Molecular Basis of Maternal Obesity-Induced Fetal Cardiac Contractile Dysfunction

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Introduction
Obesity is an exponentially increasing public health and economic issue worldwide. Currently, 18–35% of pregnant women in the U.S. are obese. Epidemiological studies suggest that maternal obesity (MO), or over-nutrition during pregnancy, is associated with increased risk of heart disease. It has been shown that maternal nutrition plays an important role in fetal heart development and function. Animal studies show that MO could lead to morphological changes to the fetal heart, among them increased heart chamber weights and thickness from mid-to late-gestation. Despite these morphological changes, MO fetal heart function was impaired under stress conditions; however, it remains unclear how the molecular and cellular mechanisms lead to the impaired fetal heart function.

Objectives
The objective of this study is to examine how maternal obesity (MO) changes fetal heart muscle cell contraction.

Materials and Methods
From 60 days before and throughout pregnancy, Rambouillet/Columbia-crossed ewes were fed either 100% of National Research Council (NRC) recommendations (control, n=5) or 150% of NRC recommendations (MO, n=5). At the 135th day of gestation (approximately two weeks before the full term of sheep pregnancy), fetuses were obtained via caesarean section from ewes. The fetuses and ewes were euthanized under anesthesia following University of Wyoming animal use and care policies. The fetal hearts were quickly removed, and the individual heart muscle cells were isolated. The mechanical properties of contraction were assessed on isolated muscle cells (e.g., how much do cells contract, and how long does it take for each contraction?). Additionally, protein was extracted from fetal heart tissue to examine the expression levels of the molecules.

Results and Discussion
We assessed the contraction ability on isolated fetal heart muscle cells and found that muscle cells from fetuses of obese mothers had decreased contraction. In contracting heart muscle cells, the time for an individual cell to contract to its shortest possible length takes longer from MO fetal hearts than from the control. Also, the cells from MO fetal hearts do not contract as well as the control, as the overall change in length per contraction is lower. Meanwhile, we also found that calcium (an important ion in the cells that controls the contraction of muscle cells) was also altered in the MO fetal hearts. Further, we looked into the molecular signaling controlling the calcium levels in the muscle cells. The regulation of calcium levels in the cells is accomplished by releasing and taking back calcium from and to the calcium reservoir. There are two pumps on the calcium reservoir: a ‘releasing pump’ that pumps calcium out of the reservoir into the cells, and an ‘uptaking pump’ that pumps calcium into the reservoir. We revealed that MO changed the releasing pump, but not the one that uptakes, leading to excessive calcium in the muscle cells.

We also studied the molecules related to muscle contraction (Fig. 1). Our results showed that the molecules related to fast-speed contraction were reduced in the MO fetal heart while the molecules related to slow-speed contraction increased, which could be a possible explanation to the slower and less contraction of the muscle cells. Additionally, MO altered the protein complex, which senses the calcium level in the cells and passes the signal to the contraction unit in the muscle cells. These findings help us understand the mechanism of why the MO fetal heart is less sensitive to calcium, which, in turn, leads to weaker contractions.

These results suggest that maternal obesity alters calcium levels in offspring heart muscle cells and changes contraction-related proteins—both of which contribute to the fetus having compromised heart contractions. Further study is needed to reveal more detailed mechanisms and discover possible interventions to correct adverse effects of MO on the fetal heart.

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Figure 1. Qiurong Wang is a postdoctoral fellow working on fetal programming in Assistant Professor Wei Guo’s lab.

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