CARDIAC EFFECTS OF OBESITY DURING PREGNANCY IN C57BL/6J MICE

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CARDIAC EFFECTS OF OBESITY DURING PREGNANCY IN C57BL/6J MICE

THESIS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Nutrition and Food Systems in the College of Agriculture, Food and Environment at the University of Kentucky

By
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Lexington, Kentucky

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2020

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ABSTRACT OF THESIS

CARDIAC EFFECTS OF OBESITY DURING PREGNANCY IN C57BL/6J MICE

Objective: Pregnancy requires profound cardiac and metabolic adaptation. Left ventricular (LV) mass is increased in response to pregnancy, but is not associated with cardiac damage. In contrast, obesity-mediated cardiac hypertrophy is pathological. Data from animal studies indicate dietary fatty acid composition may have a protective effect during states of extreme cardiac physiological adaptation. In contrast, aberrant cardiac metabolism is a hallmark of disease. Over a third of reproductive-age women in the United States are obese, but there is a paucity of data describing the effect of obesity on maternal cardiac adaptation to pregnancy. The objective of this study was to determine the effects of high-fat feeding during pregnancy on cardiac hypertrophy and metabolism in a mouse model of diet-induced obesity.

Methods/Results: Female C57BL/6J mice (8 weeks old) were fed a high fat (HF; 60% kcal from fat) or a control low fat (LF; 10% kcal from fat) diet for 8 weeks, then were either crossed with male mice to become pregnant (P) or remained non-pregnant (NP) controls. At gestational day 18, cardiac function was quantified by echocardiography in LF- and HF-fed P and NP females. On gestational 19 day, mice were euthanized for tissue collection. HF-fed females had significantly increased body weight compared to LF-fed controls, and body weight was increased in P compared to NP mice. In response to pregnancy, LF-, but not HF-fed, mice had significantly increased LV mass (P<0.01). In contrast, HF-fed pregnant mice had increased relative wall thickness (RWT: [2* LV posterior wall thickness/LV end-diastolic diameter]) compared to LF-fed pregnant mice. We quantified mRNA abundance of genes regulating fatty acid oxidation utilization in left ventricles of LF- and HF-fed pregnant and non-pregnant mice using Nanostring nCounter Analysis system. Acaa2, Acox1, and Acadl (genes regulated long-chain fatty acid oxidation) and Cpt1b (regulating fatty acid transport into the mitochondria) were upregulated with both HF-feeding and pregnancy. In contrast,
*Ehhadh*, a gene regulating production of medium chain fatty acids during fatty acid oxidation, was increased in pregnant mice, but only in the LF mice, and the expression was significantly reduced in HF-compared to LF-fed pregnant mice.

Conclusions: Physiological cardiac hypertrophy in response to pregnancy was observed in LF-fed, but not HF-fed mice. In contrast, HF-fed pregnant mice had increased RWT compared to LF-fed pregnant mice. While fatty acid utilization was increased with HF-feeding and pregnancy, the expression of *Ehhadh* was reduced in HF-compared to LF-fed mice. Medium chain fatty acids are demonstrated in the literature to be protective against pathological cardiac remodeling in experimental animals. Taken together, these data suggest obesity may impair protective fatty acid utilization pathways in pregnancy to promote adverse cardiac remodeling.

KEYWORDS: Pregnancy, CVD, Obesity, Cardiac Metabolism, Remodeling

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CHAPTER 1. INTRODUCTION

1.1 Background

Increasing evidence suggests that pregnancy is a sensitive window where adverse effects on cardiovascular function may permanently alter maternal risk for cardiovascular diseases (CVD) \(^2\). Epidemiology studies demonstrate that women with a history of pregnancy complications, such as gestational hypertension or diabetes, preterm delivery, or intrauterine growth restriction are at greater risk for mortality from CVD \(^3\). Rodent studies support that the profound cardiovascular adaptations during pregnancy may serve as a type of “stress test”, to unmask cardiovascular vulnerabilities \(^4\). These data suggest pregnancy complications are a sex-specific risk factor for CVD. Obesity is strongly associated with pregnancy complications, with a nearly stepwise increase in the incidence of preterm birth, gestational diabetes, hypertensive disorders, and other high-risk conditions with increasing category of body mass index (BMI) \(^5\). This is concerning as the prevalence of both obesity and CVD are rising in women of reproductive age in the United States \(^6\).

Pregnancy induces many structural and functional changes in the cardiovascular system to accommodate the growing uteroplacental unit. One such change is cardiac hypertrophy, or enlargement of the heart in response to increased metabolic demands. Cardiac hypertrophy with pregnancy is assumed to be transient, and is not associated with cardiac damage \(^7\). In contrast, cardiac hypertrophy occurring in response to obesity is pathological, and a prognostic indicator for CVD \(^8\). Despite the known associations between obesity, pregnancy complications, and maternal CVD, there is limited research
describing how obesity modulates cardiac hypertrophy of pregnancy. This is important, as adverse cardiac effects during pregnancy may drive future maternal risk for CVD.

1.2 Problem Statement

Women with a history of obesity-mediated pregnancy complications are at a greater risk of CVD. However, mechanisms linking pregnancy complications and CVD are unknown. Both obesity and pregnancy independently promote cardiac hypertrophy and are associated with changes in cardiac metabolism. It is not known how obesity during pregnancy modulates cardiac hypertrophy and energy metabolism.

1.3 Overall hypothesis

The overall hypothesis of this research project is that obesity during pregnancy promotes adverse cardiac remodeling associated with altered cardiac metabolism.

1.4 Research Questions

1. Does obesity promote altered cardiac hypertrophy during pregnancy in mice?
2. What is the effect of obesity during pregnancy on the expression of genes that regulate cardiac metabolism in mice?

1.5 Impact

If a woman is going to make a lifestyle change, she is more likely to do so while pregnant. This is a crucial time when healthcare professionals need evidence-based
nutritional strategies that can be tailored to accommodate individual nutritional needs and provide sustainable modifications. By providing individualized, sustainable nutritional therapies, women may reduce their risk or progression of obesity-mediated pregnancy complications and/or CVD.
CHAPTER 2. LITERATURE REVIEW

2.1 Cardiac physiology of pregnancy

Pregnancy is a dynamic process, requiring immense physiological adaptation of the cardiovascular system. This includes changes in blood volume, heart function, and changes in properties and function of blood vessels. These changes are necessary for accommodating the growing fetoplacental unit, and to meet the increased metabolic demands of the mother. Insufficient ability of the mother’s body to adapt to these cardiovascular changes can adversely affect the health of both the mother and the fetus. In fact, the cardiovascular demands of pregnancy can sometimes reveal otherwise silent cardiovascular pathologies. This is why pregnancy is often referred to as “nature’s stress test”.

2.1.1 Hemodynamics (the flow of blood through the vessels and organs in the body)

One of the biggest changes during pregnancy is the increase in blood volume. Blood volume increases early in the first trimester, and steadily increases throughout gestation. The total increase in blood volume varies widely, between 20% to an astonishing 100% of pre-pregnancy volume, usually approximated to be about a 45% increase. The vascular system accommodates this via vasodilation (widening of vessels) and an overall decrease of about 35% to 40% in systemic vascular resistance (resistance of vessels to blood flow). Vascular resistance is lowest in the first trimester, accommodating development of the placenta, followed by a slight increase in the end of the second trimester, and remains steady for the remainder of pregnancy. Blood pressure
decreases accordingly, being the lowest in the first trimester, then returning to near pre-pregnancy levels by the third trimester 7.

The increase in blood volume translates to increased stroke volume (the volume of blood pumped through the heart with each beat). Accordingly, cardiac output (the volume of blood pumped through the heart each minute) also increases up to 45% during pregnancy, where cardiac output is determined by multiplying the stroke volume by the heart rate. In summary, Cardiac output is increased by an astounding 30-50%, and peripheral vascular resistance and blood pressure decrease by roughly 20% during pregnancy 7.

2.1.2 Cardiac morphology (size, shape, and geometry)

Cardiac morphology is significantly altered during pregnancy. Cardiac morphology can be assessed via echocardiography, a noninvasive technique that uses ultrasound waves to make images of the heart. Pregnancy is well known to cause cardiac hypertrophy, an enlargement of the heart and ventricles, in response to metabolic demands, including increased blood volume. Cardiac hypertrophy is represented by the mass of the left ventricle (LV). LV mass is estimated to increase by about 40% by the third trimester of pregnancy 7. The physiological cardiac hypertrophy of pregnancy is associated with changes in shape and geometry, as well, collectively termed cardiac remodeling. Characterization of cardiac remodeling in pregnancy is not very well defined. A recent study in humans reported increased chamber size with wall thinning, termed “eccentric” remodeling 9. Changes in cardiac remodeling during pregnancy are of interest, as adverse remodeling can be a prognostic indicator of future CVD. This will be discussed further below.
2.1.3 Reverse Adaptation

Literature in humans suggests cardiac changes during pregnancy return to pre-pregnancy values, within a year. However, these studies are historical, and few studies have characterized cardiac function and structure postpartum using modern technology. Studies in healthy animals suggest that hemodynamics and cardiac morphology return to pre-pregnancy values about 7 days postpartum. However, recent rodent studies demonstrate that factors such as age and health status (i.e. obesity) may be detrimental to reverse cardiac adaptation postpartum. This is important, as a growing body of literature suggests that factors impacting cardiovascular function during pregnancy have a lasting impact on maternal cardiovascular function.

2.2 Epidemiology of pregnancy history and maternal heart health

2.2.1 Sex differences in CVD

Cardiovascular disease is the number one cause of death in both men and women in the United States, but the disease manifests differently in women compared to men. For example, women are more likely to develop certain types of heart disease, such as stroke, left ventricular (LV) diastolic dysfunction, and heart failure with preserved ejection fraction (HFpEF). Women also have a more steeply increasing risk with age compared to men. Only in the last decade have mechanisms contributing to sex differences in CVD become a major research focus. Contributing to the lack of understanding of CVD in women is the fact that females have traditionally been marginalized in human and animal studies.
Recent studies defining the role of sex hormones on cardiovascular function have contributed to significant advancements in explaining sex differences in type, timing, and mortality of CVD\textsuperscript{13}. Research examining sex disparities between men and women in terms of pathology and physiology has revealed that women are more likely to experience endothelial and microvascular dysfunctions related to coronary artery disease compared to men \textsuperscript{16}. These differences might be attributed to estrogen, which is reported to have protective effects on vascular and endothelial function, as well as metabolism and adiposity \textsuperscript{17}. However, discrepancies exist in findings from randomized-controlled trials designed to test protective effects of female sex hormones against CVDs\textsuperscript{18}. In the Women’s Health Initiative (WHI), hormone replacement therapy in postmenopausal women actually contributed to increased risk for CVD in some women \textsuperscript{19}, suggesting that sex hormones alone cannot be solely responsible for protective effects against CVD in women. In addition to sex hormones, sex chromosome compliment also contributes to development of CVD, such as aneurysms \textsuperscript{13}. These findings indicate that other sex-specific factors also contribute to differential cardiovascular function between males and females. The experience of pregnancy is one of the most profound physiological differences between males and females, requiring extensive cardiovascular adaptation.

To improve heart health in women, it is essential to define how cardiovascular stress during pregnancy affects future maternal cardiovascular function.

2.2.2 Pregnancy complications are associated with maternal risk for CVD

Pregnancy complications, such as gestational hypertension or diabetes, preterm delivery, or intrauterine growth restriction (IUGR) are associated with mortality from cardiovascular disease (CVD) \textsuperscript{3}. Results from several large cohort studies demonstrate
that women with a history of gestational hypertension and related conditions, such as preeclampsia, have an increased risk for developing CVDs like hypertension, ischemic heart disease, stroke, and death due to CVD even decades after delivery. As a group, complicated pregnancies are characterized by inflammation, vascular dysfunction, thrombosis, and insulin resistance; physiologic pathways which are common to CVD. These data suggest that adverse physiology of a woman’s reproductive history may serve as a predictor for chronic disease (see Figure 1). It is not clear whether pregnancy is a “stress test” that reveals latent cardiovascular abnormalities, or if adverse effects on the cardiovascular system during pregnancy can permanently alter the trajectory of maternal heart health (or both).

### 2.3 Obesity and pregnancy complications

Obesity is the most common medical condition during pregnancy that affects maternal and fetal health. According to the CDC, the prevalence of obesity in the United States is increasing in women of reproductive age, with approximately 55% of women aged 20-39 years old having a body mass index (BMI) of greater than 25, and approximately 31% having a BMI over 30. Maternal obesity has both short-term and long-term health consequences for mother and offspring. Obesity during pregnancy is associated with fertility problems, metabolic derangements, hypertensive disorders (such as preeclampsia), premature delivery, cesarean delivery, impaired fetal growth or macrosomia, and stillbirth.
Epidemiological data worldwide has linked maternal obesity to increased risk for metabolic and cardiovascular disease in offspring. However, mechanisms directly linking maternal obesity to subsequent cardiovascular disease are not known.

2.4 Cardiac effects of obesity

2.4.1 Obesity augments traditional risk factors

It is well established that obesity augments cardiovascular risk factors, such as blood pressure, blood lipid levels, and the development of metabolic syndrome. In men and women, obesity is a primary contributor to the development of hypertension. High blood pressure is a significant predictor for CV events. While the overall worldwide prevalence of hypertension is greater in men, with increasing age (and menopause), the incidence of hypertension in women rises. Given that the prevalence of obesity is greater in women (at all ages), the overall burden of obesity-associated hypertension may actually be greater in women than men.

Obesity contributes to dyslipidemia by increasing blood triglyceride and Free Fatty Acids (FFA) levels. Consequences of this include perturbed lipoprotein metabolism, causing the formation of atherogenic lipoprotein particles, as well as free fatty acid-mediated insulin resistance. Dyslipidemia increases the risk for CVD, such as atherosclerosis and coronary heart disease.

Excess adipose tissue with obesity, especially visceral or abdominal adipose stores, also indirectly contributes to increased cardiovascular risk through release of inflammatory mediators. Adipose tissue secretes a number of adipokines that contribute to immune function and metabolism, and a pathological consequence of excess adipose
mass is increased secretion of adipokines and other pro-inflammatory factors, such as TNF-a, IL-6, and MCP-1. These factors can have diverse adverse effects including impaired endothelial function and increased insulin resistance.

2.4.2 Obesity is an independent risk factor for CVD

In addition to augmenting cardiovascular risk factors, such as hypertension and type 2 diabetes, obesity is an independent risk factor for cardiovascular disease. Obesity is associated with global longitudinal strain, and both impaired systolic and diastolic function. In response to increased blood volume and stroke volume (SV), mean arterial pressure and ventricular filling pressures can become elevated. Obesity and excess adiposity are directly associated with cardiac hypertrophy and remodeling, and geometric changes are further augmented with increasing blood pressure. Interestingly, although absolute LV mass is greater in men, when normalized for body size, the effect of obesity to increase LV mass is reported to be greater in women versus men. Further, a direct association is reported between LV mass and body fat percentage, especially visceral adipose tissue. The proportion of body fat is generally greater in women compared to men. Taken together, these data suggest that women may be particularly susceptible to obesity-mediated alterations in cardiac morphology.

2.4.3 Cardiac effects of obesity during pregnancy

It is fairly well-documented that obese women have increased blood pressure compared to non-obese women during pregnancy. Further, obesity is a risk factor for hypertensive disorders of pregnancy, such as preeclampsia. What is less clear is the direct effect of obesity on cardiac structure and function during pregnancy, as well as, the
long-term implications. In a study comparing obese versus non-obese women at 36 weeks gestation, blood pressure and LV mass were increased with obesity, but no differences were observed with respect to CO or ventricular function. In contrast, a serial study over trimesters in 16 obese and 17 non-obese pregnancies reported differences in SV and contractility in obese women. Interestingly, the difference was most striking with respect to the change in function throughout gestation. SV was greater in obese versus non-obese women in the first trimester, however non-obese women exhibited an increase in SV and CO throughout gestation, which was not observed in obese women. A similar trend was observed in indices of contractility, with some measures of contractility actually decreasing in obese women in the third trimester. The authors concluded that obesity was associated with impaired LV contractile response. Using speckle tracking in conjunction with echocardiography, Buddeberg et al recently reported diastolic dysfunction and LV global longitudinal strain in obese pregnant women at term compared with non-obese controls. These studies provide evidence that obesity during pregnancy can adversely modulate cardiac function. However, the long-term consequences of these alterations on cardiovascular health are not known.

2.5 Cardiac metabolism

2.5.1 Overview of cardiac metabolism

The heart is a biological pump that converts chemical substrates into mechanical energy. The heart primarily consumes carbohydrates (10-30%) and fats (60-90%) while using oxygen to drive oxidative phosphorylation to generate ATP from ADP. ATP is
then used to drive contractile function (beating), to perfuse the body with blood and nutrients. Energy consumption of the human heart is about 10% of whole-body fuel consumption. The heart is described as a metabolic omnivore and has incredible flexibility to utilize a variety of substrates in the presence of oxygen to generate ATP. Energy producing substrates include triacylglycerols, fatty acids, glucose, glycogen, lactate, pyruvate, the ketone bodies acetoacetate and β-hydroxybutyrate, and amino acids, especially leucine, isoleucine, and valine (branched-chain amino acids)⁴⁵. These substrates enter the Krebs cycle primarily as acetyl-CoA, or other intermediates of the Kreb’s cycle, for production of reducing equivalents (e.g., NADH and FADH₂ are a couple), which deliver electrons to the electron-transport chain in the mitochondria. The resulting generation of a proton gradient drives the formation of ATP. In an anerobic state, the heart can also utilize lactate (via degradation of glucose) and succinate (via degradation of some amino acids). See Figure 2 for schematic of cardiac metabolism.

2.5.2 Altered cardiac metabolism hallmark of disease states

The heart has the capacity to adapt to an altered metabolic state by selecting available substrates for the most effective generation of ATP. This metabolic flexibility is lost during heart failure, and pathologic states directly influencing substrate availability (e.g. obesity, diabetes) can further contribute to impaired cardiac function ⁴⁶. It is well-known that diabetes is associated with increased fatty acid utilization and decreased glucose utilization ⁴⁷. Likewise, obesity results in increased fatty acid utilization and reduced glucose oxidation rates ⁴⁸. This is likely due to substrate availability, as obesity is associated with increased levels of circulating fatty acids and triglycerides. Conversely, the
reduction in glucose utilization is likely due to the Randle effect, where increased
utilization of fatty acids has an inhibitory effect on glucose metabolism 47.

Changes in substrate metabolism precede changes in function and may be the
first indication of functional abnormalities. Studies in humans and animals demonstrate
that prolonged increase in fatty acid utilization results in increased myocardial oxygen
consumption, i.e. increased oxidative phosphorylation, and reduced cardiac efficiency 49.
Despite obesity being associated with an increase in the number of mitochondria, studies
in ob/ob mice (a genetic mouse model of obesity) reveal that mitochondria from obese
hearts have deficits in oxidative capacity 50. This dysfunctional condition is called
oxidative uncoupling, where oxygen consumption is increased, but a proportional
increase in ATP production is not observed 51. This is a potential mechanism by which
obesity promotes impaired cardiac function. Increased fatty acid uptake and oxidation
promote the formation of damaging reactive oxygen species (ROS) from mitochondrial
complexes, but energy production declines 51. The potential consequence for reduced
cardiac efficiency is a limitation in cardiac reserve, which may be worsened in the face
of hemodynamic stressors, such as cardiac hypertrophy and increased blood pressure.

2.5.3 Cardiac metabolism during pregnancy

As described above, pregnancy is a form of cardiac stress. Notably, LV mass
increases by up to 50%, which requires energy. Interestingly, while cardiac work
increases by 20-30% during pregnancy, cardiac oxygen consumption is only increased by
approximately 15% 52. Thus, cardiac efficiency is increased during pregnancy. There is
not much known about cardiac metabolism during pregnancy. Studies from rats indicate a
progressive decline in glucose utilization, with up to a 70% reduction by late pregnancy.
Studies in dogs demonstrate a large increase in fatty acid oxidation, indicating that the ATP production in the heart during late pregnancy is almost exclusively due to increased utilization of fats.

There are no studies in humans or animals describing the combined effects of obesity and pregnancy on cardiac metabolic function. The present study will directly fill that gap.
Figure 1: “Pregnancy is a “stress test” that can reveal subclinical trajectories and identify new opportunities for chronic disease prevention”.


Figure 2: Overview of cardiac metabolism
Overview of cardiac metabolism, from Myocardial Substrate Metabolism in the Normal and Failing Heart, Stanley et al, 2005.
CHAPTER 3. METHODS

3.1 Experimental animals and study design

All studies using mice were approved by an Institutional Animal Care and Use Committee (IACUC) at the University of Kentucky and were conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. Female C57BL/6J mice (8 weeks of age; Jackson Laboratory, Bar Harbor, ME, stock # 000664) were randomly assigned to receive, ad libitum, either a high fat (HF; 60% kcal from fat; D12492, Research Diets, New Brunswick, NJ) or a control low fat (LF, 10% kcal from fat; D12450B, Research Diets Inc) diet for 8 weeks (n=30 mice/diet group) (see Figure 3 for experimental design). The control LF diet was purified and ingredient-matched to the HF diet, and the fat source for both diets was soybean oil and lard (where lard comprises the excess fat in the HF diet). The energy densities of the LF and HF diet are 3.82 and 5.21 kcal/g, respectively. Body weight was quantified weekly throughout the study using an Ohaus portable digital scale.

At 8 weeks of diet feeding, all female mice were placed in a cage with male mice of the same strain and diet. After 2 days, females were removed from the males, and placed in single housing for the duration of the study.

Echocardiography was performed on LF- and HF-fed female pregnant and non-pregnant mice 16 days following removal from male cage. The following day, mice were anesthetized with ketamine/xylazine (100/10 mg/kg, i.p.) for exsanguination and tissue harvest. Fetuses and placentas were dissected and weighed. Tissues were snap frozen in liquid nitrogen and stored at -80°C until analysis. Tissues taken included: heart, liver, kidney, spleen, para-uterine fat, and subcutaneous fat.
3.2 Echocardiography

Echocardiography was performed on isoflurane-anesthetized mice as described previously. Day 16 was chosen, because normal mouse gestation is 20 days or the equivalent of the third trimester in humans. Briefly, mice were anesthetized using 2-4% isoflurane (at effect) according to their size and then transferred to a heated platform (37°C) with 1-2% isoflurane supplied via nose cone. Hair on the chest region was shaved and removed, and electrode cream was applied on the front and hind limbs before being secured with electrical tape to electrodes on the platform. Respiration rate (RR) and heart rate (HR) were monitored and adjusted to a certain range across all mice by titrating isoflurane levels. An RR of 100 times/min and HR of 400 beats/min were targeted. Images of the cross-sectional view of the left ventricle (LV) at the papillary muscle-level in parasternal short-axis (PSAX) view were obtained in M-mode using an M550 transducer under the cardiology package on a Vevo 3100. Images were analyzed using VevoLab software using LV trace methodology.

3.3 Tissue RNA extraction and gene expression analysis

Approximately 20 mg of the left ventricle was used to extract total RNA using the Maxwell RSC (Promega, Madison, WI). RNA concentrations and quality were determined using a Nanodrop 2000. All samples had a 260/280 and 260/230 ratios > 2.0. The NanoString nCounter Metabolic Pathways Panel and nCounter Analysis System (NanoString Technologies, Seattle, WA) was used to quantify mRNA abundance of 768 genes regulating metabolism. As previously described, the Nanostring nCounter gene expression system is a multiplexed assay that uses a combination of unique capture
probes and color-coded reporter probes to capture and count individual mRNA transcripts with high sensitivity and tight correlation to real-time PCR. Fifty nanograms of RNA of each sample was hybridized to the target-specific capture and reporter probes in the CodeSet according to the manufacturer’s instructions. Samples were cooled to 4°C, loaded into nCounter SPRINT cartridges, then analyzed using the nCounter Gene Expression Assay. Raw data were normalized by creating scaling factors for the sum of the positive controls and the geometric mean of the four housekeeping genes. Data represent the mean of normalized counts.

3.4 Statistical analysis

Data are presented as mean ± SEM. Statistical analyses were performed using SigmaPlot version 12.3. All data passed normality or equal variance tests or logarithmic transformation was used to achieve normality. Two-tailed Student’s t-tests were used for analysis of data between two groups. For 2-factor analysis, a two-way ANOVA was used to analyze end-point measurements with between-group factors of pregnancy and diet, followed by Holm-Sidak for post hoc pairwise analyses. Values of P < 0.05 were considered to be statistically significant.
Figure 3. Experimental Design

Female C57BL/6 mice 8 weeks of age n=60

LF diet n=30

Pregnant, n=10

Non-pregnant, n=20

HF diet n=30

Pregnant, n=12

Non-pregnant, n=18

8 weeks diet Cross with males for 2 days

18 days after cross Echocardiography 19 days after cross Tissue collection

<table>
<thead>
<tr>
<th>Research Diets</th>
<th>Low Fat (L,F,D12450I)</th>
<th>High Fat (H,F,D12492)</th>
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<td>10 / 20 / 70 % kcal</td>
<td>60 / 20 / 20 % kcal</td>
</tr>
<tr>
<td>kcal/gram</td>
<td>3.82</td>
<td>5.24</td>
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</tbody>
</table>
CHAPTER 4. RESULTS

4.1 HF-feeding increases body weight and fat mass

After 8 weeks of diet feeding, HF-fed females had significantly increased body weight compared to LF-fed controls (P<0.001; 14A). Within HF-fed mice, the average body weight of females who eventually became pregnant was lower than those who did not become pregnant, but this was not significant (p=0.06). Further, HF-fed mice had increased fat mass and decreased lean mass (as percent body weight), compared to LF-fed mice P<0.001; Figure 4B). At study endpoint (day 18 of gestation), body weight was increased in pregnant compared to non-pregnant animals, independent of diet (P<0.001; and HF-fed pregnant mice had increased body weight compared to LF-fed mice (P<0.01, Figure 4C).

4.2 HF-feeding reduces litter size

Compared to LF-fed dams, HF-fed dams had smaller average litter size (P<0.01), and a greater number of resorbed pups (Table 1). There was no difference in pup body weight or placental weight in LF- compared to HF dams.

4.3 HF-feeding increases heart weight and LV mass, but is not augmented with pregnancy

In non-pregnant mice, excised heart weight was greater in HF- fed mice compared to LF-fed mice (P<0.001; Table 2). In LF-fed mice, heart weight was increased with pregnancy (P<0.05, Table 2), but HF-fed pregnant mice did not have significantly
increased heart weight compared to LF pregnant mice. Similarly, LV mass was increased with HF-feeding in non-pregnant mice (P<0.05, Figure 5A). However, only LF-fed mice exhibited cardiac hypertrophy with pregnancy (P<0.001); LV mass was not augmented with pregnancy in HF-fed mice (p=0.221, Figure 5A).

4.4 Wall thickness is increased in HF-compared to LF-fed pregnant mice

The increase in LV mass in NP HF-fed mice was associated with increased LV posterior wall thickness (P<0.01, Figure 5B). In contrast, increased LV mass with pregnancy in LF-fed mice was associated with an increase in the ventricle chamber (P<0.001), with no change to the wall thickness, and the diameter of the LV ventricle was significantly larger in LF- versus HF-fed pregnant mice (P<0.05). Thus, the relative wall thickness, a measure of LV geometry, was significantly increased in HF- compared to LF-fed mice during pregnancy (P<0.05, Figure 5B). Data summarizing cardiac morphology depicted in a schematic in Figure 5C.

4.5 Analysis of genes regulating metabolism in hearts

To determine the gene profile associated with changes in the cardiac structure of HF- versus LF-fed pregnant mice, we quantified mRNA abundance of 794 genes regulating metabolism involved in 34 pathways using NanoString nCounter gene expression analysis in the left ventricles of LF- and HF-fed pregnant and non-pregnant mice. Using 2-way ANOVA with pairwise comparisons, we determined that there were 47 genes with a significant effect of either gene or pregnancy with P<0.01. Using a p-value <0.05, there were 26 genes with a significant effect of diet, 35 with a significant
effect of pregnancy, and 16 with a significant interaction between diet and pregnancy (Figure 6).

Since the largest number of genes with significance differences were related to fatty acid utilization, we focused our analysis on these genes. These genes are: Acaa2, Acadl, Acox1, Cpt1b, Fabp3, and Ehhadh. For Fabp3, there was an overall effect of diet to increase the abundance of cardiac mRNA, but no effect of pregnancy (P<0.01, Figure 7F). Similarly, Acaa2, Acadl, Acox1, and Cpt1b were upregulated with HF-feeding (P<0.05, Figure 7A-D). There was also a significant of pregnancy, but this was only significant in the LF-fed group (P<0.05). Meaning, gene expression of these genes was increased in HF-fed mice (pregnant or non-pregnant), and increased in LF-fed pregnant mice, but there was no additional effect of pregnancy to increase gene expression in HF-fed pregnant mice. The expression pattern of Ehhadh was different, where Ehhadh was elevated only in the LF-fed pregnant mice (P<0.01, Figure 7E). Further, the expression level of Ehhadh in HF-fed pregnant mice was significantly lower than that of LF-fed pregnant mice (P<0.05).
Table 1: Litter size and pup/placental weights from LF- or HF-fed pregnant female mice.

<table>
<thead>
<tr>
<th>Diet</th>
<th>Pups per litter</th>
<th>Pup weight (g)</th>
<th>Total number of resorbed pups</th>
<th>Number of dams with resorbed pups</th>
<th>Placenta weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF</td>
<td>8.6 ± 0.3</td>
<td>1.01 ± 0.11</td>
<td>4</td>
<td>4</td>
<td>0.111 ± 0.005</td>
</tr>
<tr>
<td>HF</td>
<td>6.4 ± 0.5**</td>
<td>0.93 ± 0.11</td>
<td>21</td>
<td>10</td>
<td>0.111 ± 0.005</td>
</tr>
</tbody>
</table>

**, P<0.01 effect of diet

Table 2: Heart weights of LF- and HF-fed pregnant and non-pregnant female mice.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LF (NP n=20)</th>
<th>P (n=20)</th>
<th>HF (NP n=18)</th>
<th>P (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart weight (g)</td>
<td>0.118 ± 0.003</td>
<td>0.128 ± 0.004#</td>
<td>0.132 ± 0.003***</td>
<td>0.136 ± 0.004</td>
</tr>
<tr>
<td>Heart/body weight (%)</td>
<td>0.529 ± 0.012</td>
<td>0.374 ± 0.017###</td>
<td>0.412 ± 0.013***</td>
<td>0.348 ± 0.016###</td>
</tr>
</tbody>
</table>

***, P<0.001 effect of diet
###, P<0.001 effect of pregnancy
#, P<0.05 effect of pregnancy
Figure 4: Weight gain from baseline to gestational day 19
A) Body weight and (B) lean and fat mass of mice fed a LF or HF diet for 8 weeks (before pregnancy). (C) Body weight of LF- and HF-fed pregnant (gestational day 19) and non-pregnant mice at study endpoint. Data are mean ± SEM in n=10-20 mice per group. *, P<0.001 effect of diet; #, P<0.001 effect of pregnancy by 2-way ANOVA.
Figure 5: LV mass and RWT
A) LV mass and (B) relative wall thickness (RTW; 2 * posterior wall thickness divided by LV diastolic diameter) in pregnant (P) and (NP) female mice fed a low-fat (LF) or high-fat (HF) diet. Data are mean + SEM from n=20 LF NP, n=10 LF P, n=18 HF NP, and n=12 HF P. *, P<0.05 compared to LF; #, P<0.05 compared to NP analyzed by 2-way ANOVA followed by Holm-Sidak pairwise analysis. (C) Schematic representation depicting changes in LV chamber and wall thickness in response to diet and pregnancy. Notably, LV chamber diameter is increased with pregnancy in LF-fed mice; in contrast, HF-fed mice exhibit increased RWT with pregnancy compared to LF-fed mice.
Figure 6: Flow chart of cardiac genes measured using Nanostring significantly changed using 2-way ANOVA by either diet or pregnancy.
Figure 7: mRNA abundance of fatty acid utilization genes in pregnant and non-pregnant mice fed a LF or HF diet.

Data are expressed as counts of mRNA transcripts, normalized to the geometric mean of counts of four housekeeping genes. Data are mean + SEM from n= 8 (LF NP), n=9 (LF P), n=9 (HF NP), and n=10 (HF, P). *, P<0.05 effect of diet; **, P<0.001 effect of diet; #, P<0.05 effect of pregnancy, ##, P<0.01 effect of pregnancy by 2-way ANOVA followed by Holm-Sidak pairwise analysis.
CHAPTER 5. DISCUSSION

The present study examined the effects of obesity on cardiac hypertrophy of pregnancy in mice by quantifying left ventricular (LV) mass and the expression of genes that regulate metabolism in the hearts of pregnant obese versus lean mice. The major findings of this study are (1) HF-feeding increased body weight and fat mass in pregnant compared to non-pregnant controls, independent of diet, (2) HF-fed dams had smaller average litter sizes and a greater number of reabsorbed pups compared to LF-fed dams, (3) LF-fed mice exhibited cardiac hypertrophy in response to pregnancy; while LV mass was increased with HF-feeding, it was not further augmented with pregnancy, (4), relative wall thickness was decreased with pregnancy in LF-fed dams, and HF-fed dams had increased wall thickness compared to LF-fed dams, and (5) cardiac fatty acid utilization is increased with HF-feeding and with pregnancy, but HF- compared to LF-fed pregnant mice had decreased expression of Ehhadh, a gene responsible for producing medium-chain fatty acids (MCFA). These results indicate that obesity during pregnancy promotes adverse cardiac remodeling and may impair oxidation of MCFA.

This research project addresses the important concept that cardiovascular health during pregnancy may have a profound impact on lifetime maternal cardiovascular risk. We previously demonstrated that mice given a HF diet during pregnancy had augmented cardiac hypertrophy postpartum, suggesting that obesity during pregnancy is associated with elevated risk for CVD. Mechanisms for obesity-mediated cardiac dysfunction are not known.
Obesity and dyslipidemia are risk factors for cardiac hypertrophy, a predictor of adverse outcomes. Pregnancy, a condition of rapid weight gain and elevated serum lipid status, also induces cardiac hypertrophy, but this is not associated with CVD. We demonstrated that mice fed a LF diet during pregnancy exhibited cardiac hypertrophy. Similar to existing literature in humans and rodents, this was associated with a change in cardiac geometry, where the ventricle chamber was larger and the cardiac wall thinner compared to LF non-pregnant mice. This reduction in relative wall thickness (RWT) is termed “eccentric” remodeling. In contrast, HF-fed pregnant mice did not exhibit an increase in LV mass compared to HF-fed nonpregnant mice. Further, HF-fed pregnant mice exhibited increased RWT (termed “concentric” remodeling) compared to LF-fed pregnant mice. Increased RWT and concentric remodeling, is an indicator of impaired cardiac function. These data suggest that HF-feeding during pregnancy promotes adverse cardiac remodeling.

Aberrant cardiac metabolism is a hallmark of disease in patients with heart failure and diabetes mellitus; the pattern of substrate utilization under these conditions is different compared to a healthy heart. Similarly, cardiac metabolism is altered under conditions of physiologic hypertrophy. The Burmese python is an animal model of extreme metabolism. Consumption of a large meal in these infrequent eaters induces a robust and striking metabolic postprandial shift. Studies by Leinwand et al reveal that the python heart grows in mass by an astonishing 40% 2-3 days following a large meal, and that this is physiological, not pathological, cardiac hypertrophy. The researchers determined that cardiac metabolism following a meal was associated with markedly increased fatty acid utilization pathways, and that a composition of fatty acids in python
plasma promotes physiological cardiac growth. We likened this concept to physiologic cardiac hypertrophy during pregnancy, and wondered if changes in cardiac fatty acid utilization during pregnancy could have a protective effect against pathological cardiac growth.

Consistent with studies in ob/ob mice, a mouse model of genetic obesity, we report that HF-feeding increases expression of genes regulating fatty acid transport into the mitochondria (Fabp3, Cpt1b) and fatty acid β-oxidation (Acaa2, Acadl, Acox1). With the exception of Fabp3, these genes were increased with pregnancy in LF-fed mice. These data indicate that both pregnancy and obesity promote increased fatty acid utilization as a substrate in the heart, with obesity having the larger influence. However, these effects were not additive in the HF-fed pregnant mice; the mRNA count of these genes in HF-fed pregnant mice were roughly equivalent to those in the HF-fed nonpregnant mice. This suggests that obesity may “max out” fatty acid utilization through upregulation of transporters and oxidation of long- and very long-chain fatty acids. In contrast, there was one gene, Ehhadh, that did not follow this trend. This gene was not upregulated with HF-feeding, but was significantly upregulated with pregnancy. Notably, the expression level in the HF- pregnant mice was significantly reduced compared to that of the LF-pregnant mice. This suggests an important role for this gene in cardiac metabolism of pregnancy that was impaired with obesity. We wondered if there could be a relationship between function of Ehhadh and cardiac hypertrophy, and if reduction of Ehhadh could be associated with the adverse cardiac remodeling (i.e. thickened wall thickness) observed in the HF-fed pregnant mice.
Ehhadh encodes a protein that is part of the classical peroxisomal fatty acid β-oxidation pathway, with an essential role in the production of medium-chain dicarboxylic acids (MCDA) \(^{58}\). The purpose of MCDA production in cardiac metabolism is not known. Medium chain fatty acids (MCFA) serve as a rapid energy source because they are metabolized quickly, and it can be speculated that MCFA are an important substrate for the heart during pregnancy, when the heart’s energy needs are dramatically increased. Literature reports that supplemental MCFA into the diet can improve weight loss and energy expenditure, since MCFA are preferentially utilized as fuel (versus storage in adipose tissue) \(^{16}\). Studies in pregnant rats demonstrate that supplementation with MCFA, compared to LCFA, into the diet during pregnancy prevented obesity and improved lipid metabolism of offspring who were given a HF diet \(^{59}\). Thus, MCFAs have a beneficial effect on metabolism and health status.

Data from limited studies suggest a positive effect of MCFA on heart function in pathological conditions. Supplementation of MCFA improved cardiac function in rats under conditions where oxidation of fatty acids was impaired \(^{60}\). Further, MCT supplementation in the diets of rats with left ventricular hypertrophy reduced hypertrophy and cardiac oxidative stress \(^{61,62}\). This is an important piece of evidence, as it links MCFA supplementation with reversal of adverse cardiac remodeling. There are no studies of MCT supplementation on the heart in pregnancy. However, findings from our current study extend those of published literature by suggesting that production of MCFA is associated with normal cardiac hypertrophy of pregnancy. Taken together with the findings from python hearts that certain FA are protective in the face of extreme physiologic hypertrophy, our study describes a potential mechanism by which obesity
during pregnancy impairs a cardiac fatty acid oxidation pathway normally associated with healthy pregnancy.

In addition to aberrant cardiac hypertrophy of pregnancy, we observed other adverse effects of high fat feeding in pregnant mice. HF-fed mice had smaller litter sizes and more resorbed pups compared to LF counterparts. The last point was particularly evident during our experiment. Only 4 out of 10 pregnant LF mice had a fetal resorption, and we observed only 1 resorption per dam. In striking contrast, 10 of 12 HF dams had resorptions, and multiple resorbed fetuses were evident in many dams. We observed 21 versus only 4 total resorptions in HF versus LF mice. This is consistent with studies in humans demonstrating overweight women are more likely to have a higher incidence of infertility, miscarriage, and pregnancy complications. For example, the rate of miscarriage in obese women is 38.1% compared to 13.3% in with normal BMI. Further, Lo et al reported that as many as 78% of recurrent miscarriages are associated with obesity. Taken with findings from our study, obese pregnancies carry a higher risk of pregnancy complications, adverse impacts on fetal development, and higher rate of miscarriage.

5.1 Limitations and Future Studies

There were several limitations to our study and to our data analysis. We did not characterize the cellular composition of the cardiac wall in the LF vs HF animals. Although increased RWT is nearly always associated with pathology, that was not confirmed in our study. Future studies will stain sections of the LV for fibrosis, which is a hallmark of adverse cardiac remodeling. In addition, we focused our gene analysis only
on fatty acid utilization. There were other genes pathways that were significantly altered, including genes regulating amino acid metabolism, glycolysis, and mitochondrial respiration. Impairment of these pathways are demonstrated in the literature as impaired with cardiac dysfunction. Future studies will consider interaction of multiple metabolic pathways together with fatty acid utilization as contributors to the observed pathology in the HF-fed pregnant mice.

Further, our analysis of genes regulating fatty acid utilization was global, and we did not assess other genes outside of the Nanostring CodeSet regulating MCFA oxidation. Nor did we measure fatty acid components in serum or cardiac tissue extracts. Findings from our study generated the hypothesis that production of MCFA has a protective effect on cardiac hypertrophy in pregnant mice fed a HF diet. To test this hypothesis, future studies might supplement the HF diet with a source of MFCA, such as coconut oil to see if this prevents adverse remodeling during obese pregnancy.

5.2 Public Health/Clinical Significance

Over two-thirds of the reproductive age women in the US are obese. Adverse cardiac effects during pregnancy may contribute to increased risk for CVD postpartum. Therapeutics to protect heart function during pregnancy are needed. Our results indicate that MCFA may have a protective effect on cardiac adaptation during pregnancy, which is impaired in obesity. Therefore, MCFA supplementation in the diet during pregnancy may be a preventative therapeutic to protect the heart in women with obesity. However, more research is needed to determine the fatty acid profile of hearts during pregnancy, and whether supplementation with MCFA is safe. In the meantime, women who are
obese during pregnancy should focus on consuming a well-balanced diet containing adequate lean protein sources, a variety of plant-based fats, and plenty of fresh fruits and vegetables. Additionally, the inclusion of more long chain fatty acids, such as poly-unsaturated (PUFA) and mono-unsaturated fats (MUFAs), which include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) should be consumed to meet linolenic acid ($\omega$-6; LA) and alpha linolenic acid ($\omega$-3; ALA) requirements (LA – 11-13g/day and ALA – 1.1-1.4g/day for women ages 14 – 70 years old). All of which play an important role in human health and fetal development, such as reducing cardiovascular disease, inflammatory responses, and brain development. Sources of these essential fatty acids should be consumed from natural food sources (flax seed, chia seed, walnuts, fatty fish, seaweeds, etc.) and through a dietary supplement (i.e. DHA for vegetarians/vegans).
In conclusion, these results demonstrate that obesity during pregnancy did not promote altered cardiac hypertrophy, however it did promote adverse cardiac remodeling in mice. While LV mass was increased with HF-feeding, there was not further augmentation with pregnancy. In contrast, HF-fed dams had increased wall thickness compared to LF-dams. Furthermore, the results also demonstrated that obesity during pregnancy decreases the expression of Ehhadh – a gene responsible for producing medium chain fatty acids in cardiac tissues in mice. Suggesting that the combined effects of pregnancy and obesity promote adverse remodeling and altered fatty acid utilization in the heart. The clinical significance of this study is that this study provides more evidence towards the effects of obesity during pregnancy modulating cardiac hypertrophy and altered metabolism.
REFERENCES


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