Kaiser Permanente **Research**

Maternal diabetes and risk for children:

How questions lead to answers that lead to more questions





ne way researchers at Kaiser Permanente work to make our next generation healthier is by studying children's environments *before* birth.

In 2018, several researchers looked at how mothers' blood sugar levels during pregnancy affected their children's risk for diabetes, overweight/obesity, and cognitive impairment. They looked at various conditions including the type of diabetes that develops in pregnancy, called gestational diabetes.

Kaiser Permanente Southern California researchers conducted studies that showed children born to women with type 1 diabetes are associated with about twice the risk of autism as those born to women who do not have any form of diabetes. Another study showed that children exposed to untreated gestational diabetes during pregnancy are more likely to be unable to properly absorb and use sugar for energy compared with children whose mothers did not have gestational diabetes.

The work was decades in the making. Each discovery was based on a question by a passionate and dedicated researcher that emerged after a previous discovery.

Physician began early investigation at Bellflower

Work at KPSC on glucose tolerance and big babies was first published in 1995. David Sacks, MD, an obstetrician at the Kaiser Permanente Bellflower Medical Center, knew from his reading and previous research that women with elevated blood sugar were more likely to give birth to larger babies. Children of women who have diabetes are at increased risk for a variety of complications at birth as well as later in life.

"But what I was curious about was whether the risk of having big babies changed with moms' increasing blood sugar values," he said.

He recruited more than 3,000 pregnant women who planned to give birth at the Bellflower Medical Center to determine the answer. The study followed the women who had elevated blood sugars but who did not reach the level of overt diabetes.



Dr. David Sacks tells Jenny Gutierrez how research into maternal diabetes began at Kaiser Permanente Southern California over 25 years ago.

"What we showed was that the relationship was continuous," said Dr. Sacks, who is now an associate investigator with the Department of Research & Evaluation. "There was a straight line that showed that the higher the blood sugar, the higher the chance of having an overly large baby."

Joining with others to investigate the question

During this early work Dr. Sacks learned that a consortium of 15 hospitals and research centers was also studying elevated blood sugars in pregnant women, although it was looking at additional outcomes. That group invited him to join them in the Hyperglycemia and Adverse Pregnancy Outcomes, or HAPO, study, as field center principal investigator at Bellflower.

The first large-scale study published by HAPO in 2008 determined that in pregnant women, levels of maternal blood sugar lower than those which defined overt diabetes are associated with a number of negative outcomes for offspring, including increased birth weight and hormone levels that are associated with fetal growth.

Cover: At the West Los Angeles Medical Center, Dr. Michael Fassett shows patient Kneena Wolff the best way to use a blood glucose meter to test her blood sugar. Research shows keeping blood glucose under control during pregnancy is best for the baby.

Inquiry. Investigation. Implementation.



Mayra Martinez, Dr. Anny Xiang, Ting Chow, and Janet Mora Márquez discuss ways to research the effect of the intrauterine environment on a child's cognitive development.

Implementation included new way to identify gestational diabetes

Because of their findings, the researchers developed a new lower criterion to identify gestational diabetes.

At the same time, R&E researcher Jean M. Lawrence, ScD, MPH, MSSA, published a paper in *Diabetes Care* showing that the prevalence of diabetes (type 1 and type 2) among pregnant women was increasing over time while the rate of gestational diabetes was remaining constant but high at around 7.5% of pregnancies. With so many children exposed to diabetes in pregnancy, learning more about the impact of these conditions became more pressing.

Investigations spurred more inquiries

The answers from the HAPO study led to more questions, and when a new study was initiated, Dr. Lawrence became the field center PI for the HAPO Follow-up Study. That study aimed to answer the question of what happened to the moms in the original HAPO study, as well as their children. More specifically, how did maternal glucose and maternal body mass index influence a child's growth and a child's risk of prediabetes and diabetes? The study team began publishing results in 2018.

"In general, we found that outcomes 8 to 10 years after that pregnancy are along the same continuum as the ones we saw at the time of delivery," Dr. Lawrence said. "Children are more likely to have bad outcomes, such as insulin resistance, if their mom was in the higher end of the glucose distribution."

Inquiries into gestational diabetes

Anny Xiang, PhD, MS, director of R&E's Division of Biostatistics Research, began her career over 25 years ago at the University of Southern California. She was working to "understand the pathogenesis of gestational diabetes and diabetes in a cohort of Hispanic women."

She worked on research that:

- found that women with gestational diabetes are at high risk of developing diabetes after the pregnancy is over, and
- mapped the progression of gestational diabetes to type 2 diabetes.

Moving to Kaiser Permanente in 2010 opened the door for Dr. Xiang to address other questions she had about gestational diabetes, because of KPSC's large, diverse patient population.

Investigating racial/ethnic disparities in fetal growth

Dr. Xiang first focused on learning about racial and ethnic disparities in gestational diabetes.

- A 2011 study showed that black women with gestational diabetes had a much higher risk of developing diabetes after pregnancy.
- A 2015 study showed that children born to black women with gestational diabetes were more likely to be large for gestational age.

Those studies made her want to push further, for instance, "how does mom's gestational diabetes affect the brain of the fetus?"

"My interest in maternal and child health conditions is based upon the opportunity to identify people at risk and help them be healthier going forward."

– Jean M. Lawrence, ScD, MPH, MSSA



Dr. Michael Fassett examines patient Kneena Wolff as her partner, Abel Orozco, provides support. Researchers agree that for the health of the child, it's not only important to see a doctor during pregnancy, but also to see one before getting pregnant.

Inquiries progressed to cognitive functioning

In 2015, Dr. Xiang published a study in *JAMA* that showed that gestational diabetes diagnosed early was associated with autism risk in children. In 2018, she extended that work by including pregestational type 1 and type 2 diabetes and showed that both were also associated with risk of autism.

Also in 2018, she published work on attention deficit and hyperactivity disorder that showed that type 1, type 2, and gestational diabetes requiring medication during pregnancy were associated with a risk for attention deficit and hyperactivity disorder in children.

"A lot of disease tracks back to conditions during pregnancy," Dr. Xiang said. "We have now developed a large enough store of electronic health records covering many years at KPSC. With this, we can evaluate the potential effect of the intrauterine environment on a child's neurological development and other health outcomes."

Implementation as a takeaway: plan your pregnancy

Dr. Xiang notes that each piece of research seems to point to the importance of women seeing their doctors before pregnancy to make sure their babies have the best environment during pregnancy.

Dr. Lawrence and Dr. Sacks agreed.

"It's important to know whether or not you've got diabetes or prediabetes before you get pregnant," Dr. Sacks said. "Then, you and your doctor can do everything possible to make sure your baby has the healthiest start possible."