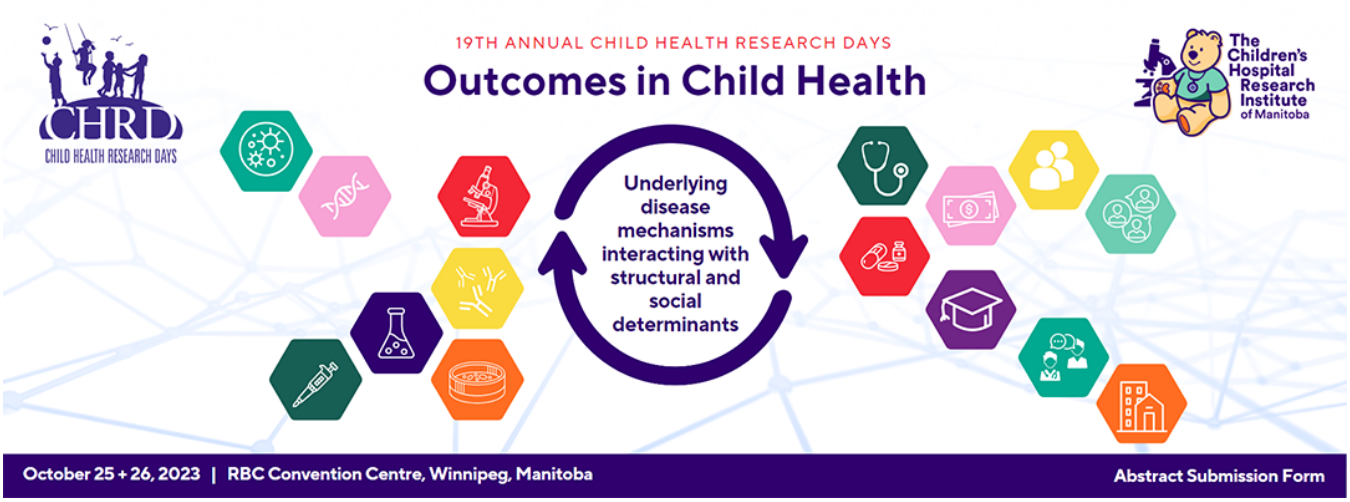

CHRD 2023: Abstract Submission Form

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Presenter Status
Masters Student

Research Category
Basic Science

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Title
SIRT3 Deficiency in the Liver and Mitochondrial Dysfunction in Gestational Diabetes

Background
Gestational diabetes mellitus (GDM) is the most common transient pregnancy complication that puts mothers and their children at risk for developing type 2 diabetes, obesity, and cardiovascular disease later in life. GDM is characterized by glucose intolerance and insulin resistance and the mechanisms involved are poorly understood. Sirtuin 3 (SIRT3) is an important mitochondrial protein deacetylase that regulates energy production in the liver.

Objective
The objective of this study is to determine whether deficiency of SIRT3 in the liver is sufficient to induce diabetes during pregnancy.

Methods
Mice with liver-specific deletion of SIRT3 (SIRT3-LKO) were generated by crossing Sirt3tm1.1Auw mice from Jackson Labs with loxP sites flanking exons 2-3 of the Sirt3 gene with Cre recombinase mice with an albumin promoter. SIRT3-LKO mice and Cre-negative controls were fed either a low-fat diet (LF; 10% kcal fat) or a high-fat and sucrose diet (HFS; 45% kcal fat) for 6 weeks before pregnancy and throughout the 3-week mouse pregnancy to induce GDM. Glucose tolerance tests were performed at e17. Pregnant mice were sacrificed at e18.5 and livers collected. Hematoxylin-eosin staining of liver sections was performed to assess lipid accumulation. Liver mitochondria were isolated at e18.5 and mitochondrial respiration was

measured using Agilent-Seahorse XFe24 to assess mitochondrial function.

Results
Compared to Cre-negative littermate controls, genetic deletion of SIRT3 in the liver was sufficient to induce glucose intolerance in pregnant mice ($p<0.05$). Histological visualization revealed hepatic steatosis in SIRT3-LKO mice. Liver mitochondria from SIRT3-LKO mice had a 30% reduction of basal respiration compared to controls.

Conclusion
Our findings suggest that SIRT3 plays an important role in maintaining adequate mitochondrial function during pregnancy, during important period when maternal demands for energy production are high. SIRT3 deficiency promoted mitochondrial dysfunction which could contribute to the accumulation of lipids in the liver and glucose intolerance during pregnancy.

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