nulliparous, multiparous with a history of preterm birth, and multiparous without a history of preterm birth. Repeated measures modeling was used to examine group differences over time, adjusting for age, BMI and first trimester smoking status. Post-hoc analysis was accomplished using Fisher's least significant differences (LSD) method for pairwise comparisons. Statistics were performed using SAS 9.4 with an alpha level of 0.05.

Results: 217 women were included in the analysis. The cytokine profiles varied significantly based on obstetric history. For all cytokines studies, the highest levels were identified in those with a history of preterm birth, followed by nulliparas, and lastly those without preterm birth. Univariate analysis demonstrated cytokine profiles of IL-6 and CRP varied significantly between subgroups, see Table. After controlling for age, BMI and smoking status, these relationships persisted and TNF-α also demonstrated significant differences between subgroups.

Conclusion: Inflammatory cytokines differ significantly based on obstetrical history. If these cytokines are to be utilized as potential biomarkers for preterm birth, there sensitivity and specificity profiles should be evaluated in particular subpopulations based on obstetric history.

Table 1. Adjusted (age, BMI and smoking status) and unadjusted associations of cervicovaginal biomarkers by group

Cervicovaginal fluid biomarker	Nulliparous (*n* = 102) *geometric mean* (geo. SE)	Parous, no history of PTB (*n* = 69) *geometric mean* (geo. SE)	Parous, history of PTB (*n* = 46) *geometric mean* (geo. SE)	unadjusted *p*	adjusted *p*
IL-6 pg/mL	3.31 (1.15)[a]	0.99 (1.47)[b]	6.76 (1.24)[c]	<.001	<.001
IL-8 pg/mL	1480.60 (1.18)	846.32 (1.57)	2613.64 (1.29)	.58	.065
IL-1α pg/mL	585.75 (1.17)	423.82 (1.52)	772.42 (1.27)	.52	.53
IL-1β pg/mL	7.07 (1.27)	2.49 (1.90)	12.94 (1.43)	.72	.081
TNF pg/mL	0.87 (1.13)[a,b]	0.50 (1.38)[a]	1.29 (1.20)[b]	.14	.033
CRP mg/L	4.79 (1.26)[a]	0.95 (1.89)[b]	10.78 (1.3)[a]	<.001	.005
MMP-8 ng/mL	80668 (1.19)	30733 (1.63)	89643 (1.31)	.044	.15
IL-10 pg/mL	0.85 (1.12)	0.91 (1.36)	1.34 (1.19)	<.001	.10