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Exposure to Gestational Diabetes Alters Cardiac Gene Expression and Metabolism in the Rat Offspring and Induces Cardiac Dysfunction with Age

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Background:

Gestational diabetes mellitus (GDM) is the most common complication of pregnancy. Children exposed to GDM are at increased risk for cardiovascular disease development later in life, though the mechanisms responsible are unknown.

Objective:

We hypothesize that fetal exposure to GDM induces cardiomyocyte mitochondrial dysfunction, and left ventricular (LV) dysfunction with age.

Methods:

GDM was induced in female rats with a high fat (45% kcal) and sucrose diet prior to mating, throughout pregnancy and lactation. Lean control females received a low fat (10% kcal) diet. LV morphology and function were assessed throughout the life course of the offspring (e18 to 12-months of age) by transthoracic echocardiography. Fetal rat ventricular cardiomyocytes (FRVC) were isolated from e20.5 offspring for mitochondrial respiration and calcium transport analysis. Serum metabolome and cardiac transcriptome profiles from 3-month old offspring were measured by LC-MS, and RNASeq.

Results:

Offspring exposed to GDM exhibit increased LV posterior wall thickness across their life course (fetal to 12-months of age; $p<0.05$) and impaired LV filling beginning at 6-months of age ($p<0.05$). Consistent with in vivo diastolic dysfunction, alterations in calcium flux and sarcoplasmic reticulum-dependent calcium re-uptake (1.5-fold and 1.6-fold greater, respectively) were observed in FRVC from GDM offspring ($p<0.05$). RNASeq analysis revealed that 3-month old offspring exposed to GDM exhibit altered calcium handling gene expression (e.g. *ATP2B2* and *ATP2A3)*. Mitochondrial oxygen consumption was reduced for glucose, and fatty acid substrates in FRVC isolated from GDM offspring ($p<0.05$). Serum metabolomic analysis revealed that β-hydroxybutyrate levels are elevated (2.4-fold, $p<0.05$) and several citric acid cycle intermediates are reduced in 3-month old GDM offspring, indicative of altered mitochondrial ATP production.

Conclusion:

GDM conditioned mitochondrial dysfunction, altered contractility, and calcium transporter gene expression in cardiomyocytes of the offspring, in concert with LV hypertrophy and diastolic dysfunction.

Our findings identify several mechanisms that link early-life GDM exposure to cardiovascular disease development.