Gardnerella vaginalis induces matrix metalloproteinases in the cervicovaginal epithelium through TLR-2 activation

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OBJECTIVE: Lactobacillus-deficient cervicovaginal (CV) microbial communities, as well as select anaerobes like Gardnerella vaginalis (GV), have been associated with adverse reproductive outcomes, including spontaneous preterm birth (sPTB). As a gram-variable bacterium, GV peptidoglycan cell wall can activate TLR-2. We previously showed that high MMP-9 in CV fluid in pregnancy is associated with an anaerobic-rich CV microbiota, short cervix, and sPTB. We posit that GV induces MMPs in CV epithelial cells through TLR-2, which degrades the epithelial barrier leading to premature cervical remodeling and sPTB.

STUDY DESIGN: Ectocervical (ECTO), endocervical (ENDO), and vaginal (VK2) cells were treated with 10^5 ± 0.5 CFUs live GV or Lactobacillus crispus (LC), a healthy CV bacteria, for 24 hours. For TLR-2 experiments, cells were pretreated with TLR-2 blocking antibody. An MMP Luminex panel was run on cell media for three biologic and two technical replicates per condition. Data were analyzed with a five-parameter logistic curve. One-way ANOVAs with Dunnett’s multiple comparisons tests were used.

RESULTS: GV induced MMP-1 in ENDO cells (p=0.01) and MMP-9 in ECTO, ENDO, and VK2 cells (p<0.001 for all) compared to non-treated controls. LC did not induce any MMPs compared to non-treated controls (Fig. 1). Epithelial cell specific effects were noted for MMP-9 with VK2 cells expressing increased levels compared to cervical cells (p<0.0001, Fig. 1). MMP-9 was selected for TLR-2 blocking experiments given induction in all cell lines after GV treatment. TLR-2 blockade mitigated GV induction of MMP-9 in cervical and VK2 cell lines (Fig. 2).

CONCLUSION: A common anaerobic microbe implicated in several adverse reproductive outcomes, including sPTB, can induce MMPs in the CV space. Upregulation of MMP-9 by GV occurs in a TLR-2 dependent fashion. These findings unveil mechanisms by which CV microbes influence host immune response and may compromise epithelial barrier integrity and promote cervical remodeling. SMFM/AAOGF (KG); 1R01HD102318, 5R01HD098867 (ME)
OBJECTIVE: Changes in maternal immunity following infections may lead to adverse maternal and neonatal outcomes, but data on the immunological consequences following SARS-CoV-2 infection in pregnancy is limited. This study evaluates the correlation of COVID19-induced alteration of maternal immunity with prenatal ultrasonographic abnormalities.

STUDY DESIGN: A prospective observational cohort study conducted at a single tertiary care center of pregnant women diagnosed with SARS-CoV-2 by reverse-transcription polymerase chain reaction between March 2020 and February 2021. Maternal serum specimens were collected at initial diagnosis, and patients underwent serial prenatal ultrasonography following diagnosis of infection. Isolated sera were subjected to high-throughput Next Generation Sequencing-based proteomics multiplexing to detect over 1400 cytokines and serum proteins. The sera proteome profiles of SARS-CoV-2 positive pregnancies with abnormal ultrasounds were compared to those of gestational age-matched healthy controls.

RESULTS: Of 72 SARS-CoV-2 positive mother-infant dyads, 28 (38.9%) had a prenatal ultrasonographic abnormality. The most common findings were placentalomegaly (PM, n=17) and fetal growth restriction (FGR, n=8). When compared to healthy pregnant controls (n=17), SARS-CoV-2 positive pregnancies with abnormal ultrasound findings had distinct highly inflammatory immune profiles. 182 and 41 cytokines were significantly altered (p < 0.05, -2 < fold change > 2) in COVID19-affected pregnancies with PM and FGR, respectively. Four common serum proteins (ERBB4, TGFBR3, NCAM1, PLA2G7) were altered for both ultrasonographic abnormalities but demonstrated inverse responses with a downregulation in PM and an upregulation in FGR.

CONCLUSION: SARS-CoV-2 infected pregnancies that develop PM or FGR have distinct immune profiles consistent with a pronounced inflammatory response, providing insight into the pathogenesis of COVID19 and changes in maternal immunity following infection. The altered cytokines may serve as potential biomarkers to predict perinatal complications after SARS-CoV-2 infection in pregnancy.

TRANSVAGINAL CERVICAL LENGTH (TVCL) MONITORING POST-CERCLAGE IS ASSOCIATED WITH LOWER RATES OF PRETERM BIRTH

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OBJECTIVE: Professional obstetric societies do not currently recommend TVCL monitoring post-cerclage. However, we sought to determine whether TVCL monitoring post-cerclage confers benefit.

STUDY DESIGN: Retrospective cohort of patients carrying singleton or twin gestations at a large tertiary healthcare system, 2014-2021. All patients with a cervical cerclage placed for any indication were included. The primary outcome was delivery gestational age (considered continuously). Secondary outcomes included (a) receipt of betamethasone (b) detection of cerclage failure (finding of asymptomatic membranes prolapsing past the level of the stitch, loss of stitch integrity, ± dilation ≥ 0.5cm by SVE with the cerclage in situ); (c) rates of PTB < 37, < 34, and < 28 weeks; (d) composite severe neonatal morbidity (IVH, PVL, BPD, NEC, death before initial hospital discharge). Patients with ≥1 TVCL post-cerclage were compared to those with no TVCL post-cerclage. Multivariate Cox proportional hazards models evaluating time-to-event tested for outcomes with and without TVCL monitoring.

RESULTS: 371 patients met inclusion criteria; 240 (64.7%) had ≥1 TVCL post-cerclage. Baseline characteristics are shown in Table 1. Patients with ≥1 TVCL post-cerclage were less likely to deliver preterm < 37, < 34, and < 28 weeks’ gestation, delivered later (35.4 ± 5.0 vs. 33.5 ± 6.4, p=0.002). Further, those with ≥1 TVCL post-cerclage were more likely to receive betamethasone and had lower