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The Effects of Dietary Interventions on Adverse Outcomes in Obese, Preeclamptic-like BPH/5 Female Mice

by

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Undergraduate honors thesis under the direction of

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INTRODUCTION

*Maternal Risk Factors of PE.* Preeclampsia (PE) is a leading cause of maternal and fetal mortality and morbidity (1). Clinically PE presents as new-onset hypertension in pregnancy along with the development of proteinuria, endothelial dysfunction, or another accompanying sign/symptom of multiorgan failure (2). Maternal hypertension is determined by blood pressure readings with a systolic value greater than 140 mmHg and a diastolic value greater than 90 mmHg (3). Symptoms of PE typically present after 20 weeks of gestation (defined as early onset); however, the disorder can arise after 34 weeks of gestation (or late onset) (3). PE is associated with uterine/placental abnormalities and adverse fetal co-morbidities such as intrauterine growth restriction and preterm birth (2). Many factors are suspected to contribute to the development of PE including: family history of PE, advanced maternal age at pregnancy (> 35 years of age), and other pre-existing medical conditions such as hypertension, diabetes or renal dysfunction (2).

*Obesity and Systemic Inflammation in Pregnancy.* There is a strong correlation between obesity and PE. With the incidence of both obesity and PE rising worldwide, there is a great need to understand how attenuation of maternal obesity can improve the adverse outcomes associated with PE (4). Adipose tissue, composed of adipocytes and stromal vascular cells, acts as an endocrine organ and impacts cell signaling (5). Adipocytes release adipokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) that promote cell-to-cell signaling of local and systemic inflammation (6). It is hypothesized that excess adipose tissue in pregnancy, i.e. maternal obesity, can cause improper remodeling of the vasculature in the uterus due to high circulating proinflammatory immune cells that can cross-talk between maternal adipose tissue and uterine/placental tissues (7). The release of proinflammatory cytokines (TNF-α and IL-6)
and other anti-angiogenic factors can result in placental ischemia as well as increase the risk of maternal hypertension and fetal growth restriction (7).

**Obesity and Cholesterol Synthesis Activity.** Circulating cholesterol is derived from two sources: dietary cholesterol or cellular cholesterol. Cellular cholesterol production and cholesterol homeostasis is maintained primarily by the liver (8) but is also produced by adipose tissue (9). In an obese state, the adipose tissue stores approximately 50% of the body’s cholesterol (9). As adipose tissue hypertrophies with obesity it stores more free cholesterol, thus an increase in cholesterol accumulation in the adipocytes parallels obesity (9). Cholesterol serves two important functions in the body: a structural and functional role in terms of cell signaling (10). The ratio of cholesterol carrying molecules, low density lipoproteins (LDLs) and high-density lipoproteins (HDLs), are also important in the atherogenic process. Increased levels of LDLs, molecules that transport cholesterol from the liver to peripheral tissue, can lead to plaque build-up and atherosclerotic disease which can cause systemic inflammation (11). Cholesterol is synthesized from acetyl-CoA and requires a series of enzymes to complete the biosynthesis pathway (Fig 1). Cholesterol has also been implicated in the pathophysiology of PE. In this study, we investigated the enzyme 3-hydroxy-3-methylglutaryl CoA synthase 1 (*Hmgcs1*), which is responsible for catalyzing the first step in the biosynthesis reaction of cholesterol (10).

![Figure 1. Cholesterol synthesis pathway. Key enzymes are indicated in blue.](image-url)
Cholesterol and Pregnancy. During pregnancy, an increase in circulating cholesterol, known as maternal physiological hypercholesterolemia (MPH), is important for ensuring normal fetal development. However, higher than normal circulating levels of cholesterol during pregnancy or maternal supraphysiological hypercholesterolemia (MSPH) are associated with endothelial dysfunction and atherosclerotic lesions in the fetoplacental vasculature and can be a risk factor for adverse fetal development (12). Normal endothelial and macrophage function are reliant on the proportion of high-density lipoproteins (HDLs) and LDLs for differentiation (13). Macrophages differentiate into either pro-inflammatory or anti-inflammatory immune cells depending on the HDL and LDL ratio; higher circulating levels of LDLs and lower levels of HDLs lead to pro-inflammatory differentiation and are reflective of the atherogenic process (13). The effects of the fetal lipoprotein profile on maternal hypercholesterolemia are being further investigated (13) but increasing knowledge of maternal cholesterol suggests an important relationship between hypercholesterolemia and inflammation seen in PE (12).

Pharmacological Intervention. There are limited treatment options for women diagnosed with PE. The latest recommendation from the American College of Obstetricians and Gynecologists, in December of 2021, suggests that women who are at high risk for developing PE should take a low dose of aspirin (81 mg/d) following 12 weeks of gestation (14). Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin inhibit cyclooxygenase (COX)-1 and/or 2 activity, enzymes responsible for prostaglandin formation and decreasing proinflammatory cytokines (15). Celecoxib is a drug used to inhibit COX-2, an enzyme that is upregulated in hypercholesterolemia, and is a beneficial treatment for diseases such as atherosclerosis and liver disease (15). Treatment with celecoxib can reverse hyperlipidemia and decrease total cholesterol, triglycerides, and LDLs (15). Although the efficacy of celecoxib has
yet to be tested in pregnant women with obesity, these lipid lowering effects of celecoxib are important to understand PE, and hence provided the rational for our study.

**BPH/5 Mouse Model of PE.** Prior to testing pharmacological interventions in pregnant women, preclinical translational research is necessary. The blood pressure high 5 (BPH/5) mouse serves as a model for PE because during gestation they develop spontaneous hypertension and exhibit adverse outcomes of PE observed in human pregnancy: proteinuria, endothelial dysfunction, and fetal growth restriction (4). BPH/5 are hyperphagic with associated increased white adipose tissue (WAT) and thus exhibit obesity (4). Examination of the WAT in BPH/5 female mice, resembles adipose tissue deposits in women, and hence its role as an endocrine organ (16). Pregnant BPH/5 mice have increased adipose tissue with increased proinflammatory cytokines (TNF-α and IL-6) and higher circulating cholesterol compared to control mice (17). In previous studies, it was found that hypercholesterolemia in BPH/5 is correlated with an upregulation of the enzyme Hmgcs1 (17). Reducing the size of adipose tissue with pair feeding has been shown to be successful for reducing inflammation in the BPH/5 mouse model; however, pair feeding has not been shown to reduce maternal cholesterol in pregnancy (18).

*Aims and Hypotheses:* The overarching goal of this research was to use celecoxib, pharmacological intervention, to understand role

**Figure 2.** Working hypothesis. Celecoxib decreases enzyme expression and serum cholesterol resulting in improved placental vascularization and decreased systemic inflammation with overall improved PE outcomes.
of adipose tissue-derived cholesterol synthesis on PE. This research has three specific aims. Aim 1: test the effects of celecoxib on cholesterol synthesis enzyme mRNA expression in reproductive WAT (rWAT) and liver of BPH/5 females. Aim 2: test pharmacological interventions on circulating cholesterol serum levels in BPH/5 females. Aim 3: understand how interventions could explain improvement in fetoplacental and maternal outcomes in the BPH/5 mouse model. Therefore, we hypothesized (Fig 2) that by reducing a main cholesterol synthesis enzyme and serum cholesterol in BPH/5 pregnancy with a lipid-lowering drug, the inflammatory state would be improved, and thus adverse outcomes associated with PE (improper placental vascularization, fetal growth restriction, and elevated mean arterial pressure) would be attenuated. It has been demonstrated that celecoxib, an anti-inflammatory medication, improves PE late gestational outcomes in BPH/5 such as placental angiogenic imbalance, maternal mean arterial pressure, and fetal growth restriction (19). We sought to demonstrate the relationship between decreased cholesterol synthesis enzymes and decreased serum cholesterol by celecoxib administration and the improvement of PE outcomes.

MATERIALS AND METHODS

Animal Model

Eight-to-twelve-week-old virgin BPH/5 and C57Bl/6J mice were used from in-house colonies at both Pennington Biomedical Research Center and LSU School of Veterinary Medicine for all experiments. In a climate-controlled facility, animals were housed with a 12-hour light/dark cycle and were fed a standard 5001 chow diet. All care for animals was reviewed and approved by Louisiana State University Animal Care and Use Committee. Additionally, animal care met the standards for NIH guidelines, USDA regulations, and American Veterinary Association Panel on Euthanasia. For tissue collection, the method of euthanasia was CO₂
inhalation, and tissues were immediately snap frozen and stored at -80°C for further experimentation. For serum analyses, blood was collected after euthanasia via cardiac puncture, centrifuged for 15 min at 3,200 rev/min, and serum was stored at -80°C until further investigation.

**Animal Study 1: Before Pregnancy**

Aim 1: To test whether pharmacological interventions affect cholesterol synthesis enzyme mRNA expression in rWAT and liver of BPH/5 female before pregnancy. Non-pregnant BPH/5 (n = 4) and C57 females (n = 3) without treatment were euthanized, and samples from both liver and rWAT were frozen and stored for further experimentation. Serum was also collected and stored for future molecular analyses.

**Celecoxib Intervention.** Non-pregnant BPH/5 females (n = 3) received a single dose of celecoxib (10mg/kg) directly into the stomach. Mice were slightly anesthetized using isoflurane, and an oral gavage tool was used to administer the treatment. Non-pregnant BPH/5 (n = 8) females where administered the vehicle for administration, sesame oil. Mice were euthanized via CO₂ inhalation 4 days after dose. rWAT was collected and stored at -80°C for further experimentation.
Animal Study 2 – Early and Mid-gestation

For pregnancy studies, timed matings were performed and the morning of copulatory plug detection was noted at embryonic day 0.5 (e0.5). rWAT and liver samples were collected from untreated BPH/5 (n= 3-7) at e7.5 and stored for experimentation.

Celecoxib Intervention. As shown (Fig 4), two groups of pregnant BPH/5 and control C57 females were treated with either celecoxib (10mg/kg) or vehicle. The first group of pregnant BPH/5 (n=4-7) treated with celecoxib at e6.5 were euthanized at e7.5 and implantation sites were visualized and counted.

The second group of pregnant BPH/5 females (n = 5) treated with celecoxib at e6.5 was euthanized at mid-gestation (e10.5 – e12.5), and blood was collected via cardiac puncture to measure cholesterol concentrations.

Cholesterol Assay. Total cholesterol concentrations were quantified in the blood serum by a colorimetric assay in duplicate. Serum was diluted 1:50 with assay diluent. Total Cholesterol Assay Kit (Colorimetric) was utilized from Cell Biolabs, Inc. San Diego, CA. Cholesterol oxidase converted serum cholesterol into hydrogen peroxide which was...
bound by a specific colorimetric probe via horseradish peroxidase. Samples were incubated in a 96-well plate and read with a standard colorimetric plate reader at 540 nm. Samples were compared to a known concentration of cholesterol using a set of standards provided by the kit and generating a standard curve.

**Gene Expression Analysis.** Quantitative reverse transcription polymerase chain reactions (qPCR) were used to measure expression levels of *Hmgcs1* in rWAT and liver of BPH/5 and C57 mice. TRIzol was used to extract total RNA from nonpregnant rWAT, nonpregnant liver, and e7.5 rWAT. Total RNA was used to synthesize cDNA. For pregnant mice, e7.5 was chosen because it represents the peak of placental decidualization but is prior to full placenta formation. Relative expression of *Hmgcs1*, a gene from the cholesterol biosynthesis pathway, was quantized using SYBR green. Primer sequences used are listed in Table 1 (17). qPCR analyses were performed in triplicate using 25ng of cDNA. Relative expression levels were compared to 18S rRNA and were expressed as a fold-change.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward Primers (5’ → 3’)</th>
<th>Reverse Primer (5’ → 3’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18S</td>
<td>CCGGGCTTCTATTTTGTTGGT</td>
<td>TAGCGGCGCAATACGAATG</td>
</tr>
<tr>
<td>Hmgcs1</td>
<td>CCCCTTCACAAATGACCACAG</td>
<td>GACAGCTGATTCAAGATTCGCG</td>
</tr>
</tbody>
</table>

**Statistical Analysis.** GraphPad Prism, version 6.0f, was used to perform statistical analysis. Analyses were used to test whether the effects of pharmacological interventions on cholesterol synthesis enzyme mRNA expression in reproductive WAT and liver of BPH/5 females were significant. Additionally, analyses were used to test whether pharmacological interventions significantly impacted circulating cholesterol serum levels in BPH/5 females. Data was analyzed using T-tests and ANOVA. Post hoc Tukey test comparisons were also performed with least square means for the effect. Data is presented as means ± SE, and significance is defined as p < 0.05.
RESULTS

**Expression of cholesterol synthesis genes in liver and rWAT of non-pregnant BPH/5 and C57 mice**

In the absence of any intervention, *Hmgcs1* gene expression in liver and rWAT of BPH/5 and C57 non-pregnant female mice were compared. As shown in Fig 6A, compared to C57 control mice, hepatic expression of *Hmgcs1* was not significantly different in non-pregnant BPH/5 females (p value = 0.87). Similarly, *Hmgcs1* gene expression quantified in rWAT (Fig 6B) was not significantly different between non-pregnant BPH/5 and control C57 females (p value = 0.49).

![Bar chart A: Non-pregnant liver *Hmgcs1*](image1)

**Figure 6. Hmgcs1 in non-pregnant liver and rWAT.** Gene expression was measured in BPH/5 and C57 pregnant females (n=3-5). p>0.05. Normalized to 18S.
Expression of cholesterol synthesis genes in liver and rWAT of pregnant BPH/5 and C57 mice

The expression of \textit{Hmgcs1} was compared in the rWAT and liver of pregnant (e7.5) and non-pregnant BPH/5. Hepatic expression of \textit{Hmgcs1} in non-pregnant BPH/5 was not significantly different in pregnant e7.5 BPH/5 females (Fig 7A). The gene expression of \textit{Hmgcs1} in pregnant e7.5 rWAT BPH/5 females was 3-fold higher when compared to non-pregnant BPH/5 mice (Fig 7B).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{\textit{Hmgcs1} in e7.5 liver and rWAT. Gene expression was measured in BPH/5 non-pregnant (NP) and pregnant (P) females (n=3-5). *p<0.05 compared to non-pregnant BPH/5 mice. Normalized to 18S.}
\end{figure}

The effect of celecoxib treatment on cholesterol synthesis enzyme gene expression in non-pregnant rWAT

Due to the increase in \textit{Hmgcs1} gene expression in rWAT in early pregnancy (e7.5), lipid lowering agents were used to determine if this increase in mRNA expression in the rWAT could be mitigated in the BPH/5 model following celecoxib treatment. BPH/5 non-pregnant females
treated with celecoxib had a significantly reduced level (75% reduction) of *Hmgcs1* mRNA expression in the rWAT after 4 days compared to vehicle treated BPH/5 (Fig 8).

**Figure 8.** *Hmgcs1* in the rWAT of non-pregnant BPH/5 females. Gene expression was measured in non-pregnant celecoxib treated BPH/5 females and non-pregnant vehicle (veh) treated BPH/5 females (n=3). #p<0.05. Normalized to 18S.

**Effect of celecoxib treatment on pregnancy rates**

The effects of celecoxib treatment on pregnancy rates were tested by visualizing and counting implantation sites at e7.5. There was no significant difference in the number of implantation sites between C57 vehicle (9.4 ± 0.6, n = 5), C57 celecoxib treatment (9 ± 0.9, n = 4), BPH/5 vehicle (7.3 ± 0.6, n = 7), and BPH/5 celecoxib treatment (7.6 ± 0.9, n =5) groups at e7.5 (Fig 9) (18).
Effect of celecoxib treatment on serum cholesterol at mid-gestation

Treatment with celecoxib in pregnancy significantly decreased circulating cholesterol levels of treated BPH/5 (0.644 ± 0.09 mM, n=5) compared to vehicle treated BPH/5 (1.8 ± 0.09 mM, n=6) (Fig 10). This decrease in cholesterol normalized BPH/5 mid-gestation cholesterol levels to that of lean C57 (0.615 ± 0.08 mM, n=6) mid-gestation cholesterol levels (Fig 10).
DISCUSSION

The aim of this research was to exploit the connection between maternal adipose tissue and circulating cholesterol by administering an anti-inflammatory therapy in the BPH/5 mouse, a mouse model of PE. We hypothesized that reducing cholesterol synthesis enzymes and serum cholesterol in pregnancy would improve the adverse outcomes associated with PE in BPH/5 females. We have shown that Hmgcs1 mRNA increases with pregnancy in BPH/5 reproductive WAT but not in the liver. Additionally, we have demonstrated that celecoxib is able to reduce Hmgcs1 mRNA in non-pregnant BPH/5 reproductive WAT as well as attenuate elevated BPH/5 serum cholesterol in pregnancy. We conclude that an early pregnancy reduction in cholesterol
after celecoxib administration may contribute to improved late gestational adverse outcomes in BPH5 mice.

*Obesity and Systemic Inflammation.* Adipose tissue contributes to a pro-inflammatory state due to the increase of circulating adipokines (5). Reduction of adipose tissue along with reduced quantity of adipokines has been shown to improve the adverse outcomes seen in BPH/5 (17). Reduction of adipose tissue by pair feeding BPH/5 female mice was associated with reduced pro-inflammatory cytokines in circulation, in the rWAT, and at the maternal fetal interface (17). However, pair feeding beginning at conception did not reduce circulating cholesterol in BPH/5 pregnancy (18). Therefore, here attempted to attenuate hypercholesterolemia of BPH/5 mice with a lipid lowering drug to examine the obesity-mediated effects of hypercholesterolemia on PE.

*Obesity and Cholesterol.* The liver is key to cholesterol homeostasis and regulates biosynthesis, uptake/release, and storage (8). Lipids are oxidized in the liver, and excess lipids are packaged and sent to adipose tissue for storage (20). Recent studies support that adipose tissue serves as a major storage site for free cholesterol and that there is an increase in circulating cholesterol with obesity (9). Prior to pharmacological intervention with celecoxib, mRNA expression of *Hmgcs1*, a key enzyme in the cholesterol synthesis pathway, was not significantly different between strains before pregnancy (Fig 6). To further elucidate the role of *Hmgcs1* in BPH/5 rWAT and liver, gene expression levels were also measured in early pregnancy (*e*7.5). *Hmgcs1* gene expression in the liver of BPH/5 mice was not different between the non-pregnant and pregnant state (Fig 7A). However, pregnant BPH/5 females at *e*7.5 had significantly higher levels of *Hmgcs1* in the rWAT compared to non-pregnant BPH/5 females (Fig 7B). It has been shown that elevated cholesterol can cause an increase in adipose tissue inflammation and result
in adipose tissue remodeling (9). We have previously described elevated leptin, Il-15, and Tnf alpha mRNA in the BPH/5 rWAT at early pregnancy (17). Therefore, we hypothesized that treatment of BPH/5 females with celecoxib, an anti-inflammatory drug, could attenuate rWAT cholesterol synthesis enzymes in BPH/5 females and hypercholesterolemia downstream.

To determine if Hmgcs1 gene expression could be reduced in the rWAT prior to pregnancy (Aim 1), celecoxib treatment was administered to non-pregnant BPH/5 females. The selective COX2 inhibiting non-steroidal anti-inflammatory drug, celecoxib, was chosen because of its anti-inflammatory and lipid lowering effects (15). Celecoxib treatment resulted in a significant decrease of Hmgcs1 gene expression in BPH/5 non-pregnant rWAT compared to the vehicle treated BPH/5 females (Fig 8). To test the safety of celecoxib administration in early pregnancy (e6.5), implantation sites were counted among both strains of BPH/5 and C57 at e7.5. There was no significant difference in the number of implantation sites between vehicle and treatment groups among either strain (Fig 9). Thus, celecoxib treatment in early pregnancy does not interfere with litter size and furthermore improves it in BPH/5 by late gestation (18). Other reports have shown that high doses of celecoxib administered late in gestation can have adverse fetal effects such as premature closure of the ductus arteriosus (21). However, the single anti-inflammatory low dose given to BPH/5 mice is less likely to cause these congenital heart defects when cardiac organogenesis is complete at e14.5 (22). To evaluate the effects of celecoxib in mid-gestation, serum was collected at e10.5 from C57 vehicle treated females, BPH/5 vehicle treated females, and BPH/5 celecoxib treated females (Aim 2). Celecoxib administration proved to significantly decrease serum cholesterol levels in pregnant BPH/5 females compared to vehicle treated BPH/5 (Fig 10). Serum cholesterol levels in mid-gestation BPH/5 were attenuated to similar levels of gestation matched C57 controls.
Elevated levels of cholesterol have been shown to cause endothelial dysfunction and atherosclerosis (12,23). We postulate these conditions are likely involved in the improper vascularization of the placenta and overall systemic inflammation seen in BPH/5 pregnant mice with PE. Other mouse studies on the effects of cholesterol in the adipose tissue have shown that an increase in dietary cholesterol resulted in an increased accumulation of macrophages that can differentiate into pro-inflammatory cells (23). Additionally, decreased insulin sensitivity, hyperlipidemia, local and systemic inflammation, and atherosclerosis were present in mice with diet-induced obesity and given dietary cholesterol (23). Increased adipose tissue and increased cholesterol together promote metabolic abnormalities, an increase in systemic inflammation, and assist in improper placental vascularization leading to the adverse outcomes associated with PE such as increased mean arterial pressure and FGR.

Experiments on the effects of both pair-fed and celecoxib treated BPH/5 females have been previously published. Both treatments have shown to improve adverse maternal and fetal outcomes associated with PE such as restoring angiogenic imbalance, lowering elevated maternal MAP, and reducing FGR (17,18). However, dietary intervention was not as successful at reducing the lipid profile as celecoxib (18). Future studies could continue to evaluate the impact of these interventions to conclude which intervention is most effective.

Although our study was performed in a mouse model, this research could be used to inform clinical trials in pregnant women at risk of developing PE. We observed how pharmacological intervention with a lipid lowering drug could improve the lipid profile of pregnant women with obesity, and we demonstrated the beneficial effects of mitigating increased serum cholesterol in early pregnancy. We have shown that celecoxib improves the lipid profile
throughout gestation explaining improved PE outcomes at late gestation, maternal MAP and FGR, as previously published (18).

This project has both philosophical and technical strengths and weaknesses. The BPH/5 mouse model is a polygenic model and not a monogenic model of hypercholesterolemia; a better model of MSPH could be generated to test cholesterol attenuation in pregnancy. The data presented here only demonstrates the effects of pharmacological intervention on a few timepoints in pregnancy. More samples could be used to confirm our findings and strengthen our results. Additionally, more variables from the lipid panel including triglycerides and free fatty acids could be quantified with anti-inflammatory treatment to further evaluate the effects of celecoxib treatment on the lipid profile. Despite its weakness, our study was able to produce a suitable quantity of results throughout a brief time frame that has the potential to raise more open-ended questions and to inspire inquiry about the relationship between increased cholesterol and PE.

Conclusions and future directions. We observed that celecoxib administration decreases Hmgcs1 gene expression in non-pregnant BPH/5 female rWAT and decreases circulating cholesterol in BPH/5 females at mid-gestation. The decrease in cholesterol in pregnancy precedes the improvement in BPH/5 maternal hypertension and fetal growth restriction by improving the inflammatory state and potentially promoting restoration of placental and circulating angiogenic balance. Future studies could further elucidate the contribution of anti-inflammatory medication and PE outcomes particularly in high-risk women with obesity. Moreover, studies could focus on the specific molecular interaction between celecoxib, adipose tissue macrophages, and the enzyme Hmgcs1. While we have shown that celecoxib successfully reduces enzyme gene expression, we do not yet know the specific mechanism of action. Additionally, future work could involve a description of the HDL and LDL ratio in obese, PE-
like BPH/5 mice. This ratio is important in macrophage and pro-inflammatory differentiation and could explain the metabolic abnormalities seen in BPH/5 PE-like pregnancies (11). It could also be beneficial to test and test pair feeding and lipid lowering medications together to examine the effectiveness of a dual method. Finally, more studies are needed to find interventions to prevent PE in obese women prior to pregnancy and within early pregnancy to result in improved PE outcomes.

LITERATURE CITED


