Travis Doussette

Dr. Hala Chaaban, director of translational research for OU's Section of Neonatal-Perinatal Medicine, measures breast milk for analysis.

1,000 Days *Toward Finding a* Cure

HAROLD HAMM DIABETES CENTER RESEARCHERS FOCUS ON HOW THE EARLIEST DAYS OF A CHILD'S LIFE MAY DETERMINE ITS FUTURE.

By April Wilkerson

IN THE BATTLE AGAINST A GROWING DIABETES EPIDEMIC, REASON FOR HOPE IS COMING FROM THE TINIEST OF FIGHTERS.

Researchers at the University of Oklahoma Health Sciences Center and OU Health Harold Hamm Diabetes Center are focusing on "The First 1,000 Days"—from conception to a child's second year of life—when a variety of influences shape a baby's health for decades to come.

The mother's diet, the composition of breast milk, the gut microbiome of both mother and baby, plus many other health and environmental factors, have a profound effect on a baby's critical window of development. Researchers believe interventions targeting that window hold the key to preventing or delaying diabetes.

"We know now that many things have early origins in the first 1,000 days," says Jed Friedman, director of the Harold Hamm Diabetes Center. "We develop metabolism patterns in the womb and during lactation that not only affect our growth, but our brain development, our fat cells and our immune system. So, if we can understand more about those triggers and why they become a pathway to juvenile and, eventually, adult diseases, we'll have a real shot at preventing and disrupting them across the generational cycle."

The need for answers is only becoming more urgent. The number of Americans diagnosed with diabetes increased from 5.5 million in 1980 to 34 million in 2020, Friedman says. Currently, one in eight Oklahomans has Type 2 diabetes, and one-third of the state's adult population is prediabetic and unaware of their condition. Native Americans have over twice the risk of developing diabetes and are almost twice as likely as non-Hispanic whites to die from diabetes or suffer from its complications, including cardiovascular disease, fatty liver disease and cancer. ▶

Erikah Brown

Pediatric endocrinologist Dr. Jeanie Tryggestad's research focuses on how a mother's diabetes can pass to her child and is pursuing a medical intervention that might someday delay or prevent Type 2 diabetes.

Another changing dynamic is concerning: Type 2 diabetes, which formerly was only seen in adults, is dramatically increasing in children, driven by the obesity epidemic, Friedman says. Related conditions like non-alcoholic fatty liver disease are taking the same course, leading to a lifetime burden of care. Both conditions seem to progress faster in youth than they do in adults.

Friedman's own research focuses largely on how pregnancies complicated by obesity, gestational diabetes or a high-fat diet drive changes in offspring DNA, including changes to the gut microbiome. A collection of trillions of microorganisms in the intestinal tract essential to good health, the gut microbiome is of particular interest to diabetes researchers because children derive their first microbiomes from their mothers.

In one study, co-led with Chongle Pan, associate professor of computer science and microbiology on OU's Norman campus, researchers discovered that the development of Type 1 diabetes is linked to shifts in the microbiome of a child. In another microbiome-related study, Friedman's team focused on the future risk to babies born to pregnant women with gestational diabetes. By giving mothers a diet high in complex carbohydrates and reduced fat, not only did the mothers' microbiome benefit, but the "good" bacteria increased in their babies' microbiomes and "bad" bacteria—which play a role in the development of obesity and metabolic disease—decreased.

Today, 50% of women of reproductive age are overweight or obese at the time of pregnancy, which predisposes the next generation to a risk for obesity and diabetes, completing a vicious cycle from mother to infant, Friedman says. To reduce that risk, many physicians prescribe metformin to pregnant women to lower their blood sugar and slow the growth of the fetus. While metformin is beneficial, it also may be causing the very problems that it seeks to prevent. To learn more, Friedman's team is studying the offspring of animal research models that receive metformin.

"Our concern is that metformin on the maternal side crosses the placenta and creates an adult dose of the drug in a developing fetus," he says. "The fetus is not accustomed to experiencing this drug at a high level, and it doesn't have a way to clear it. Even though these babies aren't overgrown when they are born, we have epidemiological evidence that, as teenagers, they start to develop obesity. We think whatever sets that in motion probably occurs with their exposure to metformin. We just don't know how or under what conditions it happens."

In another clinical study, called the TOTS trial (Therapeutic Omegas for Triglyceride Suppression), Friedman's team is studying the effectiveness of an omega-3 fatty acid supplement in blunting pregnancy-related elevations in triglycerides, a type of fat found in the blood. Pregnant women with high triglyceride levels in early pregnancy tend to give birth to infants who are above normal weight and face an increased risk of developing obesity and metabolic conditions as they age.

Triglycerides typically increase during pregnancy, but some women reach levels that are 30% to 40% higher than normal by the time they reach their third trimester. In the randomized controlled trial, women take 4 grams of an omega-3 supplement each day beginning at the 15th week of pregnancy or receive a placebo as part of the control group. A multidisciplinary team of researchers analyzes blood sugar and triglyceride levels of the women during pregnancy and follows their infants after birth.

The analysis of breast milk is also yielding insight into babies' future risk for obesity and diabetes. David Fields, associate director of the Pediatric Metabolic Research Program in the OU College of Medicine's Department of Pediatrics, has made several major discoveries about how a mother's diet and amount of activity alter the breast milk that she feeds her baby.

In one study, Fields demonstrated that when a mother drinks sugary sodas, high-fructose corn syrup is present in her breast milk within two hours. And high-fructose corn syrup is associated with fat in babies as early as 6 months of age. In another study, Fields' research showed that exercise changes signals in breast milk that increase activation of brown fat in babies. Because brown fat burns energy, it plays a positive role, he says. Brown fat is also found in animals and is responsible for "non-shivering thermogenesis," the process by which they stay warm.

"In this trial, we ask the mom to perform a moderate amount of exercise, and then she's asked to nurse her baby. We

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Above Left - David Fields, director of OU's Pediatric Metabolic Research Program, uses an MRI to measure brown fat in an infant. Brown fat burns energy and appears to be increased through a mother's exercise.

Above Right - Dr. Trent Tipple's work on "The First 1,000 Days" project may help reveal connections between diabetes and premature births.

OU Health Harold Hamm Diabetes Center Director Jed Friedman is leading the charge to stave off the devastating disease through research projects aimed at the first 1,000 days of a child's life.

then use an infrared camera to measure the activation of brown fat in the baby, and we use the MRI to quantify the volume of brown fat," Fields says. "It's a very innovative study and is perhaps the only one of its kind."

Until more recently, scientists have not understood the composition of breast milk. But research is proving that qualities of breast milk play a major role in the future health of babies.

"Historically, we have known more about cow milk than human milk," Fields says. "That's obviously because cow milk is commercialized, but we are now making progress in understanding the makeup of breast milk and how the mother's diet and activity level can improve it. With a better understanding, we can help mothers have the best quality of breast milk possible so their babies are on track for a healthy life."

Another OU Department of Pediatrics researcher, Dr. Jeanie Tryggestad, maintains a clinical practice caring for children with Type 2 diabetes, while also conducting research that focuses on the effects of a mother's diabetes on her offspring. In one study, she is investigating ways to predict beta cell failure. Beta cells are responsible for making insulin in the pancreas.

"If your beta cells fail or they are not working appropriately, you are not going to make enough insulin to meet the demands of insulin resistance, which is the underlying pathophysiology of Type 2 diabetes," Tryggestad says. "If we can identify a biomarker that predicts beta cell function or failure, then we may be able to develop an intervention that either delays the progression to beta cell failure or prevents it altogether.

"Youth-onset Type 2 diabetes is an aggressive disease with significant complications in the third decade of life," she says. "Prevention of diabetes must occur at the earliest stages, focusing on optimal health and nutrition in the mother and infant."

"The First 1,000 Days" research also extends to the realm of prematurity. Dr. Trent Tipple, chief of the Section of Neonatal-Perinatal Medicine in OU's Department of Pediatrics, says researchers are beginning to establish collaborations to better understand how the risks of conditions like diabetes may be different in babies born prematurely.

Also playing a role are the Quincy Le Norman Nutrition Center at Oklahoma Children's Hospital OU Health, as well as the OU Health Center for Pregnancy and Newborn Health. The nutrition center, which processes all formula and breast milk for Oklahoma Children's Hospital, features technology to analyze the macronutrient composition of what is being fed to babies, which is especially important with donor breast milk, Tipple says. And at the Center for Pregnancy and Newborn Health, more than 60 basic scientists, physician-scientists and laboratory personnel are engaged in projects across disciplines.

"There is a unique opportunity for us to be a part of 'The First 1,000 Days' research," Tipple says. "We can leverage the strength of our integrated delivery and high-level neonatal intensive care unit, in collaboration with our research group, to start unraveling the causes and cures that lead to diseases like diabetes and, ultimately, have a multigenerational impact."

April Wilkerson is the editor of OU Medicine.