Duke Obstetrics & Gynecology

Describe your path to becoming a physician-scientist in obstetrics.

I enjoy science that explains the causes and connected steps leading to disease presentation in medicine. The combined MD/PhD training track fit my method of learning medicine through science and mechanism, and inspired me to think that I could practice medicine and find ways to advance medical treatments by learning from my patients. I started out in research studying the highly ordered blood clotting cascade and the system of blood cell formation, called hematopoiesis. I earned my PhD in Pathology, the study of mechanisms of disease, working with physician-scientists specialized in hematology/oncology and hematopoietic stem cell transplantation. This work exposed me to the amazing complexities of immune system reactivity versus tolerance in transplantation, the fascinating biology of human development, and eventually connected me to Dr. Joanne Kurtzberg and the Carolinas Cord Blood Bank, since cord blood has special properties that make it an ideal source of hematopoietic stem cells.

Clinically, I was captivated by obstetrics in my very first clinical rotation of medical training. The fast pace, need for quick decisions, and combination of in-depth medical understanding with frequent hands-on procedures made Maternal-Fetal Medicine a clear choice for me. Obstetrics is not the most common path for MD/PhD trainees, but there are many opportunities for advancing the basic science understanding of pregnancy disorders, so I felt I could make a contribution while practicing the field of medicine that fits my personality and interests.

How you were drawn into preterm birth research?

The path to preterm birth research for me was paved in part by personal experience and in part by responding to the gaps in effective treatments I have been able to offer my patients. My first child was born prematurely, after my water broke early. She was born before I had completed medical training – in fact before I had even identified obstetrics as a specialty I would consider – so I lived through that experience as a patient without prior experience or frame of reference for my situation, much like the majority of patients I care for today. Ultimately, my daughter and I were lucky to have an overall smooth course without long-term sequelae, but the experience gave me the first-hand patient viewpoint that helps inform my counseling and discussion with my obstetric patients.

As that personal experience sparked my curiosity, (and gave me understandable anticipatory anxiety in subsequent pregnancies) I took advantage of my medical training and learned that preterm birth, or delivery of a pregnancy prior to 37 weeks of gestation, affects about 1 in 10 pregnancies. Unfortunately, the rate in the United States has been incrementally increasing for the past few years. Most women who deliver preterm do not have known or identified risk factors before the preterm delivery event, and the majority of preterm births do not have a specifically identified *cause*. Furthermore, our treatment options remain limited, as even the most effective interventions we have only work for about a third of the women we prescribe them to. I hope to use my background and training to move this bar, and eliminate some of the helpless feelings I share with the patients that are affected by preterm birth and its long-term sequelae for both moms and babies.

How does your approach to preterm birth research differ from commonly published or historical approaches?

Obstetricians have traditionally used only broad clinical characteristics, such as *spontaneous labor and delivery* versus *medically-indicated delivery* caused by issues like preeclampsia, to group different types of preterm birth for research purposes and for deciding which treatments to try for prevention. In grouping patients this way, the field has certainly made some important advances, but the screening and treatments we have to offer currently, such as cervix length ultrasound to identify vaginal progesterone candidates, or use of cervical cerclage, only seem to work for a fraction of the patients we identify as eligible. Furthermore, despite these advances, our rate of preterm birth

is still gradually climbing. There is good evidence that risk factors overlap between these clinically defined categories; that is, if a woman has a history of preeclampsia, her future pregnancy has elevated risk for *spontaneous* preterm birth as well as recurrent preeclampsia. Taken together, this means it is time for obstetric scientists like me to think outside of these traditional clinically-defined groupings and to find better ways to identify the underlying *disease mechanism* in each patient case. There are several proposed disease mechanisms that result in preterm birth, such as infection seeded by pathogens ascending from the vagina, immune system disruption, or cervical weakness – but the critical factor we are missing is the ability to pinpoint which of these disease processes is happening in an individual patient. I endorse the approach of seeing preterm birth as a common endpoint for many different individual disease states, so the primary objective is to uncover ways to clearly identify *mechanism-based* characteristics in these women so that our prevention and treatment strategies can be better tailored to the underlying cause of her pregnancy disorder. I have committed my research to better understanding the disease mechanism of immune tolerance in pregnancy, and identifying the ways in which maternal immune tolerance is disrupted in women who deliver preterm.

What have been the main barriers to this approach to date?

Immunology of pregnancy is not a new field, but our depth of knowledge is poised to explode with the recent advances in high-throughput methods to study immune cells. The concept of an immunologic 'mismatch' between mom and fetus was introduced by a famous immunologist and Nobel Laureate named Peter Medawar in the 1950s. Dr. Medawar's original proposals of how the maternal immune system can accept the fetus during pregnancy have turned out to be incorrect, but he is credited with 'opening the conversation.' Much of the foundational work on the specialized immune mechanisms in pregnancy have been done by reproductive immunologists trying to understand what causes recurrent pregnancy loss or prevents establishment of a pregnancy. The fundamental challenge to continuing this type of work into later timepoints in pregnancy (such as the gestational weeks when preterm birth occurs) is getting access to that maternal-fetal interface. For obvious reasons, we cannot biopsy a placenta or uterine lining mid-pregnancy. We rely on animal models to some degree – but the structure of the placenta is a bit different in humans, so the animal models just provide a starting point. In my lab, I have dedicated my time and research questions to learning how the peripheral circulating immune cells change in pregnancy, and to learning how to harvest and investigate the immune cells that are adherent to the placenta at delivery. I have built a repository of patient-donated placenta and blood samples from over 200 preterm deliveries, which gives me the opportunity to characterize maternal T cell function over a wide variety of preterm birth disease states.

What will it take to advance the field of immune tolerance in preterm birth?

Collaborative research and biobank resources. I am thrilled to be at Duke, where the Institutional, School of Medicine, and OB/Gyn Departmental leadership understand the need for multidisciplinary science and have aligned resources accordingly. Technology for studying immunology and cellular biology has advanced leaps and bounds in the 12 years since I finished graduate school. The Translating Duke Health Immunology initiative has provided research funding and opportunities for collaboration that allow me to apply cutting edge techniques to answer pregnancy-specific questions. Furthermore, the diversity of preterm birth requires large patient cohorts to identify meaningful patterns of disease. As an affiliate faculty of the Translating Duke Health: Duke Children's Health and Discovery Institute I can leverage the infrastructure of programs such as the HOPE1000 maternal and child biobank, and connect my findings to the work of researchers studying long-term effects of pregnancy events on childhood health.