The Development of a Diet-Induced Obese Mouse Model and its Effect on Fertility

Sameeksha Bhaye[1], Kassandra Sandoval[1], Chanaka Rabel [1], Matthew Dean[1]

[1] Department of Animal Sciences, College of Agricultural, Consumer and Environmental Sciences, University of Illinois at Urbana-Champaign, Urbana, IL, USA

Obesity is a common chronic disease worldwide affecting both men and women. Obesity is associated with many other diseases such as subfertility, insulin resistance, and diabetes mellitus. Studies have shown that women with higher BMI undergoing IVF had lower implantation and live birth rates. Similarly, high-BMI surrogates receiving healthy embryos had low implantation and pregnancy rates suggesting impairment in the uterus. However, findings from diet-induced obese (DIO) mouse models are inconsistent. Many do not report a reduction in fertility as observed in obese women. Thus, this study aimed to develop a diet-induced obese mouse model that mimics changes seen in obese women. Eight week old mice (n=36) were randomly divided into three groups and fed 10% (low-fat diet, LFD), 45% (high-fat diet, HFD), or 60% (very high-fat diet, VHFD) kcal from fat for 18 weeks. Weight was monitored weekly. During the 15th week of feeding, mice were fasted overnight, and an intraperitoneal glucose tolerance test (IPGTT) was performed. Glucose (1g/kg of body weight) was injected, and serum glucose concentrations were measured at 0, 30, 60, 90, and 120 minutes. At 18 weeks mice were fasted for 8 hours and sacrificed in proestrus. The serum was separated and stored at -80°C for serum metabolomics and for measuring glucose, insulin, and leptin concentration. The liver, uterus, ovaries, and adipose tissue (gonadal, retroperitoneal, abdominal) were collected, weighed, and fixed with paraformaldehyde or snap-frozen and stored at -80°C. A significant increase in body weight was observed from weeks 4 and 7 of feeding in the VHFD and HFD groups respectively. Additionally, mice from these groups had a high adiposity index and serum leptin concentration compared to the LFD group, indicating the development of metabolic dysfunction. The liver was enlarged in VHFD mice, whereas ovary weight was reduced in both HFD and VHFD groups. Mice in the VHFD group were intolerant to glucose at 30, 60, and 90 minutes indicating a reduction in clearance of glucose from blood, however, there was no significant change in fasting serum glucose and insulin concentrations between the groups at sacrifice. In another set, mice were housed with male mice for 60 days. The day vaginal plug was found in the mouse was considered day 0.5 of pregnancy and mice were sacrificed at day 18.5 of pregnancy. Mice were

considered infertile if a vaginal plug was not observed after 60 days of housing with a male. Both HFD and VHFD groups showed 50% and 60% reduction in fertility respectively. In mice that did get pregnant, there was no change in litter size, but there was a significant reduction in fetal weight in the 45% fat-fed mice group. There was no change in the placental weight in all the groups. Also, the placental efficiency (fetal weight/placental weight) was not different between the groups. In summary, we have developed a diet-induced obese mouse model that mimics features seen in obese women like reduction in metabolic dysfunction, reduced fertility, and intrauterine growth restriction. Future investigations will use this model to examine changes in serum metabolites, glucose, and glycogen metabolism in the uterus, and immunohistochemistry on glycogen metabolism proteins in the uterine section from the three groups.

Keywords: Diet-Induced Obesity, Fertility, Adiposity, IPGTT, Placental Efficiency

Financial Support: This work is supported by the National Institute of Health [1R01HD111706-01]