

13 Effect of prenatal tobacco use on perinatal outcomes and childhood neurodevelopment among infants born prematurely



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OBJECTIVE: Although it is well-known that nicotine is a neuroteratogen and prenatal tobacco exposure alters neurodevelopment, the effect on infants born prematurely is not yet well-described. We sought to examine the impact of prenatal tobacco exposure on childhood neurodevelopment until two years of age among infants born preterm.

STUDY DESIGN: Secondary analysis of a multicenter RCT which assessed the benefits of magnesium for prevention of cerebral palsy in preterm infants. Women were included in the secondary analysis if they delivered a singleton, non-anomalous infant <37 weeks. Our exposure was any reported prenatal tobacco use. The primary outcome was the trial composite outcome of stillbirth or infant death by 1 year of age or moderate or severe cerebral palsy, assessed at or beyond two years of age. Secondary outcomes included cerebral palsy at two years, Bayley Scales of Infant Development II (BSIDII, motor and mental) scores at 24 months, need for auditory aids, and need for corrective lenses. Chi square, Fisher Exact, and two-sample t-tests were used as appropriate. Multivariable logistic regression models were performed to control for confounding factors.

RESULTS: Of 1,921 women included, 548 (29%) used tobacco. Tobacco users were more likely to be younger, unmarried, white, have a prior preterm birth, and to have received no prenatal care. Illicit drug and alcohol use were also more prevalent among tobacco users. GA at delivery, betamethasone exposure and magnesium exposure were similar between groups. There were no differences in the composite primary outcome or in rates of CP by tobacco use (Table). BY BSIDII, moderate developmental delay (<70) was more common among tobacco users in univariate but not adjusted analysis (20.5% vs 15.9%, p = 0.035). There was no significant difference in need for auditory aids. In adjusted analysis, tobacco use was associated with increased need for corrective lenses (5.0% vs. 2.9%, aOR 2.28, 95% CI 1.28-4.07).

CONCLUSION: In preterm infants, prenatal tobacco exposure does not appear to independently increase the risk of neurodevelopmental delay or cerebral palsy. However, tobacco exposure appears to adversely impact optic nerve development, consistent with prior reports of optic nerve atrophy associated with tobacco exposure.

Table: Perinatal and childhood neurodevelopmental outcomes

Characteristic	Tobacco use n = 538	No tobacco use n = 1370	P value	Adjusted OR (95% CI) †
Composite outcome of still birth, infant death (<1y*), or moderate-severe CP (at or beyond 2y*), n (%) ¹	48/503 (9.5)	126/1323 (9.5)	>0.99	1.0 (0.69 – 1.45)
Still birth or infant death, n (%) ¹	37 (7.4)	99 (7.5)	0.93	0.99 (0.65 – 1.49)
Moderate to severe CP, n (%) ¹	11 (2.2)	27 (2.0)	0.85	1.05 (0.52 – 2.15)
Cerebral palsy at age 2y				
Mild ²	16/458 (3.5)	24/1209 (2.0)	0.07	1.83 (0.95 – 3.53)
Moderate ²	9/458 (2.0)	14/1209 (1.2)	0.21	1.67 (0.71 – 3.93)
Severe ²	2/458 (0.4)	12/1209 (1.0)	0.37**	0.43 (0.10 – 1.91)
Bayley Scales of Infant Development scores				
Psychomotor Development Index <70 ²	65/415 (15.7)	154/1125 (13.7)	0.33	1.06 (0.74 – 1.52)
Psychomotor Development Index <85 ²	140/415 (33.7)	360/1125 (32.0)	0.52	1.08 (0.84 – 1.38)
Mental Development Index <70 ⁴	85/415 (20.5)	179/1125 (15.9)	0.035	1.27 (0.94 – 1.70)
Mental Development Index <85 ²	197/415 (47.5)	490/1125 (43.6)	0.17	0.88 (0.68 – 1.13)
Ever used auditory aids ¹	2/479 (0.4)	7/1245 (0.6)	>0.99**	0.72 (0.15 – 3.47)
Ever used corrective lenses ⁶	24/479 (5.0)	36/1245 (2.9)	0.032	2.28 (1.28 – 4.07)

*Corrected for prematurity

† Backward selection model used with entry at p<0.25

** Fisher's Exact test

¹Adjusted for GA at delivery

²Adjusted for GA at delivery, race, no prenatal care, and illicit drug use

³Adjusted for GA at delivery, race, and highest education

⁴Adjusted for GA at delivery and highest education

⁵Adjusted for GA at delivery, race, highest education, and alcohol use

⁶Adjusted for GA at delivery and married

14 Relationship between human mtDNA variants, vaginal microbial species and strains, and frequency of preterm birth



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OBJECTIVE: Given the inability to consistently replicate or independently validate studies linking *G. vaginalis* and *Lactobacillus* spp. to preterm birth, differences in the ethnic or racial makeup of risk-disparate cohorts may be masking underlying true associations. As we and others have published on associations between genetic polymorphisms of the host mitochondrial genome and the microbiome, including the gut and vagina, we sought to evaluate the association of the vaginal microbiome with mitochondrial DNA (mtDNA) single nucleotide polymorphisms (SNPs) as risk-modifiers of preterm birth (PTB).

STUDY DESIGN: WGS paired-end reads identified as host were aligned to the human mitochondrial reference genome (NC_012920.1) using BWA and variant calls were generated using samtools. Only SNPs were considered for subsequent analysis. Species/mtSNP associations were performed using PLINK with the variants considered a haploid genotype and taxa a quantitative trait. For associations between variants, species and PTB, we utilized the quantitative trait interaction algorithm using term and PTB as the covariate groups. Resultant p-values were corrected for False Discovery Rates (FDR).

RESULTS: Although a number of significant taxa-SNP associations were identified in WGS (n=1588) (Figure 1A), these associations were all in relatively minor taxa and did not include the major landmark species driving the vaginal community, including *L. crispatus*, *L. iners*, *L. jensenii* or *G. vaginalis*. With respect to PTB, five SNP-species associations identified by WGS metagenomics were significantly different between term and PTB subjects (Figure 1B). However, post-hoc comparisons revealed these to be minor taxa present at low abundance and frequency – *Propionibacterium acnes*, *Haemophilus haemolytica*, *Veillonella atypica*, *Veillonella parvum*, and *Lactobacillus mucosa* (Figure 1C).

CONCLUSION: Given the significance in disparity of preterm birth between racial and ethnic groups, it is logical to consider the role of mitochondrial genetics and the microbiome. However, within this study, when we rigorously accounted for race and ethnicity using mitochondrial DNA sequencing we failed to observe an association. This was not due to underpowering, since; we identified taxa-by-mtDNA SNP associations among rare species in the vaginal microbiome. However, they were weakly predictive of PTB.

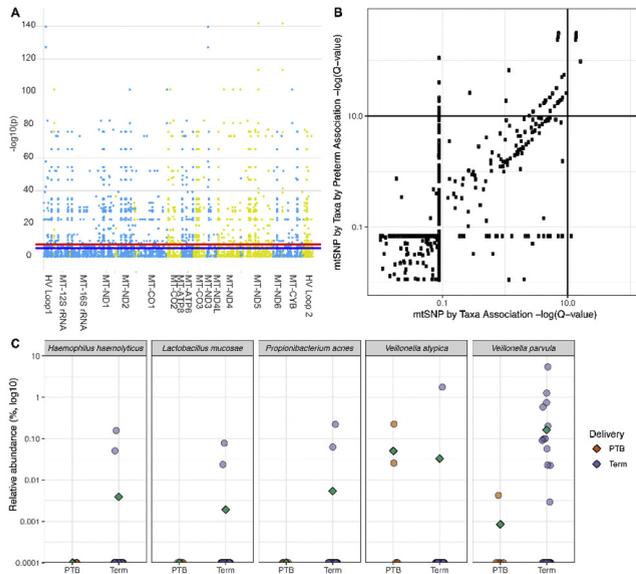


Figure 1. Associations of the vaginal microbiome (WGS metagenomics) with mitochondrial DNA single nucleotide polymorphisms in the context of preterm birth. **A.** Manhattan plot demonstrating significant associations between the average gestational abundance of individual taxa and mtSNPs as determined by PLINK associations. **B.** Identification of taxa-SNP associations significantly different in the context of preterm birth. Q-values for taxa-SNP associations are plotted on the x-axis, while q-values for quantitative trait interaction (taxa-SNP-preterm birth) are plotted on the y-axis. **C.** Relative abundance of bacterial species identified as significantly different between subjects with term and preterm deliveries based on PLINK taxa-SNP-preterm birth associations; group means are denoted by green diamonds.

15 Novel, sensor-based quantitative cervical elastography: objective quantification of cervical softness

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OBJECTIVE: Cervical ripening is a necessary physiologic phenomenon that precedes all labor, both term and preterm. Tissue elastography works by applying pressure to tissue and measuring tissue displacement. It is quantified by Young's modulus, a ratio of pressure to displacement. The harder the tissue, the less displacement and the higher the Young's modulus. It is a promising technique for measuring cervical tissue stiffness to predict preterm birth, but to-date has been semi-quantitative because the exact force applied to the cervix is difficult to quantify. We aimed to develop a novel, fully-quantitative cervical elastography system to objectively quantify cervical tissue stiffness.

STUDY DESIGN: A transvaginal ultrasound probe was modified with a pressure sensor at the tip to obtain real time synchronized pressure and tissue displacement measurements. Pressure and displacement were quantified to calculate the Young's modulus (Figure 1). This system was applied in a pilot prospective cohort study of women receiving prenatal care at a tertiary care center and enrolled in a longitudinal observational study with the larger aim of developing

novel predictive methods for PTB. Generalized linear models were used to test changes in Young's modulus (cervical stiffness) over advancing gestational age to determine if the tissue Young's modulus decreases with advancing gestational age as expected with softening. **RESULTS:** A total 26 ultrasound elastography images from 12 patients were analyzed (9 term births and 3 preterm births). The Young's modulus of cervical tissue tended to decrease with advancing gestational age (-0.65 Young's modulus units per day) (Figure 2).

CONCLUSION: We report a novel, sensor-based, fully quantitative cervical tissue elastography system using a modified transvaginal ultrasound probe for synchronized tissue deformation and pressure measurements. As expected, Young's modulus tended to decrease over pregnancy as the cervix softens. This objective quantification of cervical tissue stiffness may be a promising tool for predicting preterm birth.

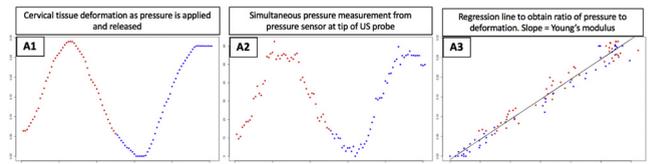


Figure 1. Panels A1-3: calculation of Young's modulus through cervical tissue deformation (A1), pressure (A2), and regression of stress-strain relationship (A3). Slope of A3 is the Young's modulus or tissue elasticity of the cervix.

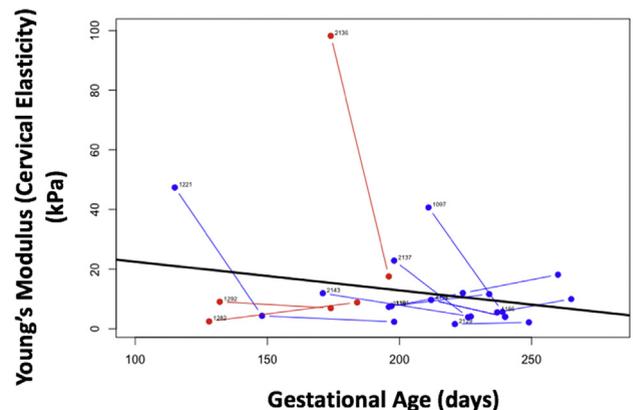


Figure 2: Young's modulus (cervical tissue softness) in patients with term birth (blue) and preterm birth (red) tends to decrease over gestation (black line).

16 Impact of severe stress after a major natural disaster on perinatal outcomes

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OBJECTIVE: Hurricane Harvey displaced over 60,000 of Houston's nearly 4.5 million residents. Natural disasters have been linked to posttraumatic stress disorders. Our objective was to evaluate the impact on perinatal outcomes of self-perceived stress among pregnant women in the weeks to months following Hurricane Harvey.

STUDY DESIGN: Data was abstracted from our perinatal research database (PeriBank). An abbreviated version of the PTSD checklist – civilian version (PCL-C), a validated tool for evaluating both pregnant women and development of PTSD, was prospectively administered to women delivering within our network. Severe stress was