

**HEALTHY  
MOMS.  
STRONG  
BABIES.**



# **MATERNAL AND CHILD HEALTH RESEARCH**

**FALL 2020**



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SVP & CHIEF MEDICAL  
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& GLOBAL PROGRAMS

**A**s I step into the role of Interim Chief Scientific Officer, I'm excited about the future of research at March of Dimes, which is the foundation of our work to improve the health of all moms and babies. Our first priority is building an integrated research agenda to address the multi-faceted maternal-child health crisis facing our nation. This new agenda will look to both medical and social science research, with an emphasis on translational science, to evaluate and increase our understanding of the numerous factors that impact maternal and infant health, and help us develop programs and policy solutions to create positive change.

As we integrate this new research agenda, you'll learn more about our social science research. In this issue, we begin by showcasing a new study to understand the importance of postpartum care for low income and women of color.

Simultaneously, we remain committed to the numerous grants currently underway through the Prematurity Research Centers. While we will emphasize translational research moving forward, we're reminded that our progress is deeply rooted in the basic research of discovery. Understanding the many processes and systemic functions involved in pregnancy is fundamental to informing which lines of inquiry will yield the most promising long-term benefits. Pregnancy and birth are basic to our human existence, and so our pursuit of life-enhancing interventions in maternal and child health must be grounded in our ability to unravel these mysteries.

In this newsletter, we showcase three more researchers who are doing just that. We know, for example, that inflammation is a major cause of pregnancy complications, including preterm birth. But what causes that inflammation, and why? Looking at the inner workings of a woman's immune system is providing important clues. We also know that certain bacteria, like Group B strep, is a major cause of infection that can cause a host of pregnancy complications.

Understanding, from an infectious disease perspective, how that occurs will result in findings with broad applicability for both treatment and prevention. Additionally, we know the microbiome of a woman's reproductive organs plays a vital role in her pregnancy and baby's health. Understanding how that system functions to promote or prevent a healthy pregnancy will have implications for every scientist working in the field.

Much of this work is being funded by March of Dimes outside of, but as an adjunct to, our Prematurity Research Centers. Broadening the scope of our research in this way strengthens the transdisciplinary nature of our work and multiplies the effect of our network to produce groundbreaking results. But as always, none of this would be possible without your support. We can't tell you how incredibly grateful we are for your compassion and commitment to help so many moms and babies.



**ELIZABETH HOWELL, MD, MPP**

Chair

Department of Obstetrics  
and Gynecology

Perelman School of Medicine  
University of Pennsylvania

# 4<sup>TH</sup> TRIMESTER DISPARITIES

**For many low-income women and women of color, a dangerous part of pregnancy is after the baby's born. A new study aims to change that.**

Dr. Elizabeth Howell has some definitive views on how medicine should be practiced. Her approach is patient-centered first and foremost, with an emphasis on quality of care—not just the traditional way of relying solely on outcomes or process measures. She is evidence-based of course, but is willing to think outside the box in order to improve the health of moms and babies. All of this makes her a perfect fit for March of Dimes' Social and Clinical Science Grant.

Like us, Dr. Howell believes you can't have healthy babies if you don't have healthy moms. And one of the biggest health threats to moms—particularly low-income women and women of color—is what happens after they deliver, the so-called “4th trimester.” That's when many maternal mortalities happen. But according to Dr. Howell, that's not where they start.

*“It's not just about preconception, antepartum, delivery and postpartum care,” she said. “It's a whole cycle we have to intervene on. We need to optimize care in every single phase. These women don't just need healthy pregnancies—they need healthy lives. If we're going to lower maternal mortality rates in this country and remove health disparities, we have to have a life course perspective.”*

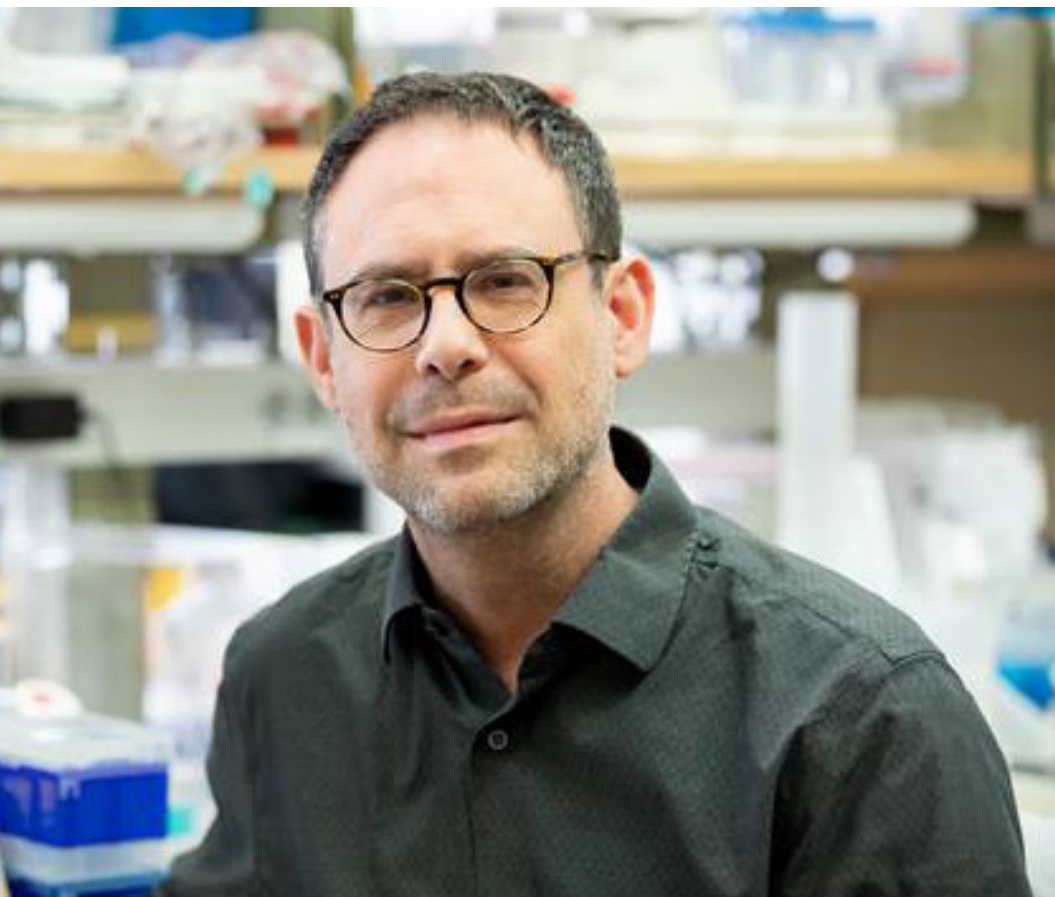
That view has evolved over the course of Dr. Howell's career, which has been focused on the racial and ethnic disparities and their disproportionate effects on the most vulnerable populations. But that focus began much earlier, and was instilled by her father, a civil rights attorney. Growing up in a household dedicated to social justice left an indelible and enduring imprint, but it was her early work in the NICU that exposed those societal fissures in terms of life and death—the unequal deaths of Black babies born preterm, and their moms who died the same way, far too soon. That led her to add an advanced public policy degree—while she was in medical school—to her M.D., and eventually to the important work she and her team are embarking on today.

Dr. Howell has enlisted a transdisciplinary team to help carry out that work, including a perinatal epidemiologist, a sociologist, a public health professional and a health psychologist. That team is partnering directly with what she calls her “accelerator board,” made up of community organizations, doulas and community health workers, some of whom have worked with Dr. Howell in previous research, and who provide critical maternal and child health services in the community.

When Dr. Howell was just starting out, funding for this work was scarce because nobody was investing in this area. That's changing. Recent CDC data shows that 51% of maternal mortalities occur between one day and 12 months postpartum. But those statistics simply reflect the correlations between pregnancy and what happens next in these women's lives. For example, a woman who develops gestational diabetes is at higher risk of developing type 2 diabetes later in life. And a woman who has preeclampsia has a much higher risk of cardiovascular disease or stroke later on. That's why Dr. Howell is concentrating on the 4th trimester (which she wants to extend into a whole year) as a critical window into women's health.

Dr. Howell's work is going to provide a new understanding of the ways structural racism has contributed to the decades-old disparities we've seen in maternal health outcomes. It's an area that, fortunately, is getting more attention, awareness and importantly, funding. “There is a whole movement in public health that's acknowledging this is the right approach,” Dr. Howell said. “People who are just looking at delivery or prenatal care are only looking at one piece of a very complicated puzzle. If we're going to make improvements, we need a comprehensive approach. And we need more organizations and people in that camp.”

We, at March of Dimes, are honored to be right there with her.



**ADRIAN ERLEBACHER, MD, PH.D.**  
Professor of Laboratory Medicine  
University of California San Francisco

# IMMUNOLOGY AND PREGNANCY

**Understanding how a mother's immune system changes to make pregnancy possible is pointing the way towards the prevention of preterm birth.**

Immunologically speaking, pregnancy shouldn't be possible. Why don't the fetus and placenta get rejected by the mother's immune system? It's because the immune system changes in profound ways to allow that. T-cells, which are responsible for attacking foreign bodies and even rejecting organ transplants, are excluded from the specialized uterine tissue that surrounds the implanted embryo. This tissue, called the decidua, is made up of stromal cells that activate an epigenetic pathway that prevents the expression of genes that otherwise would attract T-cells from the mother's bloodstream. Identifying the mechanism of this process may have implications for birth timing, and by extension, for the disruption of the timing that causes preterm birth.

Unraveling this immunological-genetic-epigenetic conundrum is the life's work of Dr. Adrian Erlebacher, which is supported by grants from March of Dimes. As a Professor of Laboratory Medicine at the University of California San Francisco, Dr. Erlebacher's research seeks to discover how the epigenetic pathways that exclude T-cells from the pregnant uterus might be relevant to labor induction, an aspect of pregnancy we still don't understand. We do know that there's a timing mechanism that measures out nine months, and a molecular alarm that, when triggered, begins the onset of labor. Understanding this mechanism in full-term pregnancies is essential to understanding how that mechanism is disrupted to precipitate preterm birth.

Dr. Erlebacher's work with animal models holds great promise. Just as breakthroughs in other areas of science and medicine are brought about through a deeper understanding of basic science—the latest immunologically-based treatments for cancer

are a prime example and came out of basic research into how to control immune cell activation—so, too, does Dr. Erlebacher's work seek to build upon a fundamental understanding of how pregnancy is regulated in other species. His team first discovered the aforementioned epigenetic pathway in mice, along with the remarkable finding that it could be pharmacologically manipulated to delay the onset of labor. The next step is to determine whether this same pathway could be relevant in human pregnancy. If so, it'll create a new foundation for understanding the causes of labor induction, for perhaps the very first time.

Taking the approach of illuminating basic biology first has profound implications for protocols and potential treatments. Looking at these biological pathways could lead to hypotheses that could be tested in women to see if the same pathways are dysregulated in those who've had a preterm birth. This is also important because quite often, epigenetic pathways can be influenced by environmental exposure, such as pollution, which is a known cause of preterm birth. Understanding this mechanism will uncover immunological sub-pathways that could possibly be modified to treat or prevent preterm birth.

*“When you start piecing the basic science together, you develop very specific theories, and move quickly to validate them to find whether or not you're on the right track,” said Dr. Erlebacher. “The push to do translational, clinically relevant work that's immediately applicable is always complemented by perspectives gained from basic research, which are connected through their interaction in fundamental biological mechanisms. Everything talks to everything else. And when we understand just how that happens, we can make great strides.”*



**MARINA SIROTA, PH.D.**

Leader of March of Dimes Central Data Repository, and Assistant Professor, Bakar Computational Health Sciences Institute and Pediatrics Department, UCSF School of Medicine



**IDIT KOSTI, PH.D.**

Postdoctoral Fellow at the Sirota Lab at the Bakar Computational Health Sciences Institute and Pediatrics Department, UCSF School of Medicine

Other authors on this study include Atul Butte, MD, Ph.D., Katherine Pollard, Ph.D., and Dr. Svetlana Lyalina, Ph.D.

# NEW INDICATORS OF PRETERM BIRTH

**A recent study aggregated data on the vaginal microbiome and pregnancy. The findings could help identify women at risk for giving birth preterm.**

There's no shortage of research on preterm birth, but sometimes too much information is almost as bad as not enough. That's why it's so important to aggregate the results generated by different scientists using disparate methods working in separate labs. Since they're all trying to solve the same problem. So why not pool the results to see the connections that could point to real answers?

That's a problem March of Dimes Prematurity Research Centers (PRCs) was built to solve—specifically, our Central Database Repository, where the data from various aspects of preterm birth research reside, not only from our centers, but also from around the world. This effort is led by Dr. Marina Sirota, an Assistant Professor at the Bakar Computational Health Sciences Institute at University of California San Francisco who is also part of the Stanford Prematurity Research Center. In addition to organizing and aggregating the molecular data on pregnancy and preterm birth, she is interested in figuring out how to ask new questions using these datasets. In a recent study, she worked with Dr. Idit Kosti, a Postdoctoral Fellow in her group, to carry out such an analysis leveraging microbiome data.

Like many of our researchers, scientists and clinicians, both researchers have had their own personal experiences with difficult pregnancies that as a result fuels their desire to spare other women and their families from a similar experience. Combining that passion with their innate curiosity to unravel the mystery of preterm birth, is what makes these two scientists so dedicated and driven.

In their most recent study, published in *Frontiers in Microbiology*, Sirota and Kosti, gathered results from five different studies from the PRCs and the public domain to give scientists everywhere a better understanding of crucial and much studied contributors to preterm birth: the microbes, microbial composition and the associated microbiomes involved in pregnancy. What they found was surprisingly important for identifying women at risk of delivering preterm.

The data showed that women who deliver early are more likely to have a more diverse population of vaginal bacteria, some of which have specifically been implicated in cases of preterm birth. Other studies have investigated the role of the vaginal microbiome before, but nothing on so large a scale as the study Kosti, Sirota and the rest of the team pulled together. And in the world of medical research, size matters.

*“Our approach as computational scientists was to step back and gather all the data on the pregnancy microbiome to see whether we could glean any insights that might be novel or different than what was observed before by individual investigators,” said Professor Sirota. “That’s the whole idea of meta-analysis, and what makes it so valuable. You find patterns that don’t come into focus when you just look at the individual studies.”*

Kosti and Sirota merged five different data sets and more than three thousand samples from more than 400 women, giving them a far greater amount of information than would be available to an individual researcher, across a more diverse population of women, their ethnicities and different stages of pregnancy. Their results identified the associations between the vaginal microbiome, specific bacteria and preterm birth.

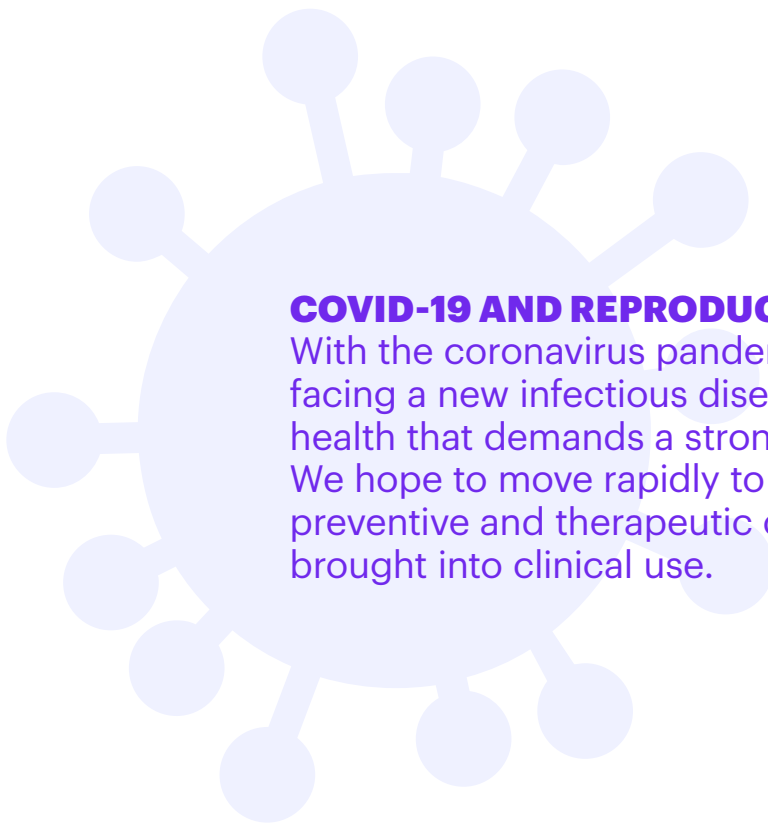
*“Women who deliver prematurely, especially those in the first trimester, have a significantly more diverse vaginal microbiome than those women who end up delivering at full term,” said Kosti. “Furthermore, we found specific bacteria that are also associated with preterm birth, some of which have been identified before but some of which are just now being linked to early delivery. We’re hoping clinicians can use this new information to develop new ways of diagnosing women at risk, as well as potential new preventative therapies.”*





**DAVID M. ARONOFF, M.D.**

Director of the Division of Infectious Diseases in the Department of Medicine at Vanderbilt University Medical Center; Addison B. Scoville, Jr. Chair in Medicine; Professor of Obstetrics and Gynecology, and Pathology, Microbiology and Immunology, Vanderbilt University Medical Center; Adjunct Professor, Vanderbilt University and Meharry Medical College



**COVID-19 AND REPRODUCTIVE HEALTH**

With the coronavirus pandemic (COVID-19), we're facing a new infectious disease threat to reproductive health that demands a strong focus from researchers. We hope to move rapidly to develop vaccines or other preventive and therapeutic options that can be quickly brought into clinical use.

# INFECTIONS AND PREGNANCY

**New advances in immunology and diagnostic technology are helping us better understand—and mitigate—the risks infections pose to reproductive health.**

Infection has always been a threat to pregnancy, causing difficulty, and often tragically devastating consequences. Until now, our understanding has been limited as to the role infections play, how they develop and why. But new research using the latest diagnostic and modeling technologies are giving scientists unprecedented investigative capabilities to predict, treat and prevent adverse birth outcomes.

One of the most pernicious sources of infection is Group B strep, which has become prolific at causing infections that lead to a range of pregnancy complications. The bacterium disguises itself with molecules very similar to those on our own body's cells, so the immune system has trouble recognizing it as an invading microorganism. This deception allows strep to colonize various parts of a woman's reproductive system that, undetected and untreated, will cause a dangerous set of circumstances for delivery. In the U.S., women are screened for this condition just prior to delivery and given antibiotics if the bacterium is found in the birth canal. But in women who deliver suddenly, there's less opportunity for prevention and mitigation, especially if infection is what triggered preterm delivery.

Studying causes of adverse pregnancy outcomes is a group of about 50 physicians and Ph.D. scientists at Vanderbilt University called the Vanderbilt Pre3 Initiative. Pre3 stands for Preventing Adverse Pregnancy Outcomes and Prematurity. The group's charter is to engage in work involving maternal and child health, ranging from basic science and fundamental discovery, to working in low- and middle-income communities and countries, to implementation projects and clinical studies. One of the group's co founders and it's director is Dr. David Aronoff. For 14 years, Dr. Aronoff and his lab have been dedicated to understanding how both bacterial and bio infections impact reproductive health.

*“As an infectious disease specialist, this is the most exciting time in my research career, in part because of the transdisciplinary nature of the work that we’re doing,” said Dr. Aronoff. “For example, one very serious problem we’re studying is the inflammation of the membranes of the amniotic sac. When these membranes get infected and inflamed, they can rupture, which is devastating for the baby and the mother if it occurs before term. Bacteria can also migrate through the membranes and infect the fetus, causing stillbirth or neonatal sepsis. In order to better understand how fetal membranes respond to infection, we’re working closely with biomedical engineers and chemists to develop what we call an instrumented fetal membrane on a chip, or IFMOC.”*

This work, which is funded by March of Dimes, has helped create three-dimensional organs on chip models that Dr. Aronoff and his team can populate with pathogens like Group B strep to understand how the membranes respond to infection, as well as the very structure of these elegantly simple membranes to define how they work from an immune perspective. These are the most sophisticated models of the human fetal membrane ever built, and they'll catalyze a community of researchers around the world whose results will allow scientists to better understand how to prevent and treat this important threat to maternal and child health.

Congratulations to March of Dimes current grantees who include experts working on everything from development of antibodies to prevent NEC and an aspirin regimen for preeclampsia to addressing racial and health disparities in birth outcomes and so much more.

- Timothy Hand, MD, CHOP
- Drew Hall, MS, UCSD
- Dr. Rupsa Boelig,  
Thomas Jefferson University Hospitals
- Dr. Louise Laurent, UCSD
- Jennifer Condon, Ph.D., Wayne State University
- Elizabeth Howell, MD, Mount Sinai
- Fleda Jackson, Majaica, LLC
- Dr. Miriam Kupperman, Ph.D, UCSF
- Deborah, Karasek, Ph.D., UCSF
- Michael J. Morowitz, MD,  
UPMC Children's Hospital of Pittsburgh
- Khosrow Adeli, Ph.D., The Hospital for Sick Children
- Dean Carson, Ph.D., Katana Pharmaceuticals
- Professor Ehud Gazit, Tel Aviv University
- Margaret Hicken, Ph.D., University of Michigan
- Michael Kramer, Ph.D., Emory School of Medicine
- Kelly Jones, Ph.D., Institute for Women's Policy
- Richard Frank, Ph.D., Harvard Medical School
- Haiden Huskamp, Ph.D., Harvard Medical School
- Norman Waitzman, Ph.D., University of Utah

## DONATE TODAY

For more information on how you can be a part of this effort, please contact:

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