Filling the Gap in Women’s Health Research | Nichole Duran Mahnert, MD

Here at Banner University Medical Center Phoenix (BUMCP), we are diligently working to build a robust clinical research program within the department of Obstetrics and Gynecology. Over the past 5 years in partnership with the University of Arizona College of Medicine Phoenix (UACOMP) we have grown our scholarship opportunities and output considerably. Our medical students, residents, fellows, faculty, basic/translational scientists, and clinical research staff have worked alongside each other to guide our scholarship vision. Scholarship in the form of research, advocacy, technology development, quality improvement, and community outreach are all important avenues to advance our shared duty to support and advance women’s health care. Our residents and fellows must complete a scholarly project over the course of their training and the quality produced is continually more impressive. We have presented our data with posters and presentations at national and international conferences, changed our hospital and clinic systems processes as the result of quality improvement projects, obtained grants to continue our research, grown our collaborative team, and published manuscripts. We look forward to continued growth and scholarship development over the years to come.

Women are the primary health care decision makers, and more likely to have health insurance and regularly use health care. Despite this, women’s health problems have been underfunded and deserve more attention to improve the quality of care that we provide. From 2008 to 2018 total NIH funds dedicated to women’s health increased by only 2% from 12% to 14%. The need for research dedicated to all aspects of focused women’s health is clear. Specific to reproductive health and family well-being, obstetrician/gynecologists play an important role to both drive the necessary research and to implement evidence-based health care. A few key topic areas that require further investigation include maternal health and menstrual disorders.

Maternal mortality is increasing in the United States and most of those deaths are preventable. Of alarming concern is that maternal mortality and morbidity among Black and Native American women is 2 to 3 times higher than white women. In Arizona where Medicaid covers over 50% of births, the maternal mortality rate is higher than the national average. With the recent postpartum medicaid expansion, maternal insurance coverage will extend through the first year after birth, a critical step to care for moms and families. Valley obstetricians are working to improve the quality of care in our community with specialized care such as the placenta accreta program led by PPA and our Maternal Fetal Medicine fellows, and the trauma in pregnancy protocol that was instituted at BUMCP. Robert Garfield, PhD is conducting
Filling the Gap in Women’s Health Research, continued

cutting edge research to examine the muscle contractility in labor, and along with Dr. Kendra Gray their work was recently published. With grant funding Dr. Maria Manriquez initiated an intensive outpatient treatment program for pregnant women with substance abuse disorders at BUMCP Women’s Institute, in addition to her other multiple other research projects dedicated to this important field. Lastly, our residents joined a COVID in pregnancy database in collaboration with our colleagues at Dignity Health and Valleywise to learn more about the pandemic effects among our pregnant population. With a busy Obstetric service, BUCMP is working to create an environment that is safe for moms and families.

Menstrual irregularities and pelvic pain are increasingly common as women have about 400 episodes of bleeding in current times compared to 40 in the past. These symptoms contribute to a large monetary, emotional, and physical cost to women and society. March was endometriosis awareness month, and we are reminded that the diagnosis of endometriosis is delayed by at least 7 years and many women are not offered sufficient treatment. The current treatments for bleeding and pain regardless of etiology are not adequate. We have ongoing research projects to examine the diagnosis, progression and treatment of endometriosis and pelvic pain. Specifically, we are examining the gut and vaginal microbiome among women with chronic pelvic pain with and without endometriosis with Dr. Herbst-Kralovetz and her lab. We have more projects on the horizon to fill the unmet needs of diagnosis and treatment among women with chronic pelvic pain and menstrual irregularities. In the space of surgical quality and safety our Gynecologic Surgery Fellows created a hysterectomy database and continue to find ways to improve perioperative surgical care. Our ultimate goal is to provide the highest quality surgical care that women deserve.

In a holistic approach to women’s health care, we have collaborated with Jennifer Huberty, PhD to investigate the role of yoga in pregnancy and the utility of the mobile meditation application among obstetrics and gynecology patients in the setting of the COVID 19 pandemic and it has been accepted for publication. The CALM application was well received by patients and we will apply this mode of meditation as part of a larger prehabilitation program for our preoperative patients. Dr. Kelley Saunders who co-leads our integrative medicine program is looking at ways to alleviate stress among trainees and faculty.

The COVID pandemic has significantly impacted us and our patients and highlights society’s dependence on women on the front lines (70% of health care workers) and at home taking care of families. Obstetrician/gynecologists are composed of a female majority and are not immune to unique pandemic effects on women. As a result, other important projects led by our residents and students include the impact of gender and race inequities not only in patient care outcomes, but also among physicians, and the impact on well-being and patient care delivery.

We are always excited to foster collaboration and look forward to hearing from you for future scholarly projects to improve the quality of women’s health care in our community.

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The Microbiome and Women’s Health | Melissa M. Herbst-Kralovetz, PhD

Background on the Vaginal Microbiome
In recent years, we have expanded our understanding of the microbiome, the collection of microorganisms, their genomes and the surrounding microenvironment at a particular site, and its relationship to health and disease. Despite these recent advances, we have known about the importance of lactobacilli to women’s health since the 1800s when first described by Dr. Döderlein, a German obstetrician/gynecologist as Döderlein’s bacillus later renamed lactobacillus. Lactobacilli dominate the vaginal microbiome in healthy, premenopausal women. Vaginal microbiota not dominated by lactobacilli have been increasingly identified to be associated with a variety of poor reproductive, obstetric and gynecologic sequelae and is an established risk factor for acquisition of sexually transmitted infections (STI). Bacterial vaginosis (BV) is the most common vaginal disorder in reproductive age women and is characterized type by a lack of lactobacilli dominance and the presence of a diverse array of facultative and obligate anaerobic bacteria.

What do these Vaginal Bacteria DO?
Dogma has suggested that lactobacilli lower vaginal pH and set up a STI-resistant environment through production of lactic acid, other metabolites and antimicrobial factors; however, more research is needed to understand the protective mechanisms employed by these beneficial bacteria. We are beginning to understand that not all lactobacilli species are the same in terms of their protective mechanisms. In addition, understanding the functional impact of the BV-associated anaerobic organisms in the local microenvironment is a focus of the Herbst-Kralovetz laboratory. Many of the BV-associated organisms, including Prevotella, Gardnerella, Atopobium, Sneathia, Megasphaera are understudied bacteria. In addition, we don’t know much about how these organisms interact with the cells lining the reproductive tract to cause disease. We have ongoing multi-omics analyses in the laboratory to better understand these mechanisms. We hypothesize along with others that these organisms have distinct functions and roles in BV as reviewed recently in Muzny et al, Current Opinions in Infectious Diseases, 2020. We utilize human 3-dimensional models of the vagina, cervix and endometrium to study host-microbe interactions along the continuum of the female reproductive tract (See Gardner et al, Journal of Infectious Diseases, 2020). These robust 3-D model systems can be also used as preclinical screening tools to evaluate vaginally-applied compounds for safety and toxicity. Recently, we used our human 3-D vaginal epithelial model to evaluate a panel of commercial and clinical vaginal lubricants and found a distinct relationship between osmolality and vaginal immunotoxicity (Wilkinson et al, Journal of Infectious Diseases, 2018). We expanded these studies to evaluate their impact on lactobacilli species and found that select lubricants, particularly ones containing chlorhexidine gluconate had the most impact of lactobacilli growth (Laniewski et al, Sexually Transmitted Diseases, 2021). To better understand the impact of these bacteria on the local microenvironment, we have utilized vaginal swabs and cervicovaginal lavages to evaluate immunometabolic changes related to vaginal microbiota composition and cancer (See Ilhan et al, EBioMedicine, 2019, Laniewski et al, Scientific Reports, 2019 and Laniewski et al, npj Precision Oncology, 2020). Coupling in vitro studies with phenotypically characterized biospecimens is necessary to better understanding the BV enigma. Future studies are focused on longitudinal study designs to monitor these vaginal bacterial communities and changes in the microenvironment over time.

Who is Impacted by Vaginal Dysbiosis and BV?
Rates of BV range from 23–52% of premenopausal women. Minority women are disproportionally impacted by BV and have higher rates of vaginal dysbiosis relative to non–Hispanic white women. Black and Mexican American women have significantly higher rates of 51.6% and 32.1% respectively relative to white, non–Hispanic women (23.3%). These higher rates of BV relate to increased adverse women’s health outcomes. As a part of the Women’s Health Research Program, we are dedicated to studying women in Arizona and our catchment area. This means expanding our efforts to thoughtfully enroll ALL women in our clinical/translational studies particularly women from underrepresented, underserved and understudied races/ethnicities. Socioeconomic, racial/ethnic, genetic/host, behavioral and environmental factors all influence the vaginal microbiota composition as depicted in Figure 1 from our Nature Reviews Urology report. For example, race/ethnicity, age, number of sexual partners, use of hormonal contraceptives, menopausal status, smoking, alcohol consumption, and douching all affect the prevalence of BV. To better understand race/ethnicity, the vaginal microbiome and HPV infection, we are supported by the National Cancer Institute to study the vaginal microbiota in American Indian/Alaska Native HPV positive and negative women partnering with NAU and a local clinic in Flagstaff, AZ.
Cancer and Vaginal Microbiota
Recently, our group and others have identified non-lactobacilli dominant vaginal microbiota to be associated with HPV infection and the severity of cervical neoplasia (see Laniewski et al, Scientific Reports, 2018). In our report, we identified specific bacteria associated with Hispanic ethnicity and found on average women that self-reported as Hispanic had higher vaginal pH and lower lactobacilli dominance. We hypothesize that vaginal microbiota play a role in HPV persistence and progression to invasive cancer as well as other gynecologic malignancies. We recently reviewed this topic for Nature Reviews Urology, 2020 in terms of the potential role of vaginal microbiota in the development of gynecologic cancers. In this report, we highlight the data supporting the role of vaginal microbiota and cervical cancer, the putative role of ascension of vaginal microbiota and the etiology of endometrial and ovarian cancer as well as potential impact of microbiota on therapeutic outcomes and toxicity related to cancer treatment.

Vaginal Microbiota and Other Women’s Health Outcomes
As a part of the Women’s Health Research Program and Microbiome Initiative at the University of Arizona, College of Medicine-Phoenix, our team of researchers and clinical research coordinators (pictured below) are partnering with clinicians, fellows, residents and researchers across Arizona and beyond to tackle unanswered questions in women’s health as represented in Figure 2. We are grateful for these collaborative partnerships with clinics and hospitals throughout the Phoenix metroplex and Arizona, support of Dr. Foley and the Department of Obstetrics and Gynecology at UA College of Medicine-Phoenix and we are interested in expanding our efforts and collaborations.

We are also grateful for funding from the National Institutes of Health (NIAID, NCI and the Office of Research on Women’s Health), Alternatives Research and Development Foundation, Mary Kay Foundation, Flinn Foundation and Valleywise Research Partnership that supported many of these studies. Please reach out to Dr. Herbst-Kralovetz at mherbst1@email.arizona.edu for more information, follow her @HerbstKralovetz on Twitter or at her lab website at https://herbstkralovetzlab.weebly.com

References Cited in The Microbiome and Women’s Health
Invited Lecture: In Honor of Dr. Cherny & Dr. Sattenspiel

Dr. John Elliott is an internationally recognized authority in Maternal-Fetal Medicine who has distinguished himself both as a practicing physician and educator. He teaches at national and international meetings, conferences, and local symposiums. Dr. Elliott has a unique and unparalleled ability to care for high-order multiple gestations. He has proven success in being able to consistently achieve highest gestational age for high-order multiple deliveries.

Lessons Learned from 36 Years of Caring for High Order Pregnancies

**Speaker:** Dr. John Elliott – Banner University Medical Center - Phoenix  
**When:** May 17, 2021 - 12:30 – 1:30PM  
**Where:** Via Zoom: https://arizona.zoom.us/j/86845228584  
**Password:** obgyn  
CME provided by The University of Arizona College of Medicine – Tucson. Participants must sign in and be present for the full hour to receive 1.0 AMA PRA Category 1 Credit(s)™ | No partial credit will be awarded.

Welcome! New Class of OBGYN Residents and Fellows Joining BUMC-P June 2021

**Speaker:** Dr. John Elliott – Banner University Medical Center - Phoenix  
**When:** May 17, 2021 - 12:30 – 1:30PM  
**Where:** Via Zoom: https://arizona.zoom.us/j/86845228584  
**Password:** obgyn  
CME provided by The University of Arizona College of Medicine – Tucson. Participants must sign in and be present for the full hour to receive 1.0 AMA PRA Category 1 Credit(s)™ | No partial credit will be awarded.

Invitation to Participate:  
Banner OBGYN Virtual Tumor Board Conference  
Interesting and instructive cases from OB/GYN and Gyn Oncology.  
**Hosted by:** Dr. Mike Keeney and Dr. Lyndsay Willmott  
**When:** Every 2nd and 4th Tuesday of the month at 6:45 a.m.  
**Where:** Via Zoom: https://us04web.zoom.us/j/74318550124  
**Password:** password  
Or call in (audio only) 480-378-7231  
Conference ID: 699 457 016#

Four Decades and Counting – A Short History of Nearly Everything in OBGYN

**Speaker:** ACOG President – Elect J. Martin Tucker, MD  
**Where:** Banner University Medical Center - Phoenix  
**When:** May 24, 2021 - 12:30 – 1:30PM  
**Password:** obgyn  
CME provided by The University of Arizona College of Medicine – Tucson. Participants must sign in and be present for the full hour to receive 1.0 AMA PRA Category 1 Credit(s)™ | No partial credit will be awarded.

If you enjoyed this issue of Women’s Health Update and would like to receive future issues electronically, please let us know at: BUMCP_Womens_Health_Update@bannerhealth.com  
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