Bariatric surgery for long term body weight loss and resolution of obesity-associated comorbidities such as reduced fertility has gained popularity in recent decades. Vertical sleeve gastrectomy (VSG) is a surgical weight loss procedure that resects 80% of the stomach creating a tube linking the esophagus to the duodenum. Because of the great effectiveness and relative simplicity of the VSG surgery in comparison with the standard Roux-en-Y gastric bypass that is riddled with potential complications, VSG is now on the rise in the U.S. With >80% of the recipients of VSG being women, of whom approximately half are of child-bearing age, the impact of the surgery on offspring is important to understand. Recent human data show that children born to women who have had bariatric surgery are at 3 fold higher risk of having intrauterine growth restriction (IUGR) compared to children born to obese women. However, the long term consequences on the health of these children are unclear. In addition, the mechanisms responsible for the adverse effects on metabolic and cardiovascular health of offspring of women with bariatric surgery are unknown.

Previously we reported that offspring born to VSG dams exhibit IUGR, a known risk factor for the development of cardio-metabolic disease, including hypertension later in life. Our preliminary data indicate that postnatal exposure to a high fat diet (HFD) exacerbates glucose intolerance in rat VSG offspring and enhances adiposity suggestive of leptin resistance. Thus, our data suggest that VSG offspring may also be at high risk for the development of metabolic disturbances later in life.

Our novel preliminary studies demonstrate that VSG dams have elevated endogenous serum testosterone levels in late gestation. Experimental studies indicate that in utero exposure to elevated exogenous androgens programs IUGR and early-onset cardiovascular disease in male and female offspring. In utero exposure to exogenous androgens also stimulates expression of angiotensin II, indicative of activation of the renin-angiotensin system (RAS), leading to elevated blood pressure.

Therefore, as shown in Figure 1, this proposal will test the novel hypothesis that fetal exposure to elevated endogenous androgens in VSG dams in late pregnancy leads to a unique model of IUGR that programs impaired pancreatic beta cell function causing glucose intolerance and leptin resistance, leading to obesity and hypertension in male and female IUGR offspring. We further hypothesize that inappropriate activation of the renin angiotensin system contributes to increased blood pressure in IUGR offspring exposed to elevated maternal endogenous androgens in VSG dams in late pregnancy. We will use state-of-the-art molecular and integrative physiological techniques to test the following specific aims:

**Specific Aim #1:** To test the hypothesis that fetal exposure to elevated maternal endogenous levels of testosterone in VSG dams programs glucose intolerance mediated by impaired pancreatic beta cell function and leptin resistance leading to obesity and hypertension in IUGR offspring.

**Specific Aim #2:** To test the hypothesis that fetal exposure to elevated maternal endogenous levels of testosterone in VSG dams programs activation of the renin-angiotensin system leading to elevated blood pressure in IUGR offspring.