

Maternal Diabetes and Adult Morbidity in the Offspring: The TEAM Study at Cincinnati Children's Hospital Medical Center

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MATERNAL DIABETES AND ADULT MORBIDITY IN THE OFFSPRING: THE TEAM STUDY AT CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

While most people are aware of the health complications associated with diabetes, the impact of maternal diabetes on their children later in life is less understood. A research group at Cincinnati Children's Hospital Medical Center (Ohio, USA) led by **Dr Jane Khoury** is working to change this. Their ongoing study, 'Level and timing of diabetic hyperglycaemia in utero: The transgenerational effect on adult morbidity' (TEAM study) is driving forward our understanding of the effects of maternal diabetes during pregnancy, to improve healthcare provision for both mothers and their children.

Types of Diabetes

Diabetes is a serious medical condition in which a person's pancreas loses the ability to produce insulin, required to regulate blood sugar levels. Over time, changes in blood sugar levels can cause a variety of complications and health problems.

There are three main types of diabetes – type 1, type 2 (pre-gestational) and gestational. When it comes to managing diabetes, testing blood sugar levels is crucial as uncontrolled blood sugar levels can result in hospitalisation – or even worse consequences.

Type 1 diabetes is often caused by an autoimmune response which incorrectly targets insulin-producing cells (beta cells) in the pancreas and is most commonly diagnosed during childhood. Type 1 diabetes is typically treated with insulin injections or using an insulin

pump to prevent hyperglycaemia, high blood sugar levels.

Type 2 diabetes is caused by the body losing its ability to respond to insulin, known as insulin resistance. While the body will still produce insulin, it is not enough to control blood sugar levels. Type 2 diabetics may not require insulin injections but patients may need to take other medications to control their sugar levels.

Gestational diabetes develops because the body is unable to produce enough insulin for the mother and the additional needs of pregnancy. This can occur anytime during pregnancy, but is usually diagnosed during the second or third trimester and regresses after giving birth. Gestational diabetes may be treated with dietary modifications or medications as necessary.



Maternal prenatal care is essential for women with pre-gestational diabetes

Understanding Diabetes in Pregnancy

While diabetes in pregnancy can cause immediate and devastating consequences such as miscarriage preeclampsia (characterised by high blood pressure and protein in the urine), preterm delivery, caesarean section delivery, and birthing a large for gestational age infant. or complications during delivery. A further concern is that children born of mothers with diabetes may also develop serious health

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problems as they age. The University of Cincinnati and Cincinnati Children's Hospital Medical Center (Ohio, USA) has an established history of research excellence in this field, dating as far back as 1978 with the landmark Diabetes in Pregnancy programme initiated by Dr Harvey Knowles and continued through 1995 under the leadership of Dr Reginald Tsang and Dr Menachem Miodovnik.

Dr Jane Khoury, the principal investigator on the TEAM study, has emphasised that this work ‘is critical to rapidly and directly determine specific contributions of the intrauterine environment to these more subtle pathophysiologies and preclinical diseases affecting the adult offspring of women with type 1 diabetes during pregnancy.’

There are approximately 29.1 million people living with diabetes in the USA, 1.25 million of whom have been diagnosed with type 1 diabetes. The number of women of childbearing age with diabetes, in particular type 2 diabetes, is increasing and so it is expected that the number of children

exposed to diabetes while in the uterus will also rise. These statistics emphasise the importance of the work of the TEAM research group in extending our understanding of the risk factors that mothers with diabetes and their children are exposed to.

Dr Khoury and the TEAM study researchers plan to identify the effects of maternal high blood sugar and its associated variability throughout the duration of pregnancy on morbidity outcomes in the young adult offspring. Findings will be used to identify the most vulnerable timepoint(s) throughout pregnancy for foetuses so that healthcare professionals and the pregnant women know when it is most important to ensure rigorous and intense monitoring of blood sugar levels. This will help inform timely, targeted clinical treatment strategies and ultimately prevent long-term health conditions in the children of mothers with diabetes.

Metabolic and Cardiovascular Consequences

The TEAM Study aims to examine obesity, insulin resistance, beta cell dysfunction, type 2 diabetes, and kidney function in the offspring of women with pre-gestational diabetes. In addition, early markers of cardiovascular dysfunction are being studied. Using information already collected regarding maternal blood sugar control, the study will pinpoint the most vulnerable periods of pregnancy related to manifestation of the morbidities in the adult offspring. Using novel statistical methods, they will identify the gestational blood sugar profile that predicts the phenotype of offspring at risk for morbidity in adulthood. Only the adult offspring of women who participated in the original Diabetes in Pregnancy Programme are eligible for the TEAM Study.

As a precursor to the TEAM Study, Dr Khoury and colleagues conducted and published a pilot study among 19 offspring of women with type 1 diabetes. They identified an association between blood sugar control during the



Neonatal assessment of weight

mother's pregnancy with blood sugar levels, blood pressure, and weight in the young adult offspring. In addition, they published a manuscript comparing the rate of mothers with type 1 diabetes delivering a large for gestational age baby in the study group (dating from 1978 to 1995), with that of a more contemporary group (2002 to 2008) from the Consortium on Safe Labor dataset provided by the Eunice Kennedy Shriver National Institute of Child Health and Human Development on the Data and Specimen Hub. There was no difference in the rate of large for gestational age (>90th percentile for gestational age, race, and sex) between the two groups, indicating that despite the technological advances in improving diabetes control, the outcome of a large baby has not been resolved.

A previous study led by investigators in the TEAM research group examined the frequency of several adverse health outcomes in four different groups of large for gestational age infants whose mothers had type 1 diabetes (asymmetric large, symmetric large, asymmetric non-large, and symmetric non-large). Where asymmetry is defined as a weight to height ratio, a 'fat' baby. The results showed that asymmetric large for gestational infants had an increased risk of adverse health problems, consistent with other studies in the field. The researchers also found that foetal abdominal growth rate

could be used to differentiate between asymmetric and symmetric large for gestational age infants at delivery.

Kidney disease, also known as diabetic nephropathy, is one of the most serious complications of diabetes. It is estimated that approximately 30–40% of all patients with insulin-dependent diabetes succumb to the failure of the kidney to filter waste from the blood. Studies conducted by the University of Cincinnati investigators identified an increased risk of pregnancy complications in mothers and their neonates associated with diabetic nephropathy. Specifically, the children of mothers with diabetic nephropathy are more likely to have poorer health outcomes compared to those without kidney complications; there is a significant increase in premature births, low birth weight babies, and high blood sugar levels in neonates. This work confirmed that children born from mothers with diabetic nephropathy are a high-risk group. 'The identification of offspring at risk, and of the optimal times to initiate potential preventive measures are each critical for improving the health outcomes of these vulnerable foetuses' notes Dr Khoury.

The TEAM researchers are now investigating further the effect of exposure to diabetes on children and their risk of later developing kidney problems in adulthood. They are

also assessing the increased effect of perinatal obesity on renal function. Their research will help to pinpoint the gestational period during which infants are particularly vulnerable to the effects of high blood sugar levels in the uterus and how this is linked to specific morbid conditions in the offspring, such as renal and cardiovascular disease, in later life.

Diabetes: Looking Ahead

With the current worldwide obesity epidemic and the associated increase in diabetes, halting further increases in potentially preventable conditions for the next generations is critical. The TEAM study will play an important role in elucidating the effects of diabetes control during gestation on the mother, baby, and offspring as an adult. The study findings will help inform women with pre-gestational diabetes planning on having children and those already expecting how best to protect themselves and their children from adverse health effects.

By helping clinicians identify foetuses at higher risk for life-time morbidities, preventative and timely interventions can be put in place during pregnancy. Dr Khoury explains that their work 'will directly inform clinical management and alert the pregnant woman herself regarding the lifetime consequences for her offspring due to hyperglycaemic excursions during gestation.'

The group has currently recruited over 100 of the offspring of the targeted cohort of women with type 1 diabetes and has already obtained, from the original study, detailed information about each mother's glycaemic control during pregnancy. The current study is expected to run until August 2022 and recruit 250 offspring in total. The findings from the study will help give us a better understanding of the underlying mechanism of how exposure to diabetes during foetal development affects the health outcomes of these offspring later on in life.



Meet the researchers

The Level and Timing of Diabetic Hyperglycaemia In Utero:
The Transgenerational Effect on Adult Morbidity (TEAM Study)
Cincinnati Children's Hospital Medical Center
University of Cincinnati College of Medicine
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Dr Jane Khoury obtained her PhD in Quantitative Epidemiology from the Department of Environmental and Public health Sciences, University of Cincinnati College of Medicine. As an established biostatistician and quantitative epidemiologist, she has held several research appointments and is currently a Professor in the Division of Biostatistics and Epidemiology with a joint appointment in the Division of Endocrinology at Cincinnati Children's Hospital Medical Center. She also holds a secondary appointment in the Division of Epidemiology, Department of Environmental and Public health Sciences, University of Cincinnati Medical Center. Dr Khoury's research interests centre on diabetes in pregnancy and the long-term effects on mother and offspring, but she also has a long-standing interest in stroke epidemiology, particularly for those with diabetes.

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CO-INVESTIGATORS IN THE DIVISION OF BIostatISTICS AND EPIDEMIOLOGY (DBE)



Mekibib Altaye, PhD is a Professor in DBE. His research interest centres on the design and analysis of correlated data focusing on high dimensional data obtained from neuroimaging studies including MRI, fMRI, DTI and MRS.



Katherine Bowers, PhD earned her doctorate in epidemiology from the Johns Hopkins University Bloomberg School of Public Health. She is currently an Associate Professor in DBE with a long-standing interest in how a wide range of exposures during pregnancy affect neurodevelopment.



Shelley Ehrlich, ScD completed her doctorate and post-doctoral training at the Harvard TH Chan School of Public Health and Massachusetts General Hospital. She is a perinatal and environmental epidemiologist in DBE, holding a secondary appointment at the University of Cincinnati College of Medicine in the Department of Environmental and Public health Sciences, Division of Epidemiology. Her research interests include the study of environmental exposures on maternal and child health outcomes.



Resmi Gupta, PhD is a senior biostatistician in DBE. She received her PhD in Biostatistics in August, 2019 from the University of Cincinnati, Department of Environmental and Public health Sciences. Her research focuses on developing prediction models to evaluate the long-term associations between a mother's glycaemic fluctuations and health risks for offspring.



Nicholas Ollberding, PhD is a quantitative epidemiologist and an Associate Professor in DBE. His applied research interests are in investigating the role of diet in the aetiology and progression of chronic disease, and the role of the developing infant intestinal microbiome on growth and early development.



Rhonda Szczesniak (VanDyke), PhD is an Associate Professor in DBE. Her research focuses on the development of dynamic prediction modelling of medical monitoring data; applications include glycemic control in type 1 diabetes in pregnancy, ambulatory blood pressure monitoring and prediction of rapid lung disease progression in cystic fibrosis.



The TEAM study team, from left to right: Mekibib Altaye (co-Investigator), Lisa Tully (Regulatory Specialist), Sang Sam (Clinical Research Coordinator), Amber McKissic (Clinical Research Coordinator), Emily Smith (Clinical Research Coordinator), Shelley Ehrlich (co-Investigator), Katherine Bowers (co-Investigator), Scot Fague (Data Manager), Resmi Gupta (Biostatistician), Jane Khoury (Principal Investigator)

OTHER KEY COLLABORATORS

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RELEVANT PUBLICATIONS

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