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Cryotherapy and LEEP are effective treatment for CIN lesions in HIV+ and HIV- women in western Kenya

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18 Immunometabolic Analysis of *Mobiluncus mulieris* and *Eggerthella* sp. Reveals Novel Insights into Their Pathogenic Contributions to the Hallmarks of Bacterial Vaginosis



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OBJECTIVES: Bacterial vaginosis (BV) is a polymicrobial condition in which depletion of health-associated *Lactobacillus* spp. in the female reproductive tract (FRT) results in a detrimental shift to a more diverse community of anaerobic bacterial species that contribute to adverse health outcomes. These sequelae can include preterm birth (strongly linked to *Mobiluncus*) and an increased risk of contracting sexually transmitted infections (STIs). *Eggerthella* sp. may also enter the bloodstream through the FRT to cause bacteremia. Our objective was to assess the individual contributions of *Mobiluncus mulieris* and *Eggerthella* sp. to the microenvironment through immunometabolic analyses.

METHODS: We used a human 3-dimensional (3D) cervical epithelial cell model in combination with immunoproteomics (Bio-Plex) and untargeted metabolomics (LC-MS/MS) analyses to examine the potential contributions of *M. mulieris* strain UPII 28-I and *Eggerthella* sp. strain MVA1 to changes in the cervical microenvironment. Statistical differences were determined by one-way ANOVA.

RESULTS: Immunoproteomic analysis revealed significant increases in markers of genital inflammation following *M. mulieris* infection, including proinflammatory immune mediators: TNF- α ($p < 0.03$), IL-8 ($p < 0.0001$), IL-6 ($p < 0.0001$) and MCP-1 ($p < 0.001$); which may be mediated through the TLR-5 response to *Mobiluncus* flagellin. *Eggerthella* sp. infection specifically elevated IL-1 α ($p < 0.004$). IL-1 α , IL-6, IL-8 and TNF- α are commonly elevated in cervicovaginal lavages in women with BV. We found that *M. mulieris* significantly decreased cysteinylglycine which is linked to glutathione metabolism that is also linked to oxidative stress and elevated levels of inflammation in women with BV. *Eggerthella* sp. were found to be metabolic powerhouses contributing to both biogenic amine production and amino acid pathways. *Eggerthella* sp. also elevate citrulline, a urea cycle metabolite linked to inflammation.

CONCLUSIONS: Through immunometabolic analysis we identified that *Eggerthella* sp. are linked to the production biogenic amines associated with the malodor of BV, whilst *M. mulieris* is linked to genital inflammation, both important diagnostic markers of BV. Future experiments will use cocktails of these bacteria to better mimic the polymicrobial nature of BV and vaginal dysbiosis.

19 Injection Drug Use Associated Infections are a Major Determinant of Maternal Morbidity in Pregnant Persons with Opiate Use Disorder



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OBJECTIVES: Infectious complications of injection drug use constitute a major medical morbidity underrecognized in the setting of the opioid epidemic. Persons who inject drugs are at risk for acquiring invasive bacterial infections and these infections are increasing in parallel to the opioid epidemic. National attention has been drawn to the opioid epidemic in pregnant people and the development of neonatal abstinence syndrome, yet these life-threatening infectious complications have not been characterized. Our primary objective was

to determine the rate of injection drug use associated infection (IDUI) complications in patients admitted to our obstetric unit with opioid use disorder (OUD). Our secondary objective was to determine if these infections were associated with maternal or neonatal morbidity and if these could be stratified by self-reported route of use.

METHODS: This was a retrospective cohort study of a random sampling of 200 women and 81 matched infants admitted 2011-2018 identified by ICD-9 code for OUD in pregnancy. Detailed chart review collected maternal and neonatal characteristics and outcomes. Composite maternal morbidity included ICU admission, intubation, or admission >7 days. Social risk factors included incarceration, sex work, intimate partner violence, housing instability, and department of human services involvement prior to presentation. IDUI were defined as pneumonia, bacteremia, deep skin infection, endocarditis, septic arthritis, osteomyelitis requiring parenteral treatment. Statistical analysis was performed using Fishers exact test and students t test.

RESULTS: Of the records reviewed, 10% (n=20) had IDUI. Bacterial endocarditis occurred in 4 (2%) and all occurred in women who reported IV drug use. Composite maternal morbidity was high in this patient population (n=41, 20.5%) and was associated with IDUI (66.7 vs 16.2% $p < 0.0001$). Self-reported IV route of use (25.3 vs 10.8%; $p = 0.017$) and greater than 3 social risk factors (31.4 vs 16.9% $p = 0.043$) were also associated with maternal morbidity. Other factors including age, BMI, preexisting medical conditions, tobacco use, and use of multiple substances were not associated composite maternal morbidity. Neonatal morbidity, preterm birth and growth restriction were not associated with IDUI.

CONCLUSIONS: Infectious complications, including endocarditis, in pregnant women with OUD are greater than what is reported in the non-pregnant population. These are associated with increased maternal morbidity. Physiologic immune alterations of pregnancy might increase the risk of IDUI and therefore a detailed history and infection focused clinical exam is warranted when caring for this patient population.

Pregnancy Characteristics	Total N=200	Injection use (n=134)	Other route of use (n=65)	p value
Age	28.6	27.8 ± 0.4	30.05± 0.6	0.004
GA at presentation (days)	119	113± 6.0	132± 8.4	0.07
GA at delivery (days)	259	258 ± 4.6	260 ± 5.1	0.84
Average LOS (days)	4.3	16±10	4±1.0	0.41
Tobacco use	89.5%	125 (95.4%)	54 (88.5%)	0.08
Multiple substances used	58.5%	82 (61.2%)	35 (54.8%)	0.32
>3 Social Risk Factors	13%	24 (17.90%)	3 (4.60%)	0.01
Composite maternal morbidity	20.5%	34 (25.4%)	7 (10.8%)	0.017
ICU admission	5%	9 (6.7%)	1 (1.5%)	0.11
Intubation	1.5%	3 (2.2%)	0	0.22
Infectious morbidity				
Injection use associated infections	10%	19 (14%)	1 (1.5%)	0.005
Endocarditis	2%	4 (3%)	0	0.15
Skin infections (Cellulitis/Abscess)	6.5%	12 (9.0%)	1 (1.5%)	0.04
Disseminated infection	7.5%	13 (9.7%)	2 (3.1%)	0.09

20 Cryotherapy and LEEP are Effective Treatment for CIN Lesions in HIV+ and HIV- Women in Western Kenya



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OBJECTIVES: Cervical cancer is the third most common cancer worldwide and the most common cancer among Kenyan women, with an age-standardized incidence rate of 33.8% in 2018. Cervical intraepithelial neoplasia (CIN) caused by human papillomavirus (HPV) in HIV+ women is over twice as likely to progress in severity compared to HIV- women. Conflicting reports exist as to the efficacy of cryotherapy or loop electrosurgical excision procedure (LEEP) as treatment for CIN among HIV+ women. This study assesses the results of cryotherapy or LEEP for CIN among HIV+ compared to HIV- women in Western Kenya.

METHODS: One-hundred and twenty HIV+ (60 cryotherapy, 60 LEEP) and 120 HIV- (60 cryotherapy and 60 LEEP) women were intended to be enrolled after a positive visual inspection with acetic acid (VIA). However, only 86 HIV+ (39 cryotherapy, 47 LEEP) and 89 HIV- (46 cryotherapy, 43 LEEP) who had follow-up of 24 months were included in this analysis. Women were eligible for cryotherapy if the lesion covered <75% of the transformation zone, did not extend into the endocervical canal, and was not \geq CIN 2 on histology. Women ineligible for cryotherapy underwent colposcopy/biopsy and those with confirmed CIN 2/3 underwent LEEP. Women were followed every 6 months with VIA, Pap smear or colposcopy/biopsy. Cryotherapy failure was defined $>$ low grade intraepithelial lesion (LSIL) on Pap smear or \geq CINI on histology, LEEP failure was defined as high grade intraepithelial lesion (HSIL) on Pap smear or \geq CIN 2 after treatment. Chi square and Fishers' exact tests were used to compare the proportions.

RESULTS: There was no statistically significant difference in treatment failure rates between HIV+ and HIV- patients (10.1% v 19.8% p = 0.09). Among patients who underwent cryotherapy, there was no statistically significant difference in treatment failure between HIV+ and HIV- women (18% v 4.4%, p = 0.073). No statistically significant difference in treatment failure was observed among HIV+ and HIV- women who underwent LEEP (16.3% v 21.3%, p = 0.599). No statistically significant difference in treatment failure was observed between all patients in the LEEP arm compared to those in the cryotherapy arm (10.6% v 18.9% p = 0.141). Seventy-four percent of HIV+ women were on antiretroviral therapy (ART) during the study, and 91% had been on ART during or prior to the study. Mean CD4 count among HIV+ women was 580.

CONCLUSIONS: In our experience, cryotherapy and LEEP are effective treatment for HIV+ and HIV- women if done for appropriate CIN lesions in low-resource settings.

21 SARS-CoV-2 Virus Not Detected in Meconium Samples of Neonates Born to COVID-19 Positive Parturients

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OBJECTIVES: The aim of this study was to examine newborn meconium PCR positivity rates in both asymptomatic and symptomatic COVID-19 positive gravidas after delivery.

METHODS: A total of 20 PCR confirmed SARS-CoV-2 positive full-term gravidas who presented to a tertiary care center with a singleton gestation were studied. Following delivery, all 20 neonates were routinely tested by RT-PCR from nasal and oropharyngeal swabs.

Additionally, the inner portion of early meconium samples was retrieved from all 20 neonates. RNA extraction was performed from each meconium sample using the QIAamp Viral RNA protocol (Spin Protocol) (Qiagen, US).

RESULTS: Of the 20 pregnant patients enrolled, 5 were clinically symptomatic. Symptoms included diarrhea, fever, and shortness of breath. One patient with fever also presented with premature rupture of membranes. Eleven patients had cesarean deliveries, and 9 delivered vaginally. The early meconium passages were collected within 60 hours from time of delivery, with a mean collection at 16 hours. All meconium samples were PCR negative. Additionally, all newborn nasal and oropharyngeal PCR swabs were negative. No neonates showed clear symptoms of COVID-19, although 3 that were delivered by cesarean section had transient tachypnea, 1 had a low initial temperature, and 1 had a desaturation event which resolved spontaneously.

CONCLUSIONS: The SARS-CoV-2 virus is known to be harbored in the gastrointestinal tract of adult and pediatric COVID-19 patients, and fecal samples have been shown to remain positive after nasopharyngeal PCR becomes negative. Newborn meconium is recognized to be highly reflective of the in-utero environment, and theoretically could reflect COVID-19 positivity for fetuses exposed to the virus. Of the 20 patients presented in this study with COVID-19 positivity in labor, regardless of symptomatology, meconium samples of their neonates did not reveal SARS-CoV-2 virus on PCR. The findings presented here are consistent with previous studies that demonstrate a very low likelihood of vertical transmission. Studies are underway attempting to enrich the subject pool by including only symptomatic gravidas infected earlier in pregnancy.

22 The NRF2/Keap1/p62 Pathway Governs the Host Response to Urinary Tract Infections

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OBJECTIVES: Investigate redox stress response in urothelial cell defense against invading Uropathogenic *Escherichia coli* (UPEC) during Urinary Tract Infection

METHODS: Bladder carcinoma 5637 cell lines, henceforth referred to as urothelial cells, were used as an *in vitro* model of UPEC infection. The oxidative stress response of urothelial cells post UPEC infection was measured using Reactive oxygen species (ROS) specific dye H2DCF-DA. At different time intervals post-infection, protein and mRNA were analyzed to dissect the temporal response of urothelial cells. At fixed time post-infection, the UPEC expulsion rate and intracellular UPEC load were estimated. Consequently, we developed KEAP1-deficient cells using CRISPR-Cas9 displayed over activated NRF2. *in vitro* data was validated using *Nrf2*^{-/-} mice. Finally, Dimethyl fumarate (DMF), an FDA-approved NRF2 inducer, was tested *in vitro* and *in vivo* for its effect on UTI course.

RESULTS: We report a whole suite of mechanisms the host uses to expel UPEC from bladder epithelial cells and based on the mechanism, we identify a potential new treatment strategy to improve bacterial clearance and UTI outcomes. We show that the NRF2 pathway is activated in response to UPEC-triggered ROS production, reduces ROS production, inflammation, and cell death, promotes UPEC expulsion, and reduces bacterial load. In contrast, loss of NRF2 leads to increased ROS production, bacterial burden, and inflammation, both *in vitro* and *in vivo*. NRF2 promotes UPEC expulsion by regulating transcription of the RAB GTPase, RAB27B. Finally, Dimethyl fumarate, an FDA-approved NRF2 inducer, reduces inflammatory

