Meet Our COVID-19 Warriors

Leading and guiding nationally recognized research, policy and patient care during a pandemic
The comprehensive work of Duke Ob/Gyn’s COVID-19 Warriors is ongoing and impactful, and it continues to influence patient care and future protocols in women’s health, and inclusion in clinical trials. They demonstrate an unyielding commitment to advocacy, leadership and patient care and have provided the tools to address issues that affect obst/gyn care in our community and across the U.S.
As the Department was about to prepare the final version of this publication for distribution, we learned of the passing of Charles B. Hammond, MD, a renowned educator, researcher, advocate for women’s health and obstetrician/gynecologist. Dr. Hammond was a mentor to many, myself included.

Dr. Hammond was the Edwin Crowell Hamblen Distinguished Professor of Reproductive Biology and Family Planning and Chair of the Department of Obstetrics & Gynecology from 1980 to 2002, and was a leader in academic Ob/Gyn at Duke and nationally for over 40 years. He received his medical degree from Duke University in 1961. During the next nine years, he completed an internship in surgery, a residency in obstetrics and gynecology and a one-year interval in the research training program, all at Duke, as well as two years as a clinical associate in the endocrinology branch at the National Institutes of Health in Bethesda, Maryland.

A nationally recognized expert in menopause and hormone replacement therapy, Dr. Hammond was also a pioneer in the treatment of gestational trophoblastic disease and founded the Southeast Regional Trophoblastic Disease Center. Countless lives were saved as a result of his innovative research and the development of treatment regimens for this once life-threatening condition.

Dr. Hammond served as President of a number of professional organizations, including the American College of Obstetricians, the American Gynecological and Obstetrical Society, the American Society for Reproductive Medicine, and the North Carolina Ob-Gyn Society.

Although not possible to present all of his accomplishments here, we are dedicating this issue of Duke Ob/Gyn to this exceptional leader and role model who was an inspirational and influential physician in our field. He will be greatly missed.

MESSAGE FROM THE CHAIR

Sincerely,

Matthew D. Barber, MD, MHS
E.C. Hamblen Professor and Chair
Duke Ob/Gyn
When the World Health Organization declared the COVID-19 outbreak a pandemic on March 11, 2020, Duke Ob/Gyn was at the ready to jump into action, regrouping day-to-day operations, prioritizing resources and strategizing best practices in patient care at a pace that will forever be associated with the devastating global event – warp speed. With the same level of laser focus as the Department of Health and Human Services’ Operation Warp Speed mandate to develop an effective, safe vaccine in record time, Duke Ob/Gyn experts in the Center for Reproductive Infectious Diseases and Immunology deployed their resources to help create national guidelines and policies and initiate research to improve the care of pregnant patients during the pandemic. The resulting work led by Duke serves as reference materials for The Society for Maternal-Fetal Medicine (SMFM) and the American College of Obstetricians and Gynecologists (ACOG), among others. Duke faculty are also leading clinical trials for a COVID-19 vaccine. On a local and national level, Department faculty have ensured that cancer patients’ needs and concerns are addressed, advocated on behalf of at-risk patients and...
populations and supported efforts to ensure that pregnant and lactating women are included and represented. The comprehensive work of Duke Ob/Gyn’s COVID-19 Warriors is ongoing and impactful, and it continues to influence patient care and future protocols in women’s health, and inclusion in clinical trials. They demonstrate an unyielding commitment to advocacy, leadership and patient care and have provided the tools to address issues that affect ob/gyn care in our community and across the U.S.

Leading By Example
In mid-March of 2020, ACOG released its Practice Advisory on COVID-19 and the protocol for outpatient assessment and management of pregnant patients with suspected COVID-19, co-authored by Brenna Hughes, MD, MSc, Vice Chair for Obstetrics and Quality. Updates have been ongoing. The document addresses community mitigation efforts and inequities in racial and ethnic minority populations and offers a Physician FAQ.

“As since the start of the pandemic, the SMFM has developed a series of clinical guidance documents and online learning opportunities for obstetric care providers. We made these resources open access with the goal of synthesizing complex and rapidly changing information for clinicians,” said Judette Louis, MD, MPH, President of SMFM. “As a member of SMFM’s COVID Task Force, Dr. Hughes has played a critical role in the development of these resources. And while she certainly has a positive impact on the care of pregnant people in North Carolina on a daily basis, her work with SMFM has improved the care of pregnant people and their families around the world.”

As a member of SMFM’s COVID Task Force, Dr. Hughes has played a critical role in the development of these resources. And while she certainly has a positive impact on the care of pregnant people in North Carolina on a daily basis, her work with SMFM has improved the care of pregnant people and their families around the world.

— Judette Louis, MD, MPH, President of SMFM

• Dr. Hughes also participates on both the National Institutes of Health Panel and the Department of Health and Human Services Panel on Guidelines for The Management of COVID-19, appointed by Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases. She has offered insight about treatment recommendations and pregnancy considerations for the recommendations that come out of the panel. At the request of the HHS Office of the Secretary, and in conjunction with the White House Task Force, the COVID-19 Treatment Guidelines Panel was created to provide frequently updated information to the public.
The authors emphasize that pregnant individuals should be given the opportunity, along with their obstetric provider, to weigh the potential risk of severe maternal disease against the unknown risk of fetal exposure, and make an autonomous decision about whether or not to accept the vaccine until pregnancy safety data are available.

Most recently, Dr. Hughes co-authored the ACOG/SMFM Joint Statement on World Health Organization recommendations regarding COVID-19 vaccines and pregnant individuals.

Guidance on Vaccination and Pregnancy

Drs. Swamy and Hughes, and MFM Fellow Amanda Craig, MD, published COVID-19 Vaccines in Pregnancy in AJOG MFM, recommending that COVID-19 vaccines should not be withheld from women solely based on their pregnancy or lactation status when they otherwise meet criteria for vaccination.
COVID-19 as part of the SMFM Weekly COVID-19 Update series. She collaborated on the creation of an infographic titled Strategies to Provide Equitable Care During COVID-19 as a national resource (see graphic).

Dr. Wheeler addressed why COVID-19 inequities exist and importantly posed the question, What can we do?

“We are all equals in the eyes of this virus, and therefore should all be taking precautions as such,” notes Dr. Wheeler in the presentation.

“SMFM’s advocacy agenda prioritizes health equity and supports policy proposals that are aimed at eliminating health care inequities for high-risk pregnant women.”

Dr. Wheeler most recently presented on “Preterm birth disparities at a single United States academic institution during the COVID pandemic” with colleagues at the 2021 SMFM Pregnancy Meeting.

Remdesivir and COVID-19 Pregnant Patients
Dr. Swamy and colleagues published Compassionate Use of Remdesivir in Pregnant Women with Severe COVID-19 in Clinical Infectious Diseases. The abstract describes outcomes in the first 86 pregnant women with severe COVID-19 who were treated with Remdesivir.

“I am honored to share this work, which was a tremendous team effort. Pregnant women receiving Remdesivir for COVID-19 had high rates of recovery and a low rate of serious adverse events,” noted Dr. Swamy.

Click here for a “Vaccine and Pregnancy” Q&A with Dr. Swamy. Please visit obgyn.duke.edu for additional information and updates.

We are all equals in the eyes of this virus, and therefore should all be taking precautions as such.

— Sarahn Wheeler, MD, Duke Ob/Gyn Director of Diversity and Inclusion
One year after its initial outbreak, the impact of COVID-19 continues on an unprecedented global scale. In the US, there have been more than 24 million diagnosed cases and more than 400,000 deaths. The virus has mandated radical changes in the delivery of healthcare on all levels. From primary care to acute illnesses and surgeries, patient interventions continue to look dramatically different than pre-pandemic.

Cancer care has not been immune to these challenges. It has experienced the same strain on resources and limited opportunities for in-person patient appointments as other areas of medical practice. This is especially concerning, given the fact that cancer patients are considered to be at higher risk for COVID-19 morbidity or mortality. Highly immunosuppressive chemotherapy regimens, as well as the possibility of exposure to the virus during treatment, contribute to additional risk.

Duke Cancer Institute gynecologic oncologist Angeles Alvarez Secord, MD, MHSc, has done extensive work to develop best practices during the crisis to minimize risk to patients from deviations in cancer care and from COVID-19 morbidity.

Dr. Secord was part of an expert panel convened by the Society of Gynecologic Oncology (SGO) to develop consensus guidelines regarding therapy during the COVID-19 pandemic with respect to gynecologic cancer care and clinical trials. The panel’s work was published in the SGO’s *Gynecologic Oncology* journal. In *Anti-cancer therapy and clinical trial considerations for gynecologic oncology patients during the COVID-19 pandemic crisis*, Dr. Secord’s team conducted in-depth studies of multiple disease states and populations, factoring in the unpredictability of care delivery and the need to limit visits to healthcare facilities. They concluded that more widespread use of telemedicine was indicated whenever appropriate. Additionally, the group recommended that providers choose treatment regimens which require less frequent visits and are less immnosuppressive.

Dr. Secord also co-authored *COVID-19 and ovarian cancer: Exploring alternatives to intravenous (IV) therapies*, an article appearing in *Gynecologic Oncology*. Her work in this effort focused on minimizing patient visits to hospitals and cancer clinics in order to mitigate the spread of COVID-19.
This study concluded that oral therapies may be viable alternatives to IV treatment of ovarian cancer, especially in virus hotspots. There are several classes of oral agents that can potentially serve as alternatives to IV therapy, including cytotoxic chemotherapy, inhibitors of poly (ADP-ribose) polymerase (PARP), targeted agents and hormonal therapies.

Dr. Secord and her team determined that patients who have persistent disease after receiving 4-6 cycles of platinum-based chemotherapy may be an appropriate candidate for maintenance therapy with an oral PARP inhibitor. Providers must assess the benefit-risk profile of each therapy and its mode of administration against factors such as the patient’s goal of care, comorbidities, need to obtain lab values and susceptibility for developing severe symptoms.

This work acknowledged that holding therapy to reduce COVID-19 exposure may not be a viable option in some cases because of concern that the patient’s cancer will progress. However, a brief treatment holiday and/or switching from IV to oral therapies may be appropriate for some patients. This conservation of healthcare resources and minimizing of inpatient or outpatient clinic visits is a simple yet powerful strategy to reduce exposure and decrease the risk of COVID-19 spread.

With the availability of the COVID-19 vaccine and its phased introduction to patients, Dr. Secord’s work regarding best practices continues. “We are following the American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines for COVID-19 vaccination recommendations and when to time the vaccine between treatments,” said Dr. Secord. “At this time there is no evidence that vaccines will not be safe for most patients with gynecologic cancer. However, patients with cancer were not included in the vaccine trials so we don’t know how safe or effective the vaccines are going to be for cancer patients. Furthermore, we do not know how patients receiving treatment will respond to the vaccine. We are recommending that people who are actively being treated for cancer get the vaccine when available, because patients with cancer are at higher risk for serious COVID-19 illness if they get the virus. We urge patients to talk with their doctors about COVID-19 vaccine recommendations.”

“We are recommending that people who are actively being treated for cancer get the vaccine when available, because patients with cancer are at higher risk for serious COVID-19 illness if they get the virus.”

— Angeles Alvarez Secord, MD, MHSc
**COVID-19 MEDIA HIGHLIGHTS**

**CNN:** COVID-19, viral mutation, antibodies and vaccines
Featuring **Geeta Swamy, MD**

**USA Today:** For pregnant and nursing women, risks of COVID-19 probably outweigh risk of vaccine, experts say
Featuring **Geeta Swamy, MD**

**National Geographic:** Should you get the COVID-19 vaccine while pregnant? Here’s what experts say.
Featuring **Geeta Swamy, MD**

**TODAY:** Pregnant women face uncertainty over getting COVID-19 vaccine
Featuring **Geeta Swamy, MD**

**Well + Good:** What Doctors Want You To Know About Pregnancy and COVID-19
Featuring **Brenna Hughes, MD, MSc**

**ABC:** Duke doctor leads national push to study COVID-19 vaccine in pregnant women
Featuring **Brenna Hughes, MD, MSc**

**Contemporary Ob/Gyn:** Pap Talk S1E2: Dr. Dotters-Katz, Duke Health on COVID-19, pandemic jam
Featuring **Sarah Dotters-Katz, MD, MMHPE**

**CBS:** Lack of data prompts COVID vaccine concerns among pregnant women
Featuring **Brenna Hughes, MD, MSc**

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**MYTH VS. FACT WITH DR. GEETA SWAMY**

I have heard if you are pregnant you should not get the COVID-19 vaccine. When we look at the risks [of COVID-19] being so significant, compared to the great benefit of the vaccine, we would recommend that pregnant women consider getting the vaccine.

I have heard that the COVID-19 vaccine will not provide my unborn child any protection from the virus. Is that true?
Based on how we know other vaccines work, there really should be the benefit of antibody transfer and therefore protection of the baby against illness.

I have heard the COVID-19 vaccine causes infertility. Is this true?
This is absolutely untrue. There is no scientific plausibility to how [infertility] would happen.

I have heard the COVID-19 vaccine is not safe if you are breastfeeding. Is that true?
Breastfeeding women absolutely, positively, should be offered the vaccine.
Duke Ob/Gyn announced the selection of the first NIH/NICHD Women’s Reproductive Health Research (WRHR) Career Development K12 Award recipients: Faculty Rebecca Previs, MD, MS (Gynecologic Oncology); and Jonas Swartz, MD, MPH (Women’s Community and Population Health).

The two faculty will participate in an extensive training program that combines cutting-edge research experiences with an innovative and proven career development framework.

Dr. Previs is a gynecology cancer specialist. Her proposal is titled “Turning ProMisE into Practice: Molecular Classification to Prognosticate Response in Medically Managed Endometrial Cancers.”

Description: Molecular characterization of uterine cancer predicts survival in patients undergoing standard of care surgery, but it has not previously been evaluated in medically managed patients. This study (1) assesses the prognostic value of molecularly characterizing patients with uterine cancer treated with a progestin-secreting intrauterine device (LNG-IUD) in a multi-institutional cohort, and (2) pilots a prospective clinical trial in patients treated with LNG-IUD for uterine cancer to evaluate feasibility of integrating molecular biomarkers.

Dr. Swartz serves as Medical Director of Family Planning and Ryan Program Director in the Division of Women’s Community and Population Health. His proposal is titled “Barriers to Postpartum Contraceptive Care, Perceived Racial Discrimination and Long-Term Maternal and Infant Health.”

Description: Better access to postpartum contraception could help mitigate North Carolina’s racial, ethnic and economic disparities in maternal and infant health. We seek to understand how barriers to postpartum care and contraceptive care, with a focus on perceived racial discrimination, affect health outcomes for women and infants.

Duke’s WRHR Scholars Award was received in the fall of 2020 by Ob/Gyn Department Chair Matthew Barber, MD, MHS (PI); Evan Myers, MD, MPH (Research Director); and Friederike Jayes, DVM, PhD (Program Coordinator).

Duke joins an impressive NIH/NICHD-funded 15-site network of Ob/Gyn Departments across the US. The program will support up to two WRHR early stage faculty at any one time.
Duke Ob/Gyn’s Center for Data Science for Women’s Health, partnering with our Quality Improvement team and clinicians in gynecologic oncology and maternal-fetal medicine, have implemented two data dashboards to evaluate potentially life-threatening gynecologic surgery complications and improve maternal morbidity and mortality. The data dashboards are utilized for evaluating venous thromboembolism (VTE), a combination of deep vein thrombosis (DVT) and pulmonary embolism (PE) after gynecologic oncology surgeries, and factors influencing the rising number of obstetric deaths.

Reaching Goals to Lower Incidence of VTE After Gynecologic Surgery

- Patients who die from PE usually succumb within 30 minutes of the event, and DVT/PE is much more common in medical and surgical hospitalized patients.\(^1\)
- VTE is the second leading cause of death in patients with cancer.\(^3\)
- PE is responsible for up to 200,000 deaths per year in the United States\(^2\) and is the most common preventable cause of hospital death, accounting for up to 10 percent of mortalities.\(^4\)
- DVT is the leading cause of preventable inpatient mortalities in the United States.\(^3\)
- Among post-operative ovarian cancer patients, the rate of PE is as high as 6.8\%.\(^5\)

“We decided on the goal of the project, and what the outcome metric and process metrics would be,” said Ob/Gyn’s Manager of Quality and Safety Kelli Kurtovic, MS, LSSBB. “The team developed definitions for outcome and process metrics and converted the definitions into queries that would pull the data from the medical records, and put the data into visualizations that allow the project team to track progress.”

The project team reviews the dashboard at least monthly to evaluate progress toward meeting the project goal and toward standardizing the processes, Kurtovic added.

“We review the charts of patients who developed VTEs to learn if we should have done something differently with that patient, and if so, we implement interventions that will prevent the issue from happening in the future. We are continually analyzing processes, and now we’ve augmented the analysis to include all VTEs diagnosed within 30 days of admission,” said Director of Data Science for Women’s Health J. Eric Jelovsek, MD, MMEd, MSDS. “Patients benefit from this, and data is shared with all gynecologic surgeons systemwide.”

Plans for further dashboard augmentation include adding benign gynecologic surgery patients; a
VTE risk score for more accurate tracking of VTE prophylaxis administration; and tracking of wound disruptions, hemorrhages and hematomas that may result from anticoagulation. Gynecologic oncology patients receiving neoadjuvant chemotherapy as a cohort may be added to the dashboard in the future to better enable analysis of whether VTE prophylaxis implemented for this patient population in early 2020 has been effective in reducing the number of VTEs.

**Focusing on Maternal Morbidity and Mortality; Analyzing Racial, Ethnic Disparities**

The dual focus of the Data Science team included addressing both gynecologic VTE, and the climbing rate of obstetric deaths. The number of reported pregnancy-related deaths in the United States steadily increased from 7.2 deaths per 100,000 live births in 1987 to 17.3 deaths per 100,000 live births in 2017. Considerable racial/ethnic disparities in pregnancy-related mortality exist.

The overall rate of severe maternal morbidities (SMM) increased almost 200 percent between 1993 and 2014 - from 49.5 per 10,000 delivery hospitalizations in 1993 to 144.0 per 10,000 in 2014.

“We used the CDC’s definitions for SMMs, which included the specific diagnosis codes for each SMM. The collaborative team enabled a system to pull the data from medical records and put the data into visualizations,” said Vice Chair for Obstetrics and Quality Brenna Hughes, MD, MSc.

Using the Dashboard Effectively

The dashboard will help the quality improvement team focus its efforts. The dashboard includes race, ethnicity, age and insurance status, thereby allowing the team to analyze each SMM for each demographic, and to understand where care may not be equitable, notes Kurtovic.

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**Pregnancy-related mortality ratios 2014–2017**

(references included in article)

- 41.7 deaths per 100,000 live births for non-Hispanic Black women
- 28.3 deaths per 100,000 live births for non-Hispanic American Indian or Alaska Native women
- 13.8 deaths per 100,000 live births for non-Hispanic Asian or Pacific Islander women
- 13.4 deaths per 100,000 live births for non-Hispanic White women
- 11.6 deaths per 100,000 live births for Hispanic or Latina women

In October 2020, urogynecologist J. Eric Jelovsek MD, MMed, MSDS, received the 2020 American Urogynecologic Society (AUGS) Innovation Lectureship Award at the Society’s Annual Pelvic Floor Disorders (PFD) Week Conference. The prestigious award recognizes an individual who has contributed innovative leadership in urogynecology, specifically demonstrating excellence in the development of new techniques, technology, outcome measures, educational initiatives and/or product development.

Dr. Jelovsek was nominated and selected for his innovation in the application of advanced predictive analytics and machine learning to develop clinical calculators used “at the point of care” to guide treatment and prevention of pelvic floor disorders.

Additionally, during PFD Week, Dr. Jelovsek was also awarded Best Clinical Abstract for the paper *Success and failure are dynamic, recurrent event states after surgical treatment for pelvic organ prolapse*. Dr. Jelovsek was lead author, and Matthew Barber, MD, MHS, Duke Ob/Gyn Department Chair, was co-author.

Here is an overview of Dr. Jelovsek’s research on machine learning, clinical prediction tools and surgical outcomes.

**What is the focus of your research?**

The focus has been around the development of clinical prediction tools. Clinical prediction is at the heart of medical decision-making.

**How do you frame your clinical prediction questions?**

The best clinical prediction questions start with the physician and the patient. Just imagine – if I had a tool that could provide me with a prediction for this patient, would it be useful? Also, when designing a reading or a study about risk factors, ask yourself – would this have been better framed as a prediction model that was designed and evaluated for providing predictions for the individual

We now know that in about 25% of the cases that these women move back and forth from success to failure over time. This affects how we estimate failure rates for our surgical procedures. It also affects what we end up doing and recommending for patients. We have to relook at using a composite failure definition or composite success definition of our outcomes for women. And in future trials, we need to modify our analysis techniques to account for longitudinal data that changes over time.

— J. Eric Jelovsek, MD, MMed, MSDS
patient? Some traditional research studies are not considered clinical prediction studies, but they should be, so reframing such questions into those aimed at building and validating prediction models would benefit our patients.

Moving onto your Best Clinical Abstract award, what are the key points or highlights from your study?

The study really brings into question the value of having a single composite surgical outcome that we’ve used in several large randomized controlled trials. We found in this study that subjective outcomes, objective or anatomic outcomes and retreatment are perceived as slightly different outcomes by patients. Therefore, combining them into a composite outcome becomes problematic.

The second major finding is that we now have some good evidence that these outcomes change over time. We used to believe that once a woman failed after prolapse surgery that she stayed a failure. We now know that in about 25% of the cases that these women move back and forth from success to failure to success over time. This affects how we estimate failure rates for our surgical procedures. It also affects what we end up doing and recommending for patients. We have to relook at using a composite failure definition or composite success definition of our outcomes for women. And in future trials, we need to modify our analysis techniques to account for longitudinal data that changes over time.

Credit: AUGS/PFD Week Interviews

“Clinical prediction is at the heart of medical decision-making. . . . The best clinical prediction questions start with the physician and the patient.”

— J. Eric Jelovsek, MD, MMEd, MSDS
In 2015, Anne Steiner, MD, MPH (left), Division Chief of Reproductive Endocrinology and Infertility and Medical Director of the Duke Fertility Center, published a landmark study on the prediction model for women considering oocyte freezing for fertility preservation. Using this model, women are able to predict their probability of achieving a live birth should they choose to freeze or not to freeze their eggs at any given age. Later, a similar model was created to help women receiving high- and low-risk gonadotoxic chemotherapy predict their probability of achieving a live birth should they choose to or decline oocyte cryopreservation prior to chemotherapy.

Women receiving chemotherapy regimens deemed as “intermediate” risk for causing premature ovarian insufficiency have a 20-70% chance of amenorrhea. In the first study, Dr. Acharya’s team sought to identify patient and treatment factors to predict personalized risk of premature ovarian insufficiency following chemotherapy. The team of Duke investigators, including Duke Ob/Gyn resident Esther Chung, MD, and Duke REI fellow Benjamin Harris, MD, MPH, obtained primary data from five prior prospective studies of young women receiving chemotherapy. Combining the data and using machine learning, they were able to create a scoring system that predicted the individualized risk of premature ovarian insufficiency with an accuracy of 80%. The team is currently seeking to further
validate the model and create a user-friendly, Web-based fertility risk calculator.

In an attempt to further help cancer patients facing gonadotoxic therapy, Dr. Acharya and her team sought to determine the most cost-effective method for fertility preservation: mature oocyte cryopreservation or ovarian tissue cryopreservation. A decision analytic cost-effectiveness model was created. They found that oocyte cryopreservation is significantly more effective, but markedly more costly, than ovarian tissue cryopreservation. However, the findings indicated that lowering the high entry cost of oocyte cryopreservation and increasing its utilization can significantly impact its overall cost-effectiveness.

Where To Next?

The Division of REI continues to advance research that will allow for more personalized medicine in reproductive endocrinology and infertility. Dr. Harris is currently conducting a follow-up study of the women enrolled in the Time to Conceive (TTC) Study, the prospective, time-to-pregnancy cohort study referenced previously.

Using data from a TTC follow-up cohort, Dr. Harris is investigating the association between markers of ovarian reserve and cumulative, future fertility (e.g. live birth, future infertility and fecundability). In addition, using data from the original TTC cohort, he seeks to develop and validate a prediction model for current fertility to assist in counseling individual patients of late reproductive age who are attempting to conceive naturally.

Through these endeavors, the REI division hopes to advance understanding of the role of markers of ovarian reserve in predicting future reproductive potential and to improve counseling and risk stratification late reproductive age women who are attempting to conceive naturally.
THC AND NICOTINE HAVE A LASTING IMPACT ON BIVALENT CHROMATIN AND AUTISM GENES IN SPERM

By Rose Schrott, PhD Candidate, Duke University Integrated Toxicology and Environmental Health Program, Reproductive Sciences Lab & Susan K. Murphy, PhD, Duke Ob/Gyn Division Chief of Reproductive Sciences

Prenatal exposure to cannabis and nicotine can influence neurodevelopmental outcomes in offspring. Researchers focusing on Reproductive Sciences have noted that rates of use of cannabis products during pregnancy and rates of autism spectrum disorders are climbing. There is minimal knowledge about how paternal use of cannabis or nicotine might contribute to these outcomes. Additionally, little is known about how these drugs influence sperm health and the sperm epigenome, or whether or not a man can pass on any of these effects to his children. This lack of information is especially relevant, since men consume the most nicotine and cannabis products in the United States.1-3

Understanding how cannabis and nicotine impact the sperm epigenome was the focus of the recently published study Sperm DNA methylation altered by THC and nicotine: Vulnerability of neurodevelopmental genes with bivalent chromatin.

Chromatin and histone proteins convey instructions capable of altering how a gene is expressed without changing the DNA sequence. DNA methylation is the most commonly studied epigenetic modification. These modifications provide a level of plasticity to the regulatory features of the genome, allowing responsiveness to the environment. These types of changes can be permanent, thereby cataloguing an individual’s history of exposures.

Previous studies by Duke’s Division of Reproductive Sciences and the Cannabis-Induced Potential Heritability of Epigenetic Revisions in Sperm (CIPHERS) Project observed significant epigenetic changes in the sperm of both men that used cannabis and rats exposed to THC (tetrahydrocannabinol, the psychoactive compound in cannabis). CIPHERS is the continuation of a 2016 pilot study supported by the John Templeton Foundation.

In the current study, researchers asked whether or not the route of exposure in rats to delta-9-tetrahydrocannabinol (THC, the main psychoactive component of cannabis) differentially impacts DNA methylation, and whether or not nicotine can
similarly elicit methylation changes at a group of genes involved in neurodevelopment. Sperm DNA from rats exposed to THC or vehicle control via oral gavage (mimicking ingestion of edible forms of THC) underwent reduced representation bisulfite sequencing (RRBS), a method that provides quantitative data for millions of CpG sites throughout the genome. Seven genes were selected for study based on the magnitude of their methylation difference in sperm of exposed versus unexposed individuals and their roles in neurodevelopment and autism. Targeted analysis of these same gene regions was used to compare sperm DNA methylation in rats exposed to THC or nicotine versus vehicle controls in a manner that mimics exposure via inhalation.

The data confirmed significant differential methylation at five of seven neurodevelopmentally active genes by both routes of exposure. Interestingly, drug-specific divergent methylation changes at several genes were observed. For example, injected THC caused a loss of methylation at the same CpG site at which nicotine caused a methylation gain.

The Reproductive Sciences and CIPHERS research teams postulated that the inherent epigenetic architecture of some neurodevelopmentally active genes might render them more susceptible to environmentally induced epigenetic disruption. To address this, two publicly available datasets were queried. The first is a list of well-curated autism candidate genes and the second, a list of genes possessing an epigenetic feature known as bivalent chromatin. They are defined by their unique ability to keep a gene in a repressed state while simultaneously keeping that gene poised for rapid activation. This allows for finely tuned spatial and temporal triggering, as is necessary for early stages of embryonic development.

The autism candidate gene list was significantly populated with genes marked with bivalent chromatin. Remarkably, however, the genes showing differential methylation in the cannabis users relative to controls in human sperm are also enriched, not only for bivalent chromatin marks, but also for autism candidate genes.

As cannabis legalization and use are increasing, it is imperative that potential health consequences that might stem from this expanding access are considered. The study showed that THC and nicotine are both capable of altering DNA methylation patterns in rat sperm at genes implicated in neurodevelopment, including autism. Further support for the idea that bivalent chromatin structure increases the vulnerability of autism candidate genes to disrupted methylation by these exposures has been documented. Work is underway to investigate whether or not these altered epigenetic marks in sperm can be passed on to subsequent generations.

1. Centers for Disease Control and Prevention. Smoking is down, but almost 38 million American adults still smoke.
3. National Institute on Drug Abuse. Sex and Gender Differences in Substance Use.
GLOBAL HEALTH: WISH MAKES THE MACARTHUR 100&CHANGE TOP 100

Goal: A revolution against cervical cancer

By the Duke Center for Global Women’s Health Technologies

Last year, The MacArthur Foundation selected the Duke Center for Global Women’s Health Technologies’ “Women-Inspired Strategies for Healthcare (WISH): A Revolution Against Cervical Cancer” as among the Top 100 out of 755 proposals in the 100&Change competition. Proposals that promise real and measurable progress in solving a critical problem of our time were solicited for the competition. The GWHT’s proposal is included in the Lever for Change* Bold Solutions Network.

*Click to watch video.

The team behind the initiative from Duke is comprised of Megan Huchko, MD, MPH, clinical lead; Nimmi Ramanujam, PhD, technology lead; and Patty Garcia, MD, MPH, policy lead. The trio has collective experience in cervical cancer prevention, technology innovation and entrepreneurship and implementation. Collectively, they have global partnerships in more than 10 countries across four continents.

Dr. Huchko has a dual appointment as an associate professor in the Department of Obstetrics & Gynecology and the Duke Global Health Institute. At Duke, Dr. Huchko started the Center for Global Reproductive Health to increase research collaborations and educational opportunities. She is also extensively involved with Duke University Bass Connections, leading project teams focused on reproductive health since 2017 (see box below).

The Duke Center for Global Women’s Health Technologies’ WISH Revolution model empowers women to get screened for cervical cancer on their own terms, enables them to get treatment by providers from their own communities and encourages advocacy for each other to create a multiplier effect, which serves more women and saves more lives. Through technological innovations combined with education, researchers hope to see this goal become a reality. Their goal is to reach 5 million women in two epicenters, Peru and Kenya, and reduce deaths by 50% in 5 years. Additionally, the WISH team plans to draw on the lessons learned to expand to India and catalyze a global, women-led revolution against cervical cancer through our long-standing international partnerships.

Additional Global Health Highlights

Big Data for Reproductive Health (2020-2021)
Faculty Perspectives: Megan Huchko
GLOBAL HEALTH: FELLOW AWARDED 1-YEAR VECD FOGARTY FELLOWSHIP

Emily Herfel, DO, Global Health fellow in Duke Ob/Gyn, is the recipient of a one-year Vanderbilt-Emory-Cornell-Duke (VECD) Fogarty Global Health Fellowship award. The funding will be used for her work in Kisumu, Kenya. “The goal is to develop, implement and assess a sustainable educational program that modifies HPV perceptions, and thereby promotes an increase in HPV primary and secondary prevention,” Dr. Herfel said. “I plan to use qualitative methods to develop and pilot a community-based, stigma reducing cervical cancer education program.” (See WISH article.)

Dr. Herfel's intervention program will be implemented in the context of an existing community-based HPV vaccination and screening project in western Kenya. “By incorporating stigma reduction strategies throughout the design, we will test if the model decreases HPV-related stigma and increases HPV-related awareness and intention to screen or vaccinate,” she said.

GLOBAL HEALTH: GYNECOLOGIC ONCOLOGY PROGRAM EXPANSION IN UGANDA

Although the global pandemic has impacted onsite education, Duke gynecologic oncologist Paula Lee, MD, MPH, International Mentor for the Uganda Fellowship Program of the International Gynecologic Cancer Society (IGCS), has continued her work through virtual teaching the next generation of faculty and clinicians. Dr. Lee has served as an educator, leader and mentor for graduates of the first gynecologic oncology fellowship in Uganda, and the second one in East Africa. This year, three fellows will complete subspecialty training, moving toward the goal of expansion of gynecologic cancer care to communities in Uganda beyond Kampala and Jinja.

“When these three fellows pass their exams, we will have five graduated fellows from this gynecologic oncology fellowship program working in global health. This will bring the total number of trained gynecologic oncologists in Uganda to eight, from one when we started the fellowship in 2017. The fellowship continues with both local and international mentorship support. Our goal is to expand community-based cancer care to rural areas further east of Jinja, focusing on prevention and screening of cervical cancer.”
THRIVING AS A MIGS SURGEON

Winning in an unpredictable healthcare environment: Highlights from AAGL

At the American Association of Gynecologic Laparoscopists 49th Global Congress on MIGS, Division Chief Craig Sobolewski, MD, presented “Thriving as a Minimally Invasive Gynecologic Surgery (MIGS) Surgeon: Winning in an Unpredictable Healthcare Environment.” Topics covered included current changes within healthcare reimbursement as the Centers for Medicare and Medicaid Services moves from a volume-based or fee-for-service model to a value-based reimbursement model and how this change might impact hysterectomy in particular.

“Value in healthcare does not simply imply the least costly option,” said Dr. Sobolewski. “Rather, ‘value’ is defined as the ratio of outcomes over cost. The Medicare Access and CHIP Reauthorization Act incentivized providers and healthcare systems to participate in value-based reimbursement models. One successful strategy that health systems or departments can utilize to promote a value-driven patient care model is to employ evidence-based clinical pathways.” Implementation of programs that work toward lower rates of surgical site infection, transfusion and 30-day readmission rates were presented as models to consider, he added.

NEWSWORTHY & NOTEWORTHY

National Leadership: Gynecologic Oncology

Angeles Alvarez Secord, MD, MHSc, has been elected President-Elect II of the Board of Directors for the Society of Gynecologic Oncology. She will serve as President for the 2023-2024 term.

National Leadership: Maternal-Fetal Medicine

Brenna Hughes, MD, MSc, has been elected to serve on the SMFM Board of Directors; Jeffrey Kuller, MD, will serve as Chair of the Publications Committee for SMFM. Dr. Kuller’s three-year term will begin in 2021. He has been a SMFM Publications Committee member since 2016 and has served as Vice Chair since 2017.

Resident Gregory Zemtsov, MD, is one of two residents to have been selected for the first time to serve on the Publications Committee.

Sarah Dotters-Katz, MD, MMHPE, has been appointed to the SMFM Fellowship Affairs Committee.

Sarahn Wheeler, MD, serves on the SMFM Diversity in the Workforce Committee and is Vice Chair of the SMFM Diversity and Inclusion Committee.
Leadership, Faculty from Duke Ob/Gyn Meet with Congressional Leaders, Address Black Maternal Health

In November of 2020, leadership and faculty from Duke Ob/Gyn met virtually with the office of Rep. Alma Adams (D-NC-12) to discuss their clinical work and research to address Black maternal health and to improve health outcomes for pregnant women. Rep. Adams is co-chair and co-founder of the Black Maternal Health Caucus, along with Rep. Lauren Underwood (D-IL-14). Reps. Adams and Underwood also introduced the Black Maternal Health Momnibus Act of 2020 in the House to address preventable maternal mortality and severe maternal morbidity in the United States and close disparities in maternal health outcomes. Vice President Kamala Harris has led the companion effort in the Senate, and Senator Cory Booker (D-NJ) is leading those efforts in the Senate this year.

Jeffrey H. Silverstein Memorial Award

Nazema Siddiqui, MD, MHSc, was the recipient of the Jeffrey H. Silverstein Memorial Award for Emerging Investigators in the Surgical and Related Medical Specialties.

Faculty Accepted to AGOS

Urogynecologists Anthony Visco, MD, and Cindy Amundsen, MD, and REI specialist Anne Steiner, MD, MPH, were accepted as Active Fellows of the American Gynecological and Obstetrical Society (AGOS).

Duke Ob/Gyn, Bass Connections Collaboration Studies

In an effort to address concerns about the global impact on maternal-fetal health of frequently unregulated e-waste, Liping Feng, MD, (Reproductive Sciences) initiated and led a program to study and evaluate the issue with colleagues and student lead, Chrissy Crute, PhD candidate. Crute’s work is partially supported by Duke Ob/Gyn. Read more: The Global Impacts of E-waste Exposure and E-waste Recycling Policy on Maternal and Fetal Health.

QI Initiative: Universal Screening for Lynch Syndrome

A multidisciplinary team led by gynecological oncologist Becca Previs, MD, MS, and residents Daniel Spinosa, MD, and Tatiana Acosta, MD, MPH, implemented universal screening for Lynch syndrome among endometrial cancer patients at Duke. Screening rates, referrals to genetic counseling and diagnoses of Lynch syndrome improved after implementation of straightforward workflow changes. Read more.

Oncofertility Consortium Vision Statement

Kelly Acharya, MD, Director of the Duke Fertility Preservation Program and liaison for the Duke Prematurity Prevention clinic, recently collaborated with REI colleagues on publication of the Oncofertility Consortium Vision Statement. The Consortium is an international community dedicated to fertility preservation care and conducting research in the field of oncofertility.
DUKE OB/GYN BY THE NUMBERS

OUR PEOPLE

- 85 Faculty
- 14 Consulting and Adjunct Faculty
- 33 Residents
- 16 Fellows
- 38 PA/NP/CNM
- 53 Ob/Gyn Staff (directly employed)
- 500+ Ob/Gyn Staff (RN, MA, etc.)
- 200+ Students/year (MD, PA, NP)

- 15 Maternal-Fetal Medicine
- 8 Gynecologic Oncology
- 7 Urogynecology
- 5 Reproductive Endocrinology & Infertility
- 3 Minimally Invasive Gynecologic Surgery
- 11 Women’s Community & Population Health
- 32 General Ob/Gyn / Community Practices
- 4 Reproductive Sciences

OUR PATIENTS

- 199,067 Total outpatient visits
- 49,707 Maternal-Fetal Medicine visits
- 9,679 Gynecologic Oncology visits
- 10,201 Urogynecology visits
- 12,150 Reproductive Endocrinology & Infertility visits
- 3,299 Minimally Invasive Gynecologic Surgery visits
- 114,031 General Obstetrics & Gynecology visits

- 6,274 annual deliveries
- 3,479 annual surgeries

- 66% low risk
- 34% high risk (MFM attending)

OUR RESEARCH

- $13,502,970 Research funding (by primary appointment)
- 25 Grants
- 181 Protocols
- 170 Active funded research projects
- 205 Peer-reviewed publications

- $6,199,677 (46%) NIH funding
- $4,228,220 (31%) Federal non-NIH funding
- $3,075,073 (23%) Non-federal funding

Learn more about Duke Ob/Gyn providers

Learn more about Duke Ob/Gyn Research
DUKE OB/GYN: RALEIGH/WAKE COUNTY EXPANSION

ACCESS THE INTERACTIVE MAP

ALUMNI
Please take a moment to let Duke Ob/Gyn know where you are now by filling out a brief online survey: bit.ly/ObGynAlumniSurvey

Visit the F. Bayard Carter Society website: bit.ly/CarterSocietyWebsite

SAVE THE DATES
2021 Donald T. Moore, MD, Endowed Lecture
Featured Speaker: Elizabeth Howell, MD, MPP
April 28, 2021 (presented virtually) | Click for more information

2021 F. Bayard Carter Society Annual Meeting
October 21, 2021
Roanoke, Virginia

2022 F. Bayard Carter Society Annual Meeting
October 13, 2022
St. Louis, Missouri

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