The Relationship between Maternal Dietary Fat Intake, Glucose Control, and Infant Birth Weight

By

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A Thesis

Presented to the Faculty of
the Graduate Programs in Human Nutrition
and School of Medicine
Oregon Health & Science University
in partial fulfillment of the
requirements for the degree of
Master of Science in Clinical Nutrition
May 2014

Oregon Health & Science University

CERTIFICATE OF APPROVAL

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Table of Contents

Acknowledgements

This thesis would not have been possible without the continuous support and encouragement from my thesis committee members, the PEN Study staff, my classmates, my friends, and my family.

First and foremost, I extend my gratitude to my thesis committee members, each who provided support in ways I expected, and in ways that were unique and unexpected. Thank you, **Dr. Gillingham**, for your assistance with understanding fatty acid metabolism, and articulating the processes in my thesis document, as well as in presentations. Your advice to defeat writer's block – "just write without thinking too hard!" – helped me from the moment I began writing my specific aims all the way through my discussion. Thank you, **Esther**, for providing details and for promptly answering numerous questions regarding the PEN Study protocol and methods. Thank you for giving me the opportunity to assist with conducting study visits and the opportunity to participate in PEN Study staff meetings. I sincerely appreciate being involved in the research implementation. Thank you, **Christie**, for your attention to detail regarding glucose control during pregnancy. Your input from a clinician's perspective was invaluable. Thank you, **Dr. Stadler**, for your endless support and patience. Thank you for spending countless hours editing many thesis drafts, and improving my scientific writing skills. Thank you for your constant encouragement and inspiration to go above and beyond what is required for thesis research. I am humbled to have worked with each of you. Thank you for considerably improving my research experience.

Thank you **Cassie**, **Joanna**, **Emily**, and **Kelly** for providing incredible peer support throughout the past two years. Your company, your creativity, and especially your smiles in rotations, in the classroom, around campus, and beyond helped make graduate school fun and enjoyable.

Thank you **Mom** and **Dad** for encouraging me to follow my passion. No one sets a greater example of doing just that than the two of you. Thank you, **Maggie**, for your constant uplifting notes – via snail-mail and e-mail. Thank you, **Philip**, for sharing your enlightening and wise perspectives regarding all aspects of life, but especially adult life. Thank you for your edits (although sometimes comical) on my thesis. Thank you, **David**, for always being happy, and for your ability to make me happy regardless of the situation.

I am grateful for all of those who provided support throughout my thesis project. Over the past two years I've developed a greater respect for evidence-based research, and look forward to continued education through research throughout my career.

List of Abbreviations and Acronyms

ASA-24	Automated Self-Administered 24 Hour Recall
BMI	Body mass index
CV	Coefficient of variation
DFS	Dietary Fat Screener
DHA	Docosahexaenoic acid
DRI	Dietary reference intake
EFA	Essential fatty acids
EPA	Eicosapentaenoic acid
FFA	Free fatty acids
GDM	Gestational diabetes mellitus
HIPAA	Health Insurance Portability and Accountability Act
HOMA-IR	Homeostatic model of assessment for insulin resistance
HOMA-β	Homeostatic model of assessment for beta cell function
hPGH	Human placental growth hormone
hPL	Human placental lactogen
IBW	Ideal body weight
IGF-1	Insulin-like growth factor-1
IGFBP-1	Insulin-like growth factor binding protein-1
LGA	Large for gestational age
MNT	Medical nutrition therapy
MUFA	Monounsaturated fatty acids
NCI	National Cancer Institute
OCTRI	Oregon Clinical and Translational Research Institute
OGTT	Oral glucose tolerance test

OHSU	Oregon Health & Science University
PEN	Pregnancy Exercise and Nutrition Study
PUFA	Polyunsaturated fatty acids
QUICKI	Quantitative insulin sensitivity check index
REDCap	Research Electronic Data Capture
SFA	Saturated fatty acids
SGA	Small for gestational age
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor-α
USDA	United States Department of Agriculture

List of Figures

List of Tables

CHAPTER 1: SIGNFICANCE AND SPECIFIC AIMS

Significance

Gestational diabetes mellitus (GDM) is glucose intolerance that originates or is first recognized during pregnancy, and which can have significant health consequences in both the mother and her fetus [1]. Of concern is that the incidence of GDM in the United States is increasing among all racial/ethnic groups [2]. Between 1994 and 2002, the incidence of GDM increased from 2.1% to 4.2%, it is currently at 10%, and it is predicted to exceed 18% with the implementation of newer screening methods and diagnostic criteria [1, 3, 4]. Women who have a family history of Type 2 Diabetes Mellitus (T2DM), personal history of GDM, previous delivery of a large-for-gestational-age infant, polycystic ovary syndrome, or are overweight or obese are at high risk for developing GDM [2, 5]. Human and animal studies suggest that GDM not only affects the mother, but also her children and grandchildren during fetal development, infancy, and childhood [6-9]. GDM increases the mother's risks for delivery complications, preeclampsia, and developing T2DM post-partum [8, 10-12]. Infants born to mothers with GDM have an increased risk of neonatal hypoglycemia, macrosomia, high body fat, respiratory distress syndrome, poor feeding, and cognitive development issues [4, 8, 9, 13-17]. Studies of rodents and humans show that offspring of mothers who had GDM have an increased lifetime risk of developing diabetes and obesity [6, 9, 18, 19]. In 2007, these and other issues associated with GDM in the US resulted in healthcare costs that exceeded $636 million [12].

One modifiable risk factor for GDM is maternal diet [4, 20, 21]. In particular, high dietary fat intake and, as a result, an excessive energy intake during pregnancy may influence the risk of developing GDM through excess maternal weight gain, although the

results are not consistent [4, 6, 10, 11, 14, 18, 22-28]. Excess maternal weight gain has been shown to elicit inflammatory responses leading to insulin resistance [29], pancreatic beta cell dysfunction, decreased insulin secretion, and worsening hyperglycemia [30]. In addition to excess weight gain, high maternal dietary fat intake results in elevated concentrations of plasma free fatty acids, increased fatty acid oxidation in peripheral tissues [26-28], reduced insulin-stimulated glucose uptake by peripheral tissues, and altered glucose homeostasis [31]. What is not well understood is how dietary fat intake, with or without high energy intake, influences glucose homeostasis among healthy women throughout pregnancy and their infant's birth weights.

To address this gap, we investigated the relationship between maternal dietary fat and energy intakes and glucose homeostasis, and maternal dietary fat and energy intakes and infant birth weight in the women participating in the Oregon Health & Science University (OHSU) Pregnancy Exercise & Nutrition (PEN) Study. Maternal energy intake and total fat, saturated fat (SFA), monounsaturated fat (MUFA), polyunsaturated fat (PUFA), essential fatty acid intakes were measured during each trimester using the Automated Self Administered 24-Hour Dietary Recall (ASA-24) and the Dietary Fat Screener (DFS). Glucose control was assessed during each trimester using fasting glucose and insulin concentrations, the homeostatic model assessments for insulin resistance (HOMA-IR) and beta cell function (HOMA-β), and the quantitative insulin sensitivity check index (QUICKI). The relationships between maternal dietary fat intake variables and measurements of glucose control were analyzed using canonical correlation analyses. Infant birth weight was obtained from medical records, and then related to maternal glucose control using a linear regression model.

Specific Aims and Hypotheses

Aim 1: To determine the relationships between maternal dietary fat intake and markers of glucose control during each trimester of pregnancy using canonical correlations.

Hypothesis 1a: Canonical components associated with unhealthy maternal fatty acid intake will be inversely related to canonical components associated with healthy maternal blood glucose control.

Hypothesis 1b: Canonical components associated with healthy maternal fatty acid intake will be directly related to canonical components associated with healthy maternal blood glucose control.

Aim 2: To determine the relationship between maternal glucose control, as indicated by QUICKI scores, during each trimester and infant birth weight using a linear regression model.

Hypothesis 2: Healthy QUICKI scores will be associated with healthy infant birth weight.

CHAPTER 2: BACKGROUND

Glucose Homeostasis during Pregnancy

Significant metabolic changes occur during pregnancy to support fetal development (Figure 1). Endogenous hepatic glucose production increases 16-30% to meet the increasing needs of the placenta and the fetus [32]. These metabolic changes result in gradual maternal adipose tissue deposition during early gestation and increased insulin resistance due to decreased suppression of lipolysis later in pregnancy [33]. As a result, insulin secretion increases in early pregnancy, but this increase is not associated with increased glucose clearance. Insulin sensitivity declines later in gestation [26]. Endogenous hepatic glucose production remains sensitive to the increased insulin concentration throughout pregnancy, but there is a progressive decrease in peripheral insulin sensitivity [34]. Healthy pregnancy results in about a 50% decrease in insulin-mediated glucose uptake and about a 200-250% increase in insulin secretion to help maintain glucose homeostasis in the mother [32, 35].

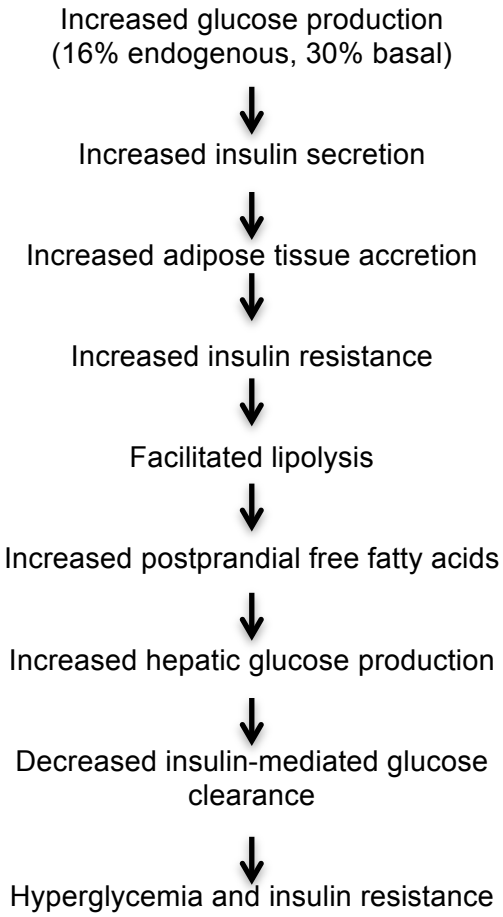

Figure 1: Metabolic Changes during Healthy Pregnancy and the Development of Severe Insulin Resistance

Hormonal Changes during Pregnancy and Impact on Glucose Homeostasis

Hormonal changes during pregnancy reprogram the mother's metabolism to provide adequate nutrients to meet the needs of the growing fetus. Maternal dietary intake influences maternal hormone concentrations [36]. These hormonal changes are indirectly correlated with maternal insulin resistance [26]. Human placental lactogen (hPL), which increases up to 30-fold during pregnancy, contributes to these physiological changes by inducing the release of insulin from the pancreas [37]. The concentration of human placental growth hormone (hPGH), a protein similar to pituitary growth hormone, increases 6-8-fold during pregnancy [26]. Both hPL and hPGH have been shown to

cause peripheral insulin resistance during pregnancy [26]. During the second trimester of pregnancy, placental syncytiotrophoblastic epithelium secretes hPGH to such a high extent that it becomes the predominant growth hormone in maternal plasma [38, 39]. The concentration of hPGH exceeds that of pituitary growth hormone in pregnant women around gestational week 20 [26, 40]. Human placental growth hormone appears to regulate maternal concentration of insulin-like growth factor-1 (IGF-1), which regulates nutrient transport to the fetus [36, 39]. Since hPGH does not cross the placenta from the mother to the fetus, it indirectly functions to assure the fetus receives adequate nutrients, and protects the fetus against insufficient nutrient availability [39, 41]. To a certain degree, high hPGH concentrations during pregnancy are considered normal. However, high circulating concentrations of hPGH are associated with extreme insulin resistance in peripheral tissues [39]. The exact relationship between elevated hPL and hPGH and insulin sensitivity is not fully elucidated [26].

Endocrine and Paracrine Effects of Adipokines and Effects on Glucose Homeostasis

Maternal adipose tissue secretes adipokines, adipocyte-derived signaling molecules, that have endocrine and paracrine effects to help meet the needs of the growing fetus [42]. Secretion of certain adipokines, including adiponectin, Tumor Necrosis Factor (TNF)-α, and resistin, has been shown to effect maternal insulin sensitivity during pregnancy [26]. The relationship between pregnancy-related hormones, adipokines, and insulin sensitivity is described in Table 1. Adiponectin is the most abundant adipokine released from adipose tissue into circulation. This protein hormone reduces glucose production in the liver and increases hepatic insulin sensitivity [43]. As gestation advances, adiponectin secretion declines [26] as a result of decreased adipocyte insulin sensitivity [43-46]. Circulating plasma adiponectin concentrations are

significantly lower ($P < 0.0001$) in women with a history of GDM (6.7 ± 0.2 μg/mL) compared to women with healthy glucose control during pregnancy (9.8 ± 0.6 μg/mL) [47]. Adipokine concentrations may be influenced by diet, and one study reported a significant inverse correlation between maternal dietary fat intake and adiponectin concentrations [36]. TNF-α decreases insulin sensitivity by interfering with the insulin signaling transduction pathway in adipocytes [48]. Furthermore, TNF-α is positively correlated with body mass index (BMI) and hyperinsulinemia [49-51]. Serum resistin concentrations are positively correlated with body fat mass and dietary fat intake [36]. Increased circulating resistin concentrations are associated with impaired glucose homeostasis [44]. However, the mechanism by which resistin impairs glucose homeostasis in pregnant women is unclear.

Table 1: The Relationship between Pregnancy-Related Hormones, Adipokines, and Insulin Sensitivity

Hormone/Adipokine	Circulating concentrations	Effects on Insulin Sensitivity
Human placental lactogen (hPL)	Increase during pregnancy	• Induces release of insulin from pancreas
Human placental growth hormone (hPGH)	Increase during pregnancy	• Regulates maternal concentration of insulin-like growth factor-1 • Over expression associated with insulin resistance
Adiponectin	Decrease with fat accumulation Decrease during pregnancy	• Increases hepatic insulin sensitivity
Resistin	Increase with fat accumulation Increase during pregnancy	• Decreases insulin sensitivity
Tumor Necrosis Factor-α (TNF- α)	Increase with obesity	• Decreases insulin sensitivity
Leptin	Increase during pregnancy Increase with fat accumulation	• Decreases insulin sensitivity

[42, 44]

Gestational Diabetes Mellitus and Impaired Glucose Homeostasis during Pregnancy

All women experience changes in glucose homeostasis during pregnancy. Increases in nutrient-stimulated insulin responses occur throughout pregnancy in conjunction with an increase in total glucose production and gluconeogenesis [52]. These changes occur slowly during the first trimester of pregnancy and become very evident at the beginning of the second trimester of pregnancy, around week 24 of gestation. However, if alterations in glucose homeostasis exceed certain limits, adverse outcomes result for both the mother and the fetus. Women with GDM show a 65% reduction in insulin-stimulated glucose uptake into muscle cells, compared to the 40% reduction in unaffected pregnancies [26]. Impaired insulin sensitivity is likely a result of abnormal concentrations of circulating adipokines in women with GDM. For example, women with GDM have increased circulating TNF-α concentrations (5.6 ± 1.0 pg/mL) compared to women with healthy glucose control during pregnancy (3.3 ± 0.4 pg/mL) [47]. Some research shows an association between significantly higher serum resistin concentrations ($P < 0.001$) in diabetic patients (20.8 ± 0.7 ng/mL) compared to healthy patients (14.9 ± 0.5 ng/mL) [42, 53-55], while other research does not support this association (5.6 ± 1.9 ng/mL vs. 6.7 ± 3.3 ng/mL, $P = 0.21$) [42, 56]. Research also illustrates significantly ($P < 0.05$) lower adiponectin concentrations in women with a history of GDM (6.70 ± 0.23 μg/mL vs. 9.8 ± 0.60 μg/mL) [47]. Endogenous hepatic glucose production is less sensitive to increased insulin concentrations in women with GDM than in healthy pregnancies [34]. However, increased insulin secretion does not fully compensate for the reduced insulin sensitivity in women with GDM, and results in hyperglycemia [26]. The eventual combination of placental hormone fluctuation, reduced

adiponectin secretion, inflammation, and excess lipolysis results in severely reduced insulin sensitivity in liver, muscle, and adipose tissue in women with GDM [26].

Screening Methods for Gestational Diabetes Mellitus

Clinics in the United States currently use a variety of screening methods to identify women with GDM. The American Diabetes Association, the American College of Obstetricians and Gynecologists, the World Health Organization, and the International Association of Diabetes and Pregnancy Study Group recommend different screening criteria to diagnose GDM. The American College of Obstetricians and Gynecologists and the American Diabetes Association recommend the Carpenter-Coustan Method, a two-step process beginning with a 50-gram oral glucose tolerance test (OGTT) administered between weeks 24 and 28 of gestation [5, 57]. Women with a blood glucose concentration above 140 mg/dL one hour after this glucose load are considered to have slightly impaired glucose tolerance and are at a significantly increased risk of developing GDM. These women are not immediately diagnosed with GDM, but are rescreened with a more stringent OGTT. The second OGTT results in a GDM diagnosis if the woman has two or more of the following blood glucose concentrations: above 180 mg/dL after one hour, above 155 mg/dL after two hours, and/or above 140 mg/dL after three hours of consuming a 100-gram oral glucose load. The World Health Organization recommends a two-hour, 75-gram OGTT method [58]. If the woman's fasting plasma glucose concentration is greater than 92 mg/dL, greater than 180 mg/dL at one hour, or greater than 153 mg/dL at two hours, she is diagnosed with GDM.

Many studies suggest that women with impaired glucose tolerance who do not meet the criteria for GDM (those who had a blood glucose concentration above 140 mg/dL during the first OGTT, but were within "safe parameters" during the second OGTT)

are still at significant risk of harmful health outcomes, not only for themselves but also their fetus [24, 27, 57]. Unfortunately, without a diagnosis of GDM, it is unlikely that these women will receive dietary counseling or diabetes education, despite their increased risk. There is evidence, though, that treating women with even mild GDM reduces morbidity in the mother and her baby [5, 59]. In 2010, the International Association of Diabetes and Pregnancy Study Group recommended universally adopting the two-hour, fasting, 75-gram OGTT for all women [60]. This more stringent test would result in increased GDM diagnoses, capturing those women who are now considered "at-risk" for GDM, but who do not meet all of the criteria for the diagnosis. The Oregon Health & Science University Hospital Center for Women's Health adopted this two-hour, 75-gram glucose load OGTT in 2013.

Clinical Definition of Insulin Sensitivity

There are many different methods to evaluate insulin sensitivity. The gold standard is the euglycemic insulin clamp method, which measures whole body insulin sensitivity. In the current study, we used fasting glucose, fasting insulin, the homeostatic models of assessment (HOMA) for insulin resistance (HOMA-IR) and pancreatic beta cell function (HOMA-β), and quantitative insulin sensitivity check index (QUICKI) equations to assess insulin sensitivity. The HOMA-IR, HOMA-β, and QUICKI methods have all been validated in various populations including pregnant women using an OGTT and comparing results to the euglycemic insulin clamp techniques [61-63].

The HOMA values characterize pathophysiology in those with abnormal glucose tolerance. The HOMA equations are calculated using fasting insulin and glucose concentrations, and reflect hepatic basal cell insulin sensitivity and pancreatic beta cell function in the fasted state. However, they are not intended to report inherent beta cell

function in isolation, nor do they measure peripheral insulin sensitivity [63]. Determining insulin sensitivity using the HOMA equations is not valid across populations who are thought to have different insulin sensitivities, for example, between a healthy and a diabetic population [62, 63]. However, using the HOMA methods is appropriate cross-culturally [63]. Healthy HOMA-IR values are defined as less than or equal to 2.6 [64]. Below are the HOMA-IR and HOMA-β equations.

HOMA-IR = [fasting glucose (mg/dL) x fasting insulin (μIU/mL)]/405

HOMA-β = [360 x insulin (μIU/mL)]/[glucose (mg/dL – 63)] %

The QUICKI method for determining insulin sensitivity is a variation of the HOMA methods [63]. The QUICKI equation also uses fasting insulin and fasting glucose concentrations to measure insulin sensitivity. The QUICKI equation is:

QUICKI = 1/(log fasting glucose + log fasting insulin)

A healthy QUICKI value is around 0.34 [65]. The use of the logarithm illustrates a linear distribution, allowing the QUICKI method to be used across various populations [62]. Quantitative insulin sensitivity check index results have a near perfect correlation with HOMA results [62, 63]. Like the HOMA methods for determining insulin sensitivity, the QUICKI method measures hepatic insulin sensitivity only.

Importance of Maternal Glucose Tolerance for Mother's Health

Adequate maternal glucose control is essential for the mother's health, healthy fetal development, the infant's health after birth, and even the infant's progeny [39, 66]. Many factors contribute to altered maternal glucose control. Chen, et al found that advanced maternal age, increased pregravid BMI, some ethnicities, neonatal gestational age at delivery, and infant birth weight are all significantly related to impaired maternal

glucose control [27]. Non-white women, particularly women who are Hispanic, have a higher rate of GDM than white women (53.2% vs. 46.8%, $P > 0.04$) [21, 27].

All women with GDM have higher fasting glucose and fasting insulin concentrations than pregnant women without GDM. Mothers who develop GDM have a high risk of developing T2DM later in life. Women who develop GDM are also at an increased risk for developing gestational hypertension, preeclampsia, and dyslipidemia, which can lead to severe fetal delivery complications [34].

Many women with GDM exhibit resolution of their insulin resistance soon after pregnancy, but it is estimated that between 7 and 12% of women with GDM will develop T2DM postpartum [67]. Since all women with GDM have a significantly increased risk of developing T2DM after pregnancy, they are encouraged to be re-screened for diabetes 6-12 weeks postpartum. However, the protocol for rescreening for T2DM needs to be more uniform to assure that all women with GDM complete a glucose tolerance test postpartum [5]. It is believed that managing GDM properly with diet and physical activity increases a woman's likelihood of regaining normal insulin sensitivity postpartum. [5]

Importance of Maternal Glucose Tolerance for Infant's Health and Development

Maintaining healthy maternal glucose homeostasis is imperative for healthy fetal development and the health of the infant after birth. Some studies show that maternal insulin resistance results in excessive glucose availability to the fetus [68], resulting in increased neonatal birth weight, putting the infant at adverse health risks through childhood, adolescence, and adulthood. Along with increased birth weight, increased maternal insulin resistance in women with GDM is associated with fetal overgrowth, particularly excessive adiposity. Excess fetal adiposity poses a long-term risk for obesity in these children, which could possibly lead to the development of diabetes [17, 68, 69].

Silverman, et al reported a strong correlation between amniotic fluid insulin concentrations and increased BMI in children 14-17 years of age. This relationship suggests a relationship between islet cell activation in utero and the development of childhood obesity [68, 69]. Less common adverse outcomes for infants whose mothers developed GDM are neonatal hypoglycemia, respiratory distress syndrome, poor feeding, and impaired cognitive development [4, 70].

Dietary Fat and Gestational Diabetes Mellitus

Medical Nutrition Therapy (MNT) for Healthy Pregnant Women

The current Dietary Reference Intakes (DRI) for healthy pregnant women recommends that specific amounts of macronutrients are consumed throughout pregnancy. According to the DRIs, healthy, normal-weight pregnant women should consume about 2,400 kilocalories a day during the first trimester, 2,700 kilocalories a day during the second trimester, and 2,900 kilocalories a day during the third trimester. The DRIs for macronutrients include 175 grams of carbohydrate a day, 71 grams of protein a day, and a variable amount of fat depending upon the mother's requirement for proper weight gain [71]. The recommended total fat intake for healthy pregnant women is the same for the non-pregnant healthy female population [72]. The current DRI for total fat intake for women between the ages of 19-50 years is 20-35% of energy from fat per day [71]. There are no specific DRIs for monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), but the American Heart Association suggests consuming up to 10% of total energy from PUFA, up to 15% from MUFA, and less than 8% from saturated fatty acids (SFA) [73].

Linolenic (ω-3) acid and linoleic (ω-6) acid, essential fatty acids not synthesized by humans, play a vital role in fetal cognitive and visual development [74, 75]. The

typical Western diet is abundant in linoleic acid and deficient in linolenic acid. Docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha linolenic acid are the three main forms of ω-3 fatty acids. Docasahexaenoic acid and EPA are biologically active, and alpha linolenic acid must be converted to DHA in the body to be biologically active, therefore most research and dietary recommendations focus on DHA and EPA [75]. Impaired glucose tolerance appears to interfere with placental fatty acid transport, therefore interfering with fetal access to the essential fatty acids [76]. Research regarding recommended dietary intake for essential fatty acids during pregnancy is limited. Most research suggests pregnant women should consume between 200-500 milligrams of DHA plus EPA per day, from food or supplements [75, 77]. Omega-3 and ω-6 fatty acids play an important role in fetal brain development, the development of other membrane rich tissues, and reduced risk of early preterm delivery [72]. Low maternal concentrations of ω-3 and ω-6 fatty acids are also associated with small for gestational age infants [78].

Medical Nutrition Therapy for Women with GDM

Medical nutrition therapy is considered one of the most important aspects in managing GDM, along with exercise, and potentially drug therapy [4]. The American Diabetes Association provides specific dietary and exercise recommendations and pharmacological therapy for women with GDM to help manage their serum glucose concentrations [4]. The Association recommends that women with GDM consume an energy intake of 25-30 kilocalories per kilogram of pre-pregnancy ideal body weight (IBW) during the second trimester of pregnancy, and 30-35 kilocalories per kilogram of pre-pregnancy IBW during the third trimester. Thirty-eight to forty-five percent of the daily energy intake should be from carbohydrate, 20-25% from protein, and 30-40% from fat

[79]. However, this dietary fat intake recommendation varies depending upon the mother's need for weight gain versus weight maintenance. The Association also recommends mothers consume three meals and three snacks per day, distributing less carbohydrate in the morning, and more in the evening to help maintain consistent serum glucose concentrations.

Women with GDM are encouraged to follow an exercise regimen. Exercise increases glucose uptake by muscle cells, regardless of serum insulin levels, thus reduces circulating blood glucose concentrations. The Association recommends women with GDM monitor their serum glucose concentrations daily, and begin insulin therapy if MNT does not adequately control their glucose concentrations after two weeks. Treatment with human insulin or a synthetic insulin is considered safe for the mother and the fetus, and effectively reduces maternal serum glucose concentrations [4]. There is universal consensus to refrain from use of insulin in the management of GDM in pregnant women until it is evident that MNT fails to manage the diabetes. Initial insulin dosage recommendations vary among practitioners [4].

Altered Glucose Homeostasis Related to Fat Metabolism

The interaction between dietary fat intake and glucose homeostasis during pregnancy is not completely understood. In the literature, a high fat diet is typically defined as a diet that provides greater than 40% of daily energy from fat [21]. This is congruent with the dietary fat recommendations mentioned previously. Excessive dietary fat intake may alter maternal glucose homeostasis due to the effects of different macronutrient distributions on substrate oxidation [21, 27, 28]. Alternatively, high dietary fat intake may also alter maternal glucose homeostasis by increasing energy consumption and leading to excess maternal weight gain [27].

Pregnant women have higher circulating free fatty acid (FFA) concentrations compared to non-pregnant women, and women with GDM have significantly higher circulating fatty acid concentrations (405.01 ± 29.53 μmol/L and 418.91 ± 28.71 μmol/L) in the second and third trimesters of pregnancy compared to women without GDM (33.75 ± 21.11 μmol/L and 325.53 ± 19.29 μmol/L) [27, 80, 81]. Increased maternal FFA concentrations in late gestation are related to decreased maternal insulin sensitivity [27, 31, 68]. Furthermore, it has been shown that a maternal high fat diet increases plasma FFA concentrations, consequently inducing an insulin resistant state [28].

One longitudinal study using a hyperinsulinemic-euglycemic clamp in pregnant women showed that insulin's ability to suppress plasma FFA concentrations was lower in women with and without GDM compared to non-pregnant women, but was inhibited more in women with GDM. When FFA concentrations were expressed relative to insulin concentration, women with GDM had significantly higher ratios [81]. Also, decreased insulin sensitivity results in the inability of insulin to suppress lipolysis [68]. Most changes in plasma FFA concentrations occur later in pregnancy, corresponding to the physiological hyperinsulinemia [68, 81]. However, resulting metabolic hormonal changes involve more than just insulin and glucose.

In addition to the amount of fat consumed, the type of fat consumed may also affect glucose homeostasis. Increased maternal intake of saturated and trans fatty acids, as a percentage of total energy intake, is associated with hyperglycemia [21]. Research suggests that women with GDM consume significantly higher amounts of saturated fats (34.1 ± 0.8 g/day vs. 32.0 ± 0.6 g/day) and lower amounts of polyunsaturated fats (12.2 ± 0.8 g/day vs. 15.0 ± 0.5 g/day) compared to pregnant women without GDM [27]. Similarly, Ley, et al discovered from 24-hour recall data that women with GDM consume more energy from total fat (37 ± 5.2% vs. 34 ± 5.3%, $P \leq 0.01$), monounsaturated fat (15 ± 2.5% vs. 13 ± 2.7%, $P \leq 0.006$), and polyunsaturated fat (8 ± 1.9% vs. 7 ± 1.6%, $P \leq$

0.03), and less from carbohydrate (49 ± 6.2% vs. 52 ± 6.2%, $P \leq 0.006$) than pregnant women without GDM during the second trimester of pregnancy [21].

Altered Glucose Homeostasis Related to Maternal Weight Gain

Increased adiposity and rapid maternal weight gain are associated with decreased insulin sensitivity. Research results are inconsistent regarding the effects of maternal dietary fat intake on weight gain, regardless if study participants consume an ad libitum diet or a diet controlled for total energy intake. It is important to note that regardless of dietary composition, glucose production increases with increased maternal body weight [34]. Some research illustrates that the fat content of the mothers' diets (12% fat versus 35% fat, $P > 0.10$) does not have significant effects on total maternal weight or weight gain [24]. Other research shows that high maternal dietary fat intake (16% fat versus 45% fat, $P < 0.05$) causes significantly higher total gestational weight gain compared to controls [14]. Frias, et al showed that macaque monkeys sensitive to high fat diets had a 48% higher weight gain during pregnancy compared to controls [22].

A maternal diet high in fat may cause metabolic changes resulting in higher rates of lipolysis more than that of pregnancy itself [27]. When lipolysis is favored, insulin resistance of adipose tissue heightens [26]. The suppression of lipolysis by insulin is reduced during late pregnancy, which contributes to larger postprandial increases in circulating free fatty acid concentrations, increased hepatic glucose production, and severe insulin resistance [26]. Frias, et al also found that macaque mothers sensitive to a high fat diet (32% of kilocalories from fat) had a 4-fold higher insulin area-under-the-curve during a glucose tolerance test, a 5-fold higher fasting leptin concentration, and higher fasting insulin concentrations compared to controls [22]. Moore, et al discovered that fasting basal glucose concentrations in pregnant dogs fed a high fat diet were not

significantly different than their non-pregnant or normally fed pregnant counterparts, but the high fat fed animals had greater than a three-fold higher area under the curve of glucose after the OGTT [25]. The same study showed no significant difference in plasma insulin concentrations between the groups, illustrating impaired glucose tolerance in the pregnant high-fat fed animals in the absence of hyperinsulinemia [25].

Effects of a High Fat Maternal Diet on Offspring

Maternal high fat diets affect fetal development, the neonate, and the infant's development through adolescence and adulthood. According to the fetal origins hypothesis, the maternal high fat diet also effects the mother's third generation, or grandchildren [7]. The effects of a high fat diet are not, however, related to the number of offspring in pregnancies but to other adult onset diseases such as obesity and T2DM [14, 24].

The heightened insulin resistance associated with high dietary fat intake increases postprandial FFA concentrations, increasing hepatic glucose production, and providing greater fuel availability to the fetus of women with GDM [26]. Studies of mice illustrate that offspring of dams who consumed a high fat diet are heavier than offspring of mice fed a control diet (1.64 ± 0.17 g versus 1.21 ± 0.13 g, $P < 0.01$), have higher blood pressure, and have hyperglycemia [18]. A maternal high fat diet has also been shown to predispose the fetus to T2DM later in life [6, 18].

Assessment of Dietary Fat Intake

Automated Self Administered 24 Hour Recall

The National Cancer Institute (NCI) developed the Automated Self Administered 24 Hour Recall (ASA-24) in 2009 in collaboration with the research from Westat (Rockville, MD) to provide an inexpensive and practical dietary recall tool for large-scale

research [82]. The system is a web-based tool that enables automated, self-administered, 24 hour dietary recalls. It consists of a Respondent Website for research participants and a Researcher Website used to manage study logistics and obtain data analyses. The first version, a Beta version, was released in August 2009, and used by over 200 researchers who collected more than 45,000 recalls for various studies [83]. The current version, ASA-24-2011, was released in September 2011, has improved usability and new features, and is freely available to researchers, clinicians, and teachers. Twenty-four hour dietary recalls are the preferred tool for monitoring dietary intake of populations because they provide high quality dietary intake data with minimal bias [82]. The ASA-24 provides more than 70 different dietary outcome values ranging from total energy to individual fatty acid intake [84].

The ASA-24 includes a dynamic user interface that includes multi-level food prompts to obtain accurate nutrient and food group analysis for each participant. Participants enter all foods they consumed in the past 24 hours. They may choose to browse food categories or search from a list of food and drinks from the United State Department of Agriculture's (USDA) Food and Nutrient Database for Dietary Studies if the system does not recognize their entry. An animated guide with audio and visual cues prompts the participant to report all details of dietary consumption including eating occasions, time of consumption, and portion sizes. Items entered by participants that are not recognized by ASA-24 are included in a separate list in the responses to enable research staff members to code for these items separately outside the ASA-24 [84].

The ASA-24 is based on the USDA interviewer-administered Automated Multiple-Pass Method dietary recall system, which has been validated for accurate estimations of total energy and protein intakes compared to individuals' biomarkers (doubly labeled water and urinary nitrogen) [82]. The USDA's Food and Nutrient Database for Dietary Studies was used in the analysis that validated the ASA-24.

Dietary Fat Screener

The Dietary Fat Screener (DFS) is a short dietary assessment instrument composed of 16 items that assesses an individual's usual intake of fat as a percent of total energy intake. The NCI developed the DFS along with other short dietary assessment instruments to characterize populations' median intakes of certain nutrients, examine interrelationships between diet and other variables, and compare findings from smaller studies to larger population studies [85].

The screener is composed of 31 questions, and the foods asked about on the screener were selected because they are the most important predictors of variability in fat intake as a percent of total energy intake consumed among American adults according to the USDA's Continuing Survey of Food Intakes of Individuals [85]. The scoring algorithm uses a regression model to calibrate the screener in an external dataset, which uses the 24-hour recall as a reference instrument. Under the measurement error model, the screener leads to unbiased estimates of relative risk in diet-disease studies [85]. The DFS has been evaluated against an extensive food frequency questionnaire as well as a 24-hour dietary recall [85, 86].

Infant Birth Weight related to Maternal Dietary Fat Intake and Glucose Homeostasis

Maternal nutrition is fundamental to fetal growth. Nutrient transfer from the mother to the fetus across the placenta drives fetal growth. An abundance of studies show positive associations between maternal height, pre-pregnancy BMI, maternal weight gain, and GDM with infant birth size parameters [3, 6, 14, 15, 18, 23, 87]. It is unclear though, whether this association is due to hormonal changes associated with GDM, or to other common underlying factors of GDM such as increased BMI or inadequate dietary intake [3, 14]. In a study of women with GDM, Uvena-Celebrezze, et

al reported a significant correlation between maternal fasting glucose concentrations (84 ± 13 mg/dL) during the second and third trimesters of pregnancy and infant birth weight (3356 ± 541 g, $P < 0.01$) [88]. Fewer studies have examined the direct relationship between maternal dietary intake, particularly maternal dietary fat intake, and infant birth size [36, 89, 90]. Results of the studies exploring this relationship are very inconsistent [68, 89, 91, 92].

Lagiou, et al reported that among 224 pregnant women and their offspring, there was no significant relationship between maternal energy intake, macronutrient intake including animal fat, vegetable fat, carbohydrate, and protein, and infant birth weight [90]. Another study on pregnant women found that not only is there no relationship between maternal macronutrient intake and infant birth weight, there is also no relationship between maternal macronutrient intake and placental weight, either [92].

Some studies do support a relationship between maternal dietary fat intake and infant birth weight. Kitajima et al showed that maternal fasting serum triglyceride concentrations in women at 24-32 weeks gestation were significantly positively associated with infant birth weight, independent of maternal obesity, gestational weight gain, or gestational plasma glucose concentrations ($P < 0.01$) [93]. However, the same study found no relationship between total cholesterol or free fatty acid concentrations and infant birth weight [93]. This suggests that maternal dietary fat intake may correlate to infant birth weight, because serum triglycerides increase with high fat diets.

In a study conducted by Catalano, et al, infants whose mothers developed GDM presented with higher body fat stores at birth (12.4 ± 4.6 %) compared with infants of the same weight born to mothers who did not develop GDM (10.4 ± 4.6 %; $P = 0.0001$). The increased body fat percentage is likely a significant risk factor for obesity in early childhood [68]. One study found that large-for-gestational-age (LGA) infants born to mothers with GDM had increased fat body mass (662 ± 163 g vs. 563 ± 206 g, $P = 0.02$)

and decreased lean body mass (3400 ± 314 g vs. 3557 ± 310 g, $P = 0.0009$) compared to LGA infants born to mothers without GDM [94]. There is also evidence that there is a direct correlation between maternal fasting glucose concentrations in mothers with GDM and neonatal fat mass [88]. This study further illustrated the significant correlation between infant fat mass and birth weight. The direct relationship between infant birth weight and maternal dietary fat intake in these studies is less clear because of the many confounding factors associated with GDM, such as increased BMI or poor maternal glucose control.

As previously mentioned, hormonal changes during pregnancy contribute to significant physiological shifts in the mother during pregnancy. Leptin, adiponectin, resistin, and insulin-like growth factor binding protein-1 (IGFBP-1) are all related to maternal dietary fat intake [36]. Jansson, et al reported that during the first trimester, fat intake is positively correlated with circulating leptin concentrations and inversely associated with circulating adiponectin concentrations. Maternal BMI did not contribute to these relationships [36]. The same study found that during the third trimester, total dietary fat intake was correlated with serum resistin concentration, also independently of BMI [36]. In a multiple regression model, the study illustrated that first trimester maternal plasma resistin concentration is positively, and third trimester maternal plasma IGFBP-1 concentration is negatively correlated with birth weight *z* scores. Insulin-like growth factor binding protein-1 inhibits insulin growth factor-I (IGF-I) action, explaining that the link between low IGFBP-1 concentrations and increased fetal growth, and therefore increased infant birth weight, is due to increased IGF-I bioavailability [36]. This study further demonstrates that maternal dietary intake variables influence concentrations of maternal hormones, which then alters fetal growth by affecting maternal metabolite levels and placental function.

Effects of High or Low Birth Weight Later in Life

There are many maternal factors that contribute to fetal growth and infant birth weight. Small for gestational age infants and LGA infants are both at increased risks for acute health implications and for developing diseases later in life [95]. According to the thrifty phenotype hypothesis, fetuses developing in nutritionally poor intrauterine environments (whether that is under- or over-nutrition) become programmed to preserve as much energy as possible [96]. As a result, the infant has a much higher risk of developing chronic diseases such as T2DM, hypertension, and metabolic syndrome throughout their life [6, 15, 96].

CHAPTER 3: RESEARCH STUDY METHODS

Study Design

The principal goals of this exploratory sub-analysis were to examine the relationships between maternal dietary fat intake and glucose control during pregnancy, and between maternal glucose control and infant birth weight. The sub-analysis was conducted with data obtained from women participating in the Oregon Health & Science University (OHSU) Pregnancy Exercise and Nutrition (PEN) Study. The PEN Study was a prospective, randomized, controlled, feasibility study of a new, interactive curriculum designed to improve diets and physical activity levels of women throughout pregnancy. However, for this secondary analysis, all participants were evaluated as one group, regardless of their randomization to the intervention or control group in the PEN Study. Pertinent data was also analyzed as the intervention group versus the control group to assure whole group analyses were not skewed.

Women randomized to the control group received standard care by their health care providers during pregnancy. As participants in the PEN Study, they received a U.S. Department of Health and Human Services Office on Women's Health pregnancy handout entitled Pregnancy: Staying healthy and safe (http://www.womenshealth.gov/pregnancy/you-are-pregnant/staying-healthy-safe.cfm). The handout included diet and fitness recommendations during pregnancy, information on smoking cessation and substance abuse, and other pregnancy-related health information.

Women randomized to the intervention group participated in a scripted, team-based, peer-led interactive curriculum, and accompanying web-based intervention to promote healthy dietary and physical activity practices during pregnancy. The intervention group was expected to attend 20 weekly, 30-minute, peer-led educational

sessions, and follow dietary and physical activity recommendations included in the educational curriculum.

Each participant provided informed consent and signed Health Insurance Portability and Accountability Act authorization forms before enrollment. All study related procedures were reviewed and approved by the OHSU Institutional Review Board.

Subjects

Participants were pregnant women who were OHSU employees or spouses of OHSU employees. Participants enrolled in the PEN Study in their first trimester of a single gestation pregnancy. Participants were recruited using flyers and posters displayed around the OHSU campus, pamphlets placed in obstetric clinics, and notices included on the OHSU internal website. Women judged to be healthy by self-report, review of medical history, medication use, lab screenings, and physical exam were considered eligible for participation. Inclusion and exclusion criteria are presented in Table 2. A physician's note was required for each participant enrolled in the PEN Study specifying that their patient may be enrolled in the program, and that they would share relevant patient data.

Table 2. Inclusion and Exclusion Criteria	
Inclusion	**Exclusion**
- Healthy pregnant adult - OHSU employee or spouse of an OHSU employee - Single gestation pregnancy - 5-12 weeks gestation	- Type 1 or Type 2 Diabetes Mellitus - Cardiovascular disease - Obstructive lung disease - Musculoskeletal dysfunctions - Hypertension or previous diagnosis of hypertension - Use of anti-hypertensive medications - Elevated fasting blood sugar (> 110 mg/dL) at entry - Exceeding 40 years of age - Smoking and/or drinking during pregnancy

Randomization

Participants were randomly assigned into the intervention group or control group. Group assignment was balanced for body mass index (BMI) and age. To accomplish this balanced randomization, each group of 10 new participants was entered into a table organized by participant identification number, BMI, and age. The table was ordered by BMI, and participants with the same or similar BMIs were sorted by age. Participants with similar BMI and age were paired and assigned to the control or intervention group using the iPhone application “Coin Flip +”. Two steps were taken to determine group assignment. The first step ordered the participant pair. Heads indicated the participant be listed first in the pair, and tails indicated the participant be listed second. The second step assigned the first participant of the pair to one of the two groups. Heads indicated

the participant was assigned to the intervention group, and tails indicated the participant was assigned to the control group.

Measurements

Study measurements were obtained during first, second, and third trimester study visits.

Demographic Information

Each participant completed a questionnaire to provide the following demographic information: ethnicity, race, education level, employment status, household income, and number of people in household. They also provided information about their personal pregnancy history including previous delivery date, gestational age of the infant in weeks at delivery, birth weight, gender, type of delivery, place of delivery, and preterm labor delivery status for each birth prior to their current pregnancy.

Weight and Height Measurements

Trained research staff measured participant weight and height in the OHSU Health Promotion & Sports Medicine Human Performance Lab. Weight was obtained with an electronic scale to the nearest 0.5 gram (Fairbanks; HS 110AX Class III; Kansas City, MO) while the participant was dressed in light clothing without shoes. Height was measured with a stadiometer to the nearest 0.01 centimeter (Invicta Plastics Limited; Design Application No. 2007246; Leicester, England) while the participant was not wearing shoes. Body mass index was calculated as the weight in kilograms divided by the height in meters squared.

$$BMI = [\text{weight (kg)}]/[\text{height (m}^2\text{)}]$$

Dietary Energy and Fat Assessment

Total dietary energy intake was quantified using the Automated Self Administered 24 Hour Recall (ASA-24). Dietary fat intake was quantified using the ASA-24 and the Dietary Fat Screener (DFS). Both of these instruments provided estimates of total dietary fat (g/day), saturated fatty acid (SFA, g/d), monounsaturated fatty acid (MUFA, g/d), polyunsaturated fatty acid (PUFA g/d), eicosapentaenoic acid (EPA mg/d), and docosahexaenoic acid (DHA mg/d) intake by the ASA-24 only. Dietary fat intake was quantified as a percentage of total energy intake, and dietary fat density was quantified as grams of each type of fat per 1,000 kilocalories.

Automated Self Administered 24-Hour Recall

The ASA-24-2011, developed by the National Cancer Institute (NCI), is a web-based software program that collects details of the respondent's food intake during the previous 24 hours from midnight to midnight. To initiate the dietary intake assessment, an OHSU Oregon Clinical and Translational Research Institute (OCTRI) bionutritionist sent the participant an unannounced email two to five days after each trimester visit with a login and password to access the ASA-24. The email prompting the participant to complete the recall was only provided on weekdays (Monday through Friday, reflecting the previous day's diet intake), and was sent in the morning to allow sufficient time for completion. Each participant was expected to complete the recall by the end of the day that she receives the notification. After completing the ASA-24, the participant notified the bionutritionist via email, and reported any issues with the recall. If the participant did not complete the ASA-24 on the scheduled day, a research staff member established another day during the same trimester for completion.

Once all recalls for each participant were completed, the bionutritionist logged into the ASA-24 Research Website, and sent a request to NCI for the data to be

exported. Within one to two days, the data was returned in a file that provided each participant's nutrient analysis.

Dietary Fat Screener

The Dietary Fat Screener 2000, developed by the NCI, is a short assessment instrument that estimates participants' usual intake of percentage energy from fat. Similarly to the ASA-24, the OCTRI bionutritionist emailed a link to each participant to access the Dietary Fat Screener (DFS) for online completion at the same time they complete the ASA-24. The participants' responses were stored in a Research Electronic Data Capture, version 5.6.0, (REDCap) database, where research staff could access the data.

Blood Sample Collection Analysis

Fasting blood samples were collected by venepuncture at each clinic visit, and sent to the OHSU Clinical Chemistry Lab for analysis of plasma glucose and serum insulin. Plasma glucose concentration was measured by the Siemens Vista 1500 colorimetric assay. The lowest concentration of glucose able to be detected by this method is 1 mg/dL. The coefficient of variation (CV) for a blood glucose concentration of 100 mg/dL is 3%. The CV for a blood glucose concentration of 200 mg/dL is 2%. This assay was performed at the OHSU Clinical Chemistry Lab, Portland, OR. Serum insulin concentration was measured by a chemiluminescent immunoassay. The lowest concentration of insulin able to be detected is 1 μlU/mL. The CV for this procedure is 7%. This assay was performed at the ARUP Laboratories, Salt Lake City, UT.

Oral Glucose Tolerance Test

Each participant followed her obstetrician's standard of care for the oral glucose tolerance test. At OHSU, the standard of care for pregnant women is to consume a 75-gram dose of glucose (Oral Glucose Tolerance Drink, Azer Scientific, Morgantown, PA) between 22-26 weeks of gestation, and to have her blood drawn while fasting, and one and two hours after consuming the glucose load. If the participant's fasting plasma glucose concentration is greater than 92 mg/dL, greater than 180 mg/dL at one hour, or greater than 153 mg/dL at two hours, she is diagnosed with GDM. Results of the OGTT were obtained from the participant's OHSU electronic medical record or directly from the participant's medical provider.

Infant Weight Measurements and Delivery Information

Infant birth weight was collected from the participant's electronic medical records (EPIC) or directly from the participant's physician's office. Infant birth weight was adjusted for gestational age using the 2013 Fenton Growth Charts [97]. Gender, gestational age in weeks and days, weight, length, and head circumference were entered into an online calculator that indexed the infant's weight to their gestational age (http://peditools.org/fenton2013/index.php), and provided the infant birth weight percentile adjusted for gestational age. Additional information collected about the delivery and birth included date of delivery, gestational age, maternal weight at delivery, infant length, and delivery method.

Calculations

Maternal Glucose Control

Maternal glucose control was quantified using fasting insulin and fasting glucose concentrations, homeostatic models of assessment (HOMA) for insulin resistance (HOMA-IR) and pancreatic beta cell function (HOMA-β), and the quantitative insulin sensitivity check index (QUICKI). The HOMA and QUICKI equations are:

HOMA-IR = [fasting glucose (mg/dL) x fasting insulin (ulU/mL)]/405

HOMA-β = [360 x fasting insulin (ulU/mL)]/[fasting glucose (mg/dL) – 63)] %

QUICKI = 1/(log fasting glucose (mg/dl) + log fasting insulin (μIU/mL))

Data Management

All data collected as a result of participation in this study was kept completely confidential. Participants were assigned unique identification numbers, and their names were removed from data collection documents. Forms and participant identification were kept in a locked filing cabinet in the OHSU Hatfield Research Building. Study data and participant information was managed using REDCap, and only those study staff with assigned passwords are permitted to access participant data. REDCap is a secure, web application designed to support data capture for research studies, providing web-based case report forms, real-time data entry validation, audit trails, and a de-identified data export mechanism to common statistical programs. REDCap was developed by a multi-institutional consortium, including OHSU, and was initiated at Vanderbilt University. The system is protected by a login and Secure Sockets Layer (SSL) encryption. Information obtained from the participants' electronic medical records was optically scanned, and typed into REDCap. Data files not appropriate for REDCap (such as the large ASA-24 output documents) were stored on a secure server, the password protected, HPSM

Division OHSU X-drive, and was only available to research staff performing study related analyses.

Data Cleaning and Evaluation

Relevant data was transferred into standard spreadsheets (Microsoft Excel for Mac 2011 Version 14.3.6 and SAS Enterprise Version 6.1), and standard distribution curves were generated to assess normality of each set of outcome variables. Box-plots were used to identify outliers and skewedness. If any data points stood out from others by visual inspection, they were further investigated to ensure data was entered correctly.

Statistical Analysis

Descriptive statistics were used to characterize study participants, and included means, ranges, and frequencies of participant demographic, dietary, and glucose control data, and infant birth weight. Prior to analyzing the data, outliers were defined as any participant who claimed consuming ≤ 10% of energy from fat in one day. No women were excluded for dietary reasons.

Canonical Correlation Analysis

Canonical correlation analyses were used to describe the relationship between dietary fat intake and glucose control during each trimester of pregnancy. This analysis technique identifies combinations (components) of the two sets of variables of interest and determines the correlation between the components. Dominant patterns among the significant variables of the data sets were extracted to represent the data in a set of fewer, orthogonal variables. The analysis provided simplification, data reduction, modeling, and outlier detection of data sets. Correlations between dietary fat

components and glucose control components of $r > 0.60$ were considered to be of biological importance.

Total fat, SFA, MUFA, and PUFA represent the components of dietary fat variables. Fasting glucose, fasting insulin, HOMA-IR, HOMA-β, and QUICKI represent the components of glucose control variables. For each trimester, original dietary fat variables were represented by "F" components, and original glucose control variables were represented by "G" components. The minimum number of variables in the two sets being compared limits the maximum number of canonical components. Here, we produced four canonical components to determine the relationships between dietary fat intake and glucose control. F1, F2, F3, and F4 are canonical components for dietary fat intake. G1, G2, G3, and G4 are canonical components for glucose control.

Each combination of variables from the two sets (FI – F4 and G1 – G4) are used to generate the highest correlation possible while being uncorrelated with the other combinations from the same variables. These values were used to identify which original variable(s) influenced each component the most. Correlations between original variable groups and their respective components with $r > 0.30$ indicated the variable(s) that most heavily influenced the component. In aggregate canonical component sets, the variable(s) with the largest component value(s) was/were defined as the variable(s) that most heavily influenced the component.

The first components of each group (F1 and G1) accounted for the majority of the variance among the data, followed by each subsequent component. Individual component correlations accounting for greater than 30% of data variance were considered clinically relevant. The correlations between component sets described the relationships between all original variables.

Linear Regression Analysis

Linear regression was use to determine the relationship between maternal glucose control, as indicated by QUICKI, and infant birth weight. The linear regression model included gestational weight gain (as a percentage of recommendation indexed to week of gestation), pre-pregnancy BMI, and parity, to account for potential confounding factors. The SAS Enterprise statistical software program (Version 6.1; Cary, NC) was used to analyze all data.

CHAPTER 4: RESULTS

Pregnancy Exercise & Nutrition (PEN) Participant Characteristics

Thirty women were recruited to participate in the PEN Study. Two participants in the intervention group withdrew during the first trimester due to time constraints, and were not replaced. For this secondary analysis, all participants were evaluated as one group, regardless of their randomization to the intervention or control group in the PEN Study. To assure that group allocation did not cause misrepresentation of outcomes of the cohort as a whole, each pertinent variable was analyzed for significant differences between control and intervention group. No significant differences between groups were detected.

Characteristics of the PEN participants are illustrated in Tables 3 and 4. The average age ± standard deviation at enrollment was 33 ± 3 years with a range of 27 – 37 years, and 89% of the participants were white. Sixty-one percent of participants had a graduate degree, and 78% had a household income of at least $75,000. It was the first pregnancy for 64%, the second for 29%, and the third for 7%. On average, PEN participants gained 123% of the weight gain recommended by the Institute of Medicine based on pre-pregnancy BMI [98]. The average gestational age of infants born to PEN participants was 39.6 ± 2.1 weeks, and their average birth weight and length were 3.4 ± 0.5 kg and 49.5 ± 5.9 cm, respectively. The average infant birth weight percentile, adjusted for week of gestation according to the 2013 Fenton Growth Charts [97], was at the 52.0 ± 29.5 percentile.

Table 3. Participant Demographic Characteristics (n = 28)	
Race (White, %)	89
Education (%)	
2 Year College Degree	7
4 Year College Degree	32
Graduate Degree	61
Household Income (%)*	
$25,000-$74,999	22
$75,000-$149,999	63
More than $150,000	15
Parity (%)	
0	64
1	29
2	7
*n = 27	

Table 4. Maternal and Infant Anthropometric Characteristics*	
Maternal pre-pregnancy weight† (kg)	67.5 ± 11.9 (45.5 - 97.3)
Maternal pre-pregnancy BMI (kg/m^2)	24.9 ± 3.6 (18.9 - 35.1)
1st trimester weight (kg)	69.3 ± 12.8 (48.7 - 99.1)
2nd trimester weight (kg)	75.2 ± 13.4 (55.6 – 105)
3rd trimester weight (kg)	79.8 ± 13.5 (57.7 – 109)
Last recorded weight before delivery (kg)	83.6 ± 14.3 (59.6 - 113.4)
Recommended weight gain‡ (%)	123 ± 53 (26 – 252)
Duration of gestation (weeks)	39.6 ± 2.1 (33.1 – 42)
Infant birth weight (kg)	3.4 ± 0.53 (2.5 – 4.5)
Infant birth weight§ (percentile)	52.0 ± 29.5 (1 - 97)
Infant birth length (cm)	49.5 ± 5.9 (21.5 – 55)

*Mean ± SD (range)
†Self-reported pre-pregnancy weight
‡Based on 2009 Institute of Medicine Pregnancy Weight Gain Recommendations
§Based on 2013 Fenton Growth Charts

Summary of Dietary Intake throughout Pregnancy

Maternal total energy, macronutrient, and individual fatty acid intakes during each trimester are described in Table 5. There was a significant increase in total energy intake from trimester one to three, $p < 0.05$. Average intake of protein and carbohydrate as a percent of total energy intake increased, and average intake of fat as a percent of total energy intake decreased from trimesters one to three. Average intake of carbohydrate as a percent of total energy intake increased from 49 ± 8 to 51 ± 8% between trimesters

one and three. There was a significant increase in carbohydrate intake as a percent of total energy intake from trimester one to two, $p < 0.05$. Similarly, there was a significant increase in carbohydrate density (g/1000 kcal) from trimester one to two, $p < 0.05$. Average intake of protein as a percent of total energy intake increased from 14 ± 4 to 15 ± 4% between trimesters one and three. Average intake of fat as a percent of total energy intake decreased from 37 ± 8 to 34 ± 7% between trimesters one and three. There was a significant decrease in fat intake (g/d) from trimester one to three, $p < 0.05$. There was a significant decrease in fat intake as a percent of total energy intake from trimester one to two, $p < 0.01$. Similarly, there was a significant decrease in fat density (g/1000 kcal) from trimester one to two, $p < 0.01$. Average intake of fat as a percent of total energy intake during the first trimester exceeded the Institute of Medicine, Food and Nutrition Board's recommended range of 20-35% [71] but was within the recommended range during the second and third trimesters (31 ± 6 and 34 ± 7%, respectively). Percent of total energy from fat was also estimated using the Dietary Fat Screener during each trimester. Participants consumed an average of 29 ± 4 percent energy from fat during the first trimester, 29 ± 3 percent during the second trimester, and 28 ± 3 percent during the third trimester. These values are lower than those estimated using the ASA-24 method and reflect intake over the past month compared to intake over the past 24 hours.

As the average consumption of fat, as a percent of total energy intake, decreased throughout gestation, so did the percent of total energy intake derived from subclasses of fatty acids. Saturated fatty acid intake as a percent of total energy intake comprised 12 ± 4, 10 ± 3, and 11 ± 4 percent of total energy intake during the first, second, and third trimesters, respectively, exceeding the American Heart Association (AHA) recommendation of less than 8% of total energy during each trimester [73]. There was a significant decrease in SFA intake (g/d) from trimester one to two, $p < 0.05$.

Similarly, there was a significant decrease in SFA density (g/1000 kcal) from trimester one to two, $p < 0.05$. Consumption of MUFA was 13 ± 4, 11 ± 3, and 12 ± 3 percent of total energy intake during the first, second, and third trimesters, respectively. This was less than the AHA recommendation of 15% of total energy from MUFA [73]. Consumption of PUFA as a percent of total energy intake was 8 ± 3 during the first trimester, 7 ± 2 during the second trimester, and 8 ± 3 during the third trimester, and this too was lower than the AHA's recommendation of 10% of total energy intake [73]. Participants consumed an average of 40 ± 140, 60 ± 190, and 50 ± 150 mg/d of EPA and 40 ± 130, 100 ± 270, and 80 ± 210 mg/d of DHA during the first, second, and third trimesters respectively. Average consumption of EPA plus DHA was lower than the American College of Nurse-Midwives recommendation of 200-500 mg/d during pregnancy [75, 77].

Table 5. Maternal Dietary Intake during the First, Second, and Third Trimesters of Pregnancy

Dietary Component	Trimester		
	1	2	3
Energy (kcal/day)	2040 ± 621 (975 – 3216)	2049 ± 599 (1003 – 3638)	2100 ± 665* (413 – 3464)
Carbohydrate			
Grams/day	247 ± 69 (104 – 390)	275 ± 92 (143 – 542)	261 ± 82 (64 – 439)
Percent of total energy (%)	49 ± 8 (36 – 71)	54 ± 7† (41 – 70)	51 ± 8 (40 – 76)
Density (g/1000 kcal)	123 ± 21 (91 – 178)	134 ± 18† (103 – 176)	127 ± 21 (99 – 189)
Protein			
Grams/day	70 ± 24 (31 – 122)	79 ± 31 (28 – 161)	80 ± 30 (68 – 84)
Percent of total energy (%)	14 ± 4 (9 – 24)	16 ± 4 (8 – 22)	15 ± 4 (9 – 23)
Density (g/1000 kcal)	35 ± 9 (21 – 60)	39 ± 10 (19 – 55)	38 ± 10 (22 – 58)

Table 5, continued. Maternal Dietary Intake during the First, Second, and Third Trimesters of Pregnancy			
Dietary Component	**Trimester**		
	1	**2**	**3**
Fat			
Grams/day	86 ± 39 (15 – 181)	70 ± 24 (34 – 122)	82 ± 35† (14 – 168)
Percent of total energy (%)	37 ± 8 (13 – 51)	31 ± 6‡ (18 – 42)	34 ± 7 (15 -44)
Density (g/1000 kcal)	41 ± 9 (15 – 56)	34 ± 7‡ (20 – 47)	38 ± 8 (17 – 48)
Saturated Fatty Acid (g/d)	30 ± 18 (2 – 77)	23 ± 10† (9 – 54)	27 ± 12 (4 – 53)
Percent of total energy (%)	12 ± 4 (2 – 22)	10 ± 3 (5 – 17)	11 ± 4 (3 – 21)
Density (g/1000 kcal)	14 ± 5 (3 – 24)	11 ± 3† (6 – 19)	13 ± 4 (3 – 23)
Monounsaturated Fatty Acid (g/d)	31 ± 17 (5 – 86)	25 ± 9 (10 – 44)	29 ± 15 (5 – 78)
Percent of total energy (%)	13 ± 4 (4 – 24)	11 ± 3 (6 – 17)	12 ± 3 (6 – 20)
Density (g/1000 kcal)	14 ± 5 (5 – 27)	12 ± 3 (7 – 19)	14 ± 4 (7 – 23)
Polyunsaturated Fatty Acid (g/d)	19 ± 9 (6 – 45)	17 ± 6 (5 – 33)	18 ± 11 (3 – 49)
Percent of total energy (%)	8 ± 3 (5 – 14)	7 ± 2 (4 – 13)	8 ± 3 (3 – 15)
Density (g PUFA/1000 kcal)	9 ± 3 (5 – 15)	8 ± 2 (4 – 14)	8 ± 3 (3 – 17)
Eicosapentaenoic Acid (mg/d)	40 ± 140 (0 – 670)	60 ± 190 (0 – 870)	50 ± 150 (0 – 590)
Density (mg/1000 kcal)	30 ± 101 (0 – 440)	29 ± 96 (0 – 409)	21 ± 63 (0 – 260)
Docosahexaenoic Acid (mg/d)	40 ± 130 (0 – 670)	100 ± 270 (0 – 1210)	80 ± 210 (0 – 840)
Density (mg/1000 kcal)	31 ± 95 (0 – 437)	47 ± 133 (0 – 572)	35 ± 88 (0 – 373)

Values expressed as mean ± SD (range)
*Includes one participant with low energy intake but fat intake of at least 10% of total energy
†Significantly different from first trimester, $P < 0.05$
‡Significantly different from first trimester, $P < 0.01$

Summary of Maternal Glucose Control during Pregnancy

Due to laboratory errors, one fasting insulin sample was lost during the first trimester, and a different fasting insulin sample was lost during the second trimester. As a result, the sample size for this analysis was 27 during the first and second trimesters, and 28 during the third trimester.

Maternal glucose control throughout gestation is summarized in Table 6. The average fasting glucose concentrations were 84 ± 7 mg/dL, 81 ± 7 mg/dL, and 79 ± 7 mg/dL during the first, second, and third trimesters, respectively. The average fasting insulin concentration during the first trimester was 8 ± 4 μU/mL, 9 ± 6 μU/mL during the second trimester, and 11 ± 5 μU/mL during the third trimester. The Center for Women's Health at OHSU considers maternal glucose and insulin concentrations of less than 95 mg/dL and between 10.08 – 11.52 μU/mL to be healthy during pregnancy, respectively. Due to the physiological changes during pregnancy that support fetal growth, there were significant differences in circulating concentrations of glucose and insulin between the first and second and first and third trimesters: the average circulating glucose concentration was lower and the average circulating insulin concentration was higher later in pregnancy. The average HOMA-IR value was 1.7 ± 1.0 during the first trimester, 2.0 ± 1.5 during the second trimester, and 2.3 ± 1.1 during the third trimester. There was a significant difference in average HOMA-IR values during the first and third trimesters. The average HOMA-β was 2.0 ± 1.0 during the first trimester, 2.4 ± 1.4 during the second trimester, and 3.0 ± 1.3 during the third trimester. There were significant differences in average HOMA-β values during the first and second trimesters, and during the first and third trimesters. The average QUICKI value was 0.36 ± 0.04 during the first trimester, 0.36 ± 0.03 during the second trimester, and 0.35 ± 0.03 during the third trimester. There was a significant difference between average QUICKI values during the first and third trimesters. Similarly to the differences between glucose and insulin

concentrations throughout pregnancy, the significant differences in HOMA-IR, HOMA-β, and QUICKI values throughout pregnancy were likely due to the physiological changes during pregnancy that support fetal growth.

In addition to the markers of glucose control described above, 22 of the 28 participants also completed a 2-hour oral glucose tolerance test. The average glucose concentrations were 80 ± 8, 119 ± 30, and 100 ± 19 mg/dL at fasting, one hour, and two hours, respectively. Based on the diagnostic glucose concentration cut points of 92 mg/dL, 180 mg/dL, and 153 mg/dL at fasting, one hour, and 2 hours, respectively, one participant was diagnosed with GDM.

Table 6. Markers of Maternal Glucose Control during Pregnancy

	Trimester		
Marker of Glucose Control	**1**	**2**	**3**
Fasting Glucose (mg/dl)	84 ± 7 (71 – 103)	81 ± 7* (69 - 97	79 ± 7† (66 – 95)
Fasting Insulin (μIU/mL)	8 ± 4 (2 – 19)	9 ± 6* (3 – 33)	11 ± 5† (4 – 20)
HOMA-IR	1.7 ± 1.0 (0.4 – 4.8)	2.0 ± 1.5 (0.6 – 7.9)	2.3 ± 1.1† (0.7 – 4.5)
HOMA-β	2.0 ± 1.0 (0.5 – 4.2)	2.4 ± 1.4* (0.8 – 7.1)	3.0 ± 1.3† (1.2 – 5.2)
QUICKI	0.36 ± 0.04 (0.30 – 0.44)	0.36 ± 0.03 (0.29 – 0.42	0.35 ± 0.03† (0.31 – 0.41)

Values expressed as mean ± SD (range)
HOMA-IR: Homeostatic model of assessment for insulin resistance
HOMA-β: Homeostatic model of assessment for beta cell function
QUICKI: Quantitative insulin sensitivity check index
*Significantly different from first trimester, $P < 0.05$
†Significantly different from first trimester, $P < 0.01$

Relationship between Maternal Dietary Intake and Glucose Control during Pregnancy: Canonical Correlations

Relationship between Maternal Dietary Fat Intake and Glucose Control during the First Trimester

The correlation between maternal dietary fat intake and glucose control during the first trimester is shown in Table 7 and Figures 2 and 3. The first set of canonical components for dietary fat intake and glucose control, F1 and G1, respectively, are highly correlated with a correlation value of 0.72 (Table 7a, Figure 2). The proportion of variance accounted for within each canonical component is illustrated in Table 6b. The canonical components F1 and G1 account for 45% of total variance among the data.

The first canonical component for dietary fat intake, F1, is driven primarily by MUFA intake and inversely by SFA intake, as indicated by a predictor correlation value of 0.35 for MUFA and a strong negative predictor correlation value for SFA of -0.43 (Table 7c). Women with large values of F1 consumed high amounts of MUFA and low amounts of SFA compared to sample means during the first trimester.

The first canonical component for glucose control, G1, is an aggregate of glucose control variables, with QUICKI being the strongest predictor variable, of 0.16, during the first trimester (Table 7d). Large positive values of G1 are directly associated with higher than average values of QUICKI, compared to sample means. Therefore, women with large values of G1 had higher than average QUICKI during the first trimester. The positive correlation between F1 and G1 ($r = 0.72$; Table 7a) indicates a relationship between higher than average consumption of MUFA, lower than average consumption of SFA, and higher than average QUICKI values.

The second significant set of canonical components for maternal dietary fat intake and glucose control during the first trimester, F2 and G2, also have a strong correlation of 0.67 (Table 7a, Figure 3). The canonical components F2 and G2 account

for 34% of total variance among the data, and when combined with the F1 and G1 components, account for 79% of the correlation variance among the data.

The second canonical component for dietary fat intake, F2, is driven largely by total fat, SFA, and MUFA, as indicated by predictor correlation values of 0.98 for total fat, 0.82 for SFA, and 0.83 for MUFA (Table 7c). Women with large values of F2 consumed high amounts of total fat, SFA, and MUFA, and low amounts of PUFA compared to sample means.

The second canonical component for glucose control, G2, is driven by fasting glucose, and slightly inversely driven by QUICKI, as indicated by a predictor correlation value of 0.53 for fasting glucose, and a negative predictor correlation value of -0.13 for QUICKI (Table 7d). Women with large positive values of G2 had high fasting glucose values and low QUICKI values, compared to sample means. The positive correlation between F2 and G2 ($r = 0.67$) indicates a relationship between higher than average consumption of total fat, SFA, and MUFA, and higher than average fasting glucose values.

We chose to analyze correlations between the first two canonical components only, because the first two canonical components account for more than 30% of total variance each, and 78.9% of total variance combined. The third and fourth canonical components (F3, G3, F4, and G4) do not account for a large enough proportion of the data's variance to consider them to be clinically relevant.

Table 7. Relationship between Maternal Dietary Fat Intake and Glucose Control during the First Trimester

a. Correlation between Canonical Components of Maternal Dietary Fat Intake and Glucose Control*

Variate	Canonical Correlation (R)
F1 vs. G1	0.72
F2 vs. G2	0.67
F3 vs. G3	0.53
F4 vs. G4	0.32

b. Proportion of Data accounted for in Each Canonical Component

Component	Individual Proportion	Cumulative Proportion
F1 & G1	45%	45%
F2 & G2	34%	79%
F3 & G3	16%	95%
F4 & G4	5%	100%

c. Correlation Between Dietary Fat Variables and Their Canonical Components†

	Canonical Components for Dietary Fat Intake			
Original Variables for Dietary Fat	**F1**	**F2**	**F3**	**F4**
Total Fat	-0.05	0.98	-0.19	0.05
SFA	-0.43	0.82	0.35	0.15
MUFA	0.35	0.83	-0.14	-0.41
PUFA	0.23	0.23	-0.77	0.55

d. Correlation Between Glucose Control Variables and Their Canonical Components†

	Canonical Components for Glucose Control			
Original Variables for Glucose Control	**G1**	**G2**	**G3**	**G4**
Fasting Glucose	0.06	0.53	0.33	0.20
Fasting Insulin	0.08	0.19	0.92	0.33
HOMA-IR	0.09	0.20	0.86	0.41
HOMA-β	0.08	0.15	0.95	0.23
QUICKI	0.16	-0.13	-0.96	-0.08

*Values > 0.6 are considered clinically relevant
†Values > 0.3 are considered clinically relevant. Canonical components with aggregate correlation values are driven by the variable with the largest correlation value.
SFA: Saturated Fat
MUFA: Monounsaturated fat
PUFA: Polyunsaturated fat
HOMA-IR: Homeostatic Model of Assessment for Insulin Resistance
HOMA-β: Homeostatic Model of Assessment for beta cell function
QUICKI: Quantitative Insulin Sensitivity Check Index

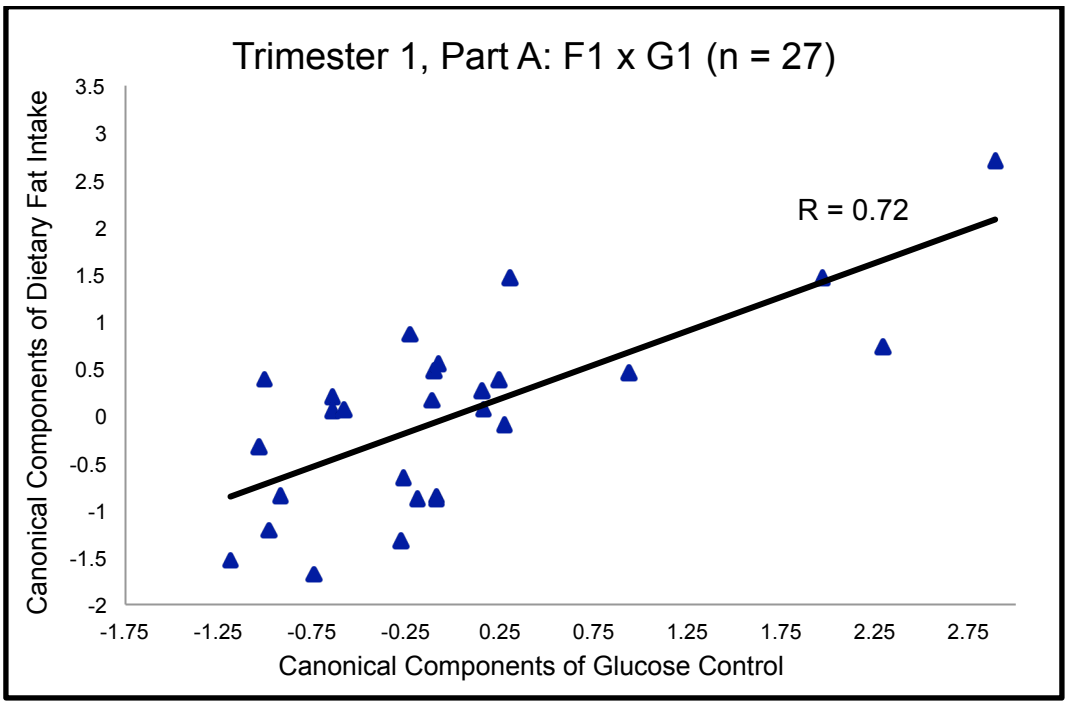

Figure 2: Relationship Between Maternal Dietary Fat Intake and Glucose Control during the First Trimester (F1 and G1): Higher than average consumption of MUFA and lower than average consumption of SFA was associated with higher than average QUICKI values.

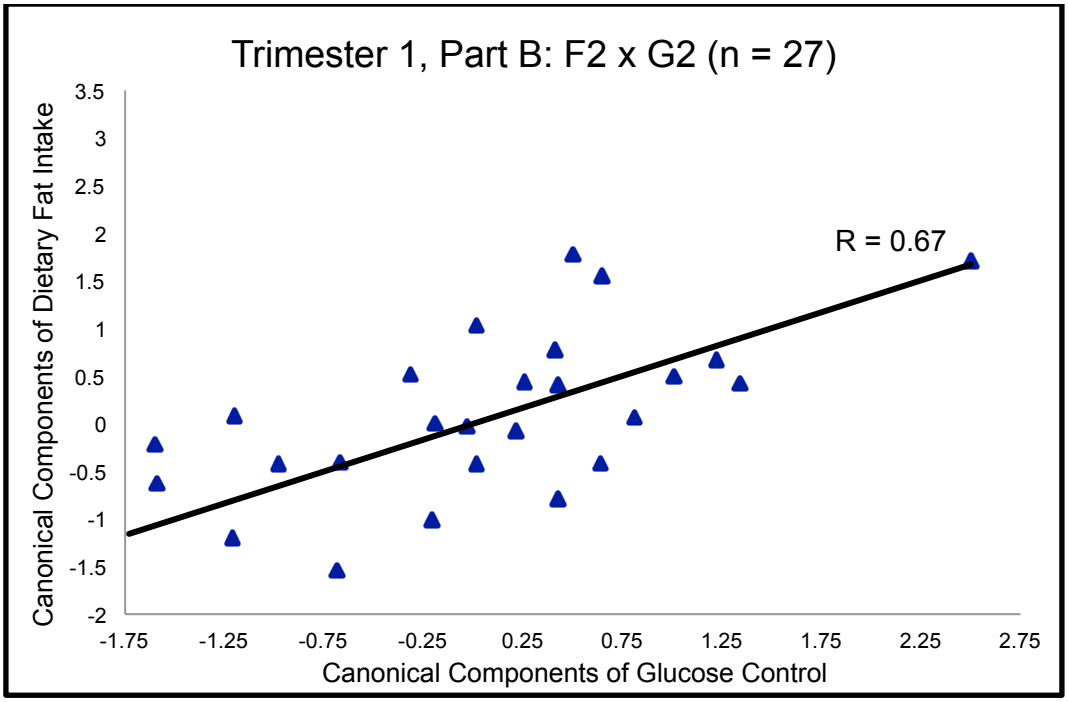

Figure 3: Relationship Between Maternal Dietary Fat Intake and Glucose Control during the First Trimester (F2 and G2): Higher than average consumption of total fat, SFA, and MUFA was associated with higher than average glucose concentrations.

Relationship between Maternal Dietary Fat Intake and Glucose Control during the Second Trimester

The correlation between maternal dietary fat intake and glucose control during the second trimester is shown in Table 8 and Figure 4. The first set of canonical components for dietary fat intake and glucose control, F1 and G1, respectively, are highly correlated with a correlation value of 0.66 (Table 8a, Figure 4). The proportion of variance accounted for within each canonical component is illustrated in Table 8b. The canonical components F1 and G1 account for 64% of total variance among the data.

The first canonical component for dietary fat intake, F1, is driven primarily by total fat, SFA, and MUFA, as indicated by predictor correlation values of 0.62 for total fat, 0.63 for SFA, and 0.46 for MUFA (Table 8c). Women with large values of F1 consumed high amounts total fat, SFA, and MUFA, and low amounts of PUFA during the second trimester, compared to sample means.

The first canonical component for glucose control, G1, is driven primarily by fasting glucose, fasting insulin, HOMA-IR, HOMA-β values, and inversely by QUICKI, as indicated by predictor correlation values of 0.66 for fasting glucose, 0.56 for fasting insulin, 0.59 for HOMA-IR, 0.50 for HOMA-β, and -0.57 for QUICKI (Table 8d). Women with large values of G1 had high fasting glucose, fasting insulin, HOMA-IR, and HOMA-β values, and low QUICKI values during the second trimester, compared to sample means.

The positive correlation between F1 and G1 ($r = 0.66$) indicates that higher than average consumption of total fat, SFA, MUFA, and low consumption of PUFA is directly associated with higher than average fasting glucose, fasting insulin, HOMA-IR, and HOMA-β values, and indirectly related with QUICKI values.

Table 8. Relationship between Maternal Dietary Fat Intake and Glucose Control during the Second Trimester

a. Correlation between Canonical Components of Maternal Dietary Fat Intake and Glucose Control*

Variate	Canonical Correlation
F1 vs. G1	0.66
F2 vs. G2	0.49
F3 vs. G3	0.30
F4 vs. G4	0.16

b. Proportion of Data accounted for in Each Canonical Component

Component	Individual Proportion	Cumulative Proportion
F1 & G1	64%	64%
F2 & G2	26%	89%
F3 & G3	8%	98%
F4 & G4	2%	100%

c. Correlation Between Dietary Fat Variables and Their Canonical Components†

	Canonical Components for Dietary Fat Intake			
Original Variables for Dietary Fat	**F1**	**F2**	**F3**	**F4**
Total Fat	0.62	-0.32	-0.71	-0.05
SFA	0.63	0.14	-0.37	-0.67
MUFA	0.46	-0.18	-0.72	0.49
PUFA	0.28	-0.82	-0.29	0.41

d. Correlation Between Glucose Control Variables and Their Canonical Components†

	Canonical Components for Glucose Control			
Original Variables for Glucose Control	**G1**	**G2**	**G3**	**G4**
Fasting Glucose	0.66	-0.36	0.65	0.05
Fasting Insulin	0.56	0.32	0.53	-0.27
HOMA-IR	0.59	0.29	0.58	-0.16
HOMA-β	0.50	0.36	0.44	-0.40
QUICKI	-0.57	0.16	-0.37	0.39

*Values > 0.6 are considered clinically relevant
†Values > 0.3 are considered clinically relevant. Canonical components with aggregate correlation values are driven by the variable with the largest correlation value.
SFA: Saturated Fat
MUFA: Monounsaturated fat
PUFA: Polyunsaturated fat
HOMA-IR: Homeostatic Model of Assessment for Insulin Resistance
HOMA-β: Homeostatic Model of Assessment for beta cell function
QUICKI: Quantitative Insulin Sensitivity Check Index

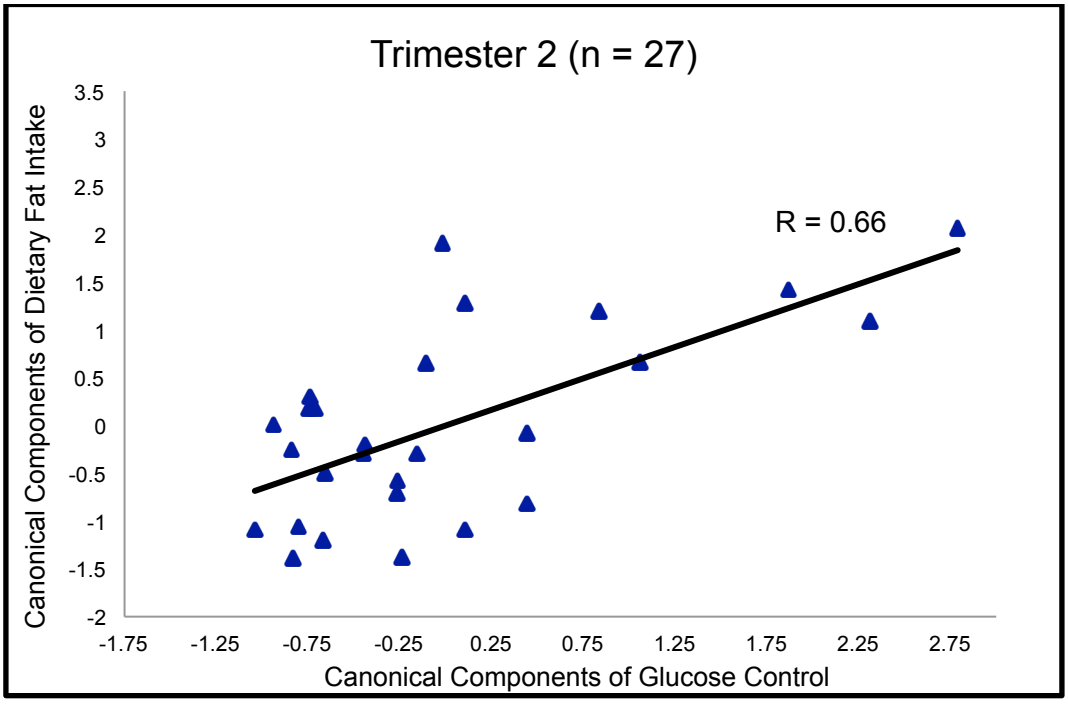

Figure 4: Relationship Between Maternal Dietary Fat Intake and Glucose Control during the Second Trimester (F1 and G1): Higher than average consumption of total fat, SFA, and MUFA, and low consumption of PUFA was directly associated with higher than average fasting glucose, fasting insulin, HOMA-IR, and HOMA-β values, and Indirectly associated with QUICKI values.

Relationship between Maternal Dietary Fat Intake and Glucose Control during the Third Trimester

The correlation between maternal dietary fat intake and glucose control during the third trimester is shown in Table 9 and Figure 5. The first set of canonical components for dietary fat intake and glucose control, F1 and G1, respectively, are highly correlated with a correlation value of 0.65 (Table 9a, Figure 5). The proportion of variance accounted for within each canonical component is illustrated in Table 9b. The canonical components F1 and G1 account for 64% of total variance among the data.

The first canonical component for dietary intake, F1, is driven primarily by total fat, MUFA, and PUFA, as indicated by predictor correlation values of 0.74 for total fat, 0.77 for MUFA, and 0.46 for PUFA (Table 9c). Women with large values of F1 consumed high

amounts total fat, MUFA, and PUFA during the third trimester, compared to sample means.

The first canonical component for glucose control, G1, is driven primarily by QUICKI, as indicated by a predictor correlation value of 0.35 (Table 9d). Women with large values of G1 had high QUICKI values during the third trimester, compared to sample means.

The positive correlation between F1 and G1 (r = 0.65) indicates that higher than average consumption of total fat, MUFA, and PUFA is positively associated with higher than average QUICKI values. Therefore, higher than average SFA intake is associated with lower than average QUICKI values.

Table 9. Relationship between Maternal Dietary Fat Intake and Glucose Control during the Third Trimester

a. Correlation between Canonical Components of Maternal Dietary Fat Intake and Glucose Control*

Component	Canonical Correlation
F1 vs. G1	0.65
F2 vs. G2	0.48
F3 vs. G3	0.30
F4 vs. G4	0.09

b. Proportion of Data accounted for in Each Canonical Component

Component	Individual Proportion	Cumulative Proportion
F1 & G1	64%	64%
F2 & G2	27%	91%
F3 & G3	9%	99%
F4 & G4	1%	100%

c. Correlation Between Dietary Fat Variables and Their Canonical Components†

	Canonical Components for Dietary Fat Intake			
Original Variables for Dietary Fat	**F1**	**F2**	**F3**	**F4**
Total Fat	0.74	-0.08	-0.16	0.65
SFA	0.12	0.67	-0.07	0.73
MUFA	0.77	-0.42	0.34	0.33
PUFA	0.46	-0.65	-0.57	0.21

d. Correlation Between Glucose Control Variables and Their Canonical Components†

	Canonical Components for Glucose Control			
Original Variables for Glucose Control	**G1**	**G2**	**G3**	**G4**
Fasting Glucose	0.00	0.12	-0.24	0.92
Fasting Insulin	-0.25	-0.27	0.27	0.72
HOMA-IR	-0.24	-0.25	0.25	0.83
HOMA-β	-0.26	-0.27	0.29	0.58
QUICKI	0.35	0.11	-0.01	-0.81

*Values > 0.6 are considered clinically relevant
†Values > 0.3 are considered clinically relevant. Canonical components with aggregate correlation values are driven by the variable with the largest correlation value.
SFA: Saturated Fat
MUFA: Monounsaturated fat
PUFA: Polyunsaturated fat
HOMA-IR: Homeostatic Model of Assessment for Insulin Resistance
HOMA-β: Homeostatic Model of Assessment for beta cell function
QUICKI: Quantitative Insulin Sensitivity Check Index

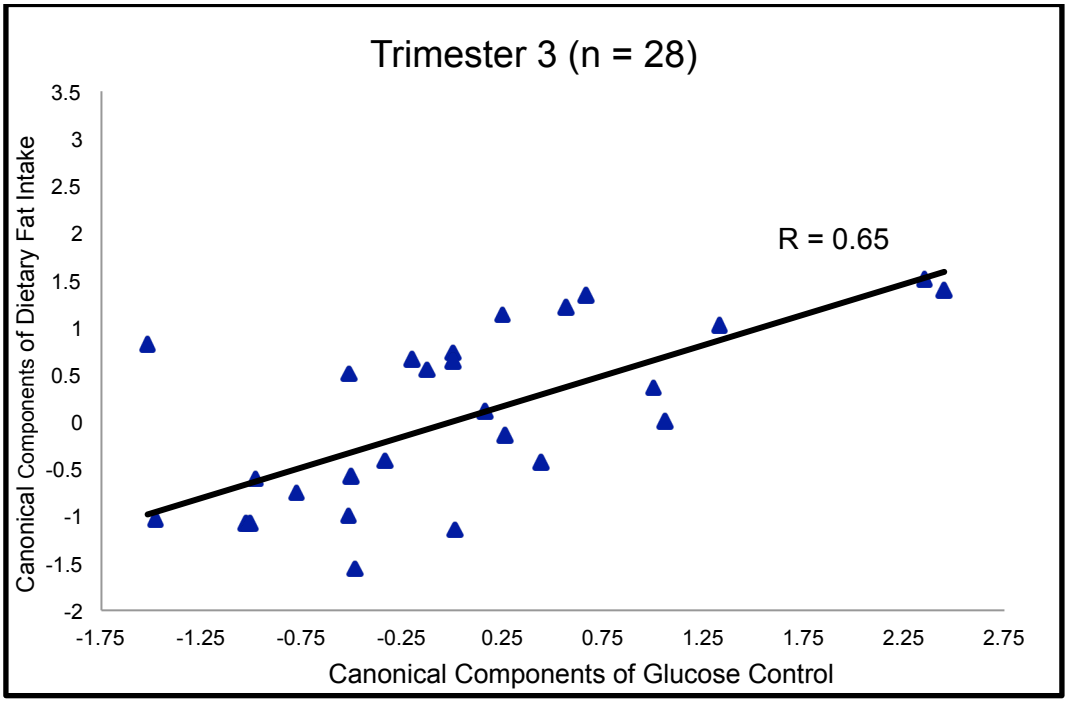

Figure 5: Relationship Between Maternal Dietary Fat Intake and Glucose Control during the Third Trimester (F1 and G1): Higher than average consumption of total fat, MUFA, and PUFA was associated with higher than average QUICKI values.

Relationship between Maternal Essential Fatty Acid Intake and Glucose Concentrations Following a 75-g Oral Glucose Tolerance Test

Correlational analysis was used to determine the relationship between maternal essential fatty acid intake during the first two trimesters and the results of the second trimester oral glucose tolerance test (OGTT). The correlations between first trimester eicosapentaenoic acid (EPA) and docosahexanaeoic acid (DHA) intakes and the OGTT were weak, as indicated by correlation coefficients less than 0.3 (Table 10). Maternal EPA and DHA intakes during the second trimester suggest a negative correlation with glucose concentrations following the OGTT (Table 10). As maternal EPA and DHA consumption increased, glucose concentrations following the OGTT decreased.

Table 10. Correlation Coefficients of Maternal Essential Fatty Acid Intake and Circulating Glucose Concentrations after a 75-g Glucose Load (n=22)				
	Trimester 1		Trimester 2	
	EPA	DHA	EPA	DHA
Fasting	0.09	0.07	-0.20	-0.22
1 Hr	0.15	0.13	-0.23	-0.23
2 Hr	0.28	0.26	-0.28	-0.29
OGTT completed during second trimester EPA: eicosapentaenoic acid DHA: docosahexaenoic acid				

Infant Birth Weight

Multiple linear regression analysis was used to develop a model to predict infant birth weight percentile from maternal QUICKI values during the first, second, and third trimesters. The regression model included maternal gestational weight gain (as a percentage of the 2009 IOM recommendations for gestational weight gain), pre-pregnancy maternal body mass index (BMI), and parity. The correlation between infant birth weight percentile and various potential predictor variables are shown in Table 11. Although none of the predictor variables were significantly correlated with infant birth weight percentile, the two most strongly correlated variables were maternal percent recommended gestational weight gain and parity. Maternal variables that were significantly correlated included percent recommended gestational weight gain and second and third trimester QUICKI values; first, second, and third trimester QUICKI values and pre-pregnancy BMI; and percent recommended gestational weight gain and pre-pregnancy BMI.

Table 11. The Correlation between Infant Birth Weight Percentile and Various Maternal Predictor Variables (n=27)				
	Pearson Correlation Coefficients			
Variable	% Recommended GWG	Pre-pregnancy BMI	Parity	Birth weight percentile
First Trimester QUICKI	-0.30	-0.58*	-0.22	-0.14
Second Trimester QUICKI	-0.45†	-0.52*	0.04	0.14
Third Trimester QUICKI	-0.56†	-0.52*	0.02	0.06
% Recommended GWG		0.55*	-0.28	0.21
Pre-pregnancy BMI			0.16	0.10
Parity				0.32
*$p < 0.05$ Infant birth weight (percentile) based on 2013 Fenton Growth Charts				

The standardized coefficient values and regression coefficient values illustrating the relationship between maternal glucose control and infant birth weight percentile are shown in Table 12. The standardized coefficients are the correlation estimates of the analysis after the predictor variables have been standardized so that their variances are equal to one. The standardized coefficients refer to how many standard deviations the dependent variable will change per standard deviation increase in the predictor variable. They indicate which predictor variable may have the greatest effect on the dependent variable, infant birth weight percentile. Standardized coefficient values are advantageous for multiple linear regression models that include variables with different units. However, caution was used when interpreting the standardized coefficients given the high sampling error associated with small sample sizes. Because of our small sample size, egression coefficients more accurately reflect the relationship between maternal glucose control (QUICKI) and infant birth weight percentile. Regression coefficients were 0.23, 0.30, and 0.29 during the first, second, and third trimesters, respectively.

Table 12. Standardized Coefficients and Regression Coefficients of Maternal Glucose Control as a Predictor of Infant Birth Weight Percentile			
	1st Trimester (n = 27)	2nd Trimester (n = 27)	3rd Trimester (n = 28)
QUICKI	-0.03	0.31	0.31
% Recommended GWG	0.48	0.55	0.60
Pre-pregnancy BMI	-0.26	-0.11	-0.16
Parity	0.49	0.49	0.51
R^2	0.23	0.30	0.29

Summary of the Relationship between Maternal Dietary Fat Intake and Markers of Glucose Control during Pregnancy

The two specific aims of this study were to determine the relationship between maternal dietary fat intake and maternal glucose control, and to determine the relationship between maternal glucose control and infant birth weight. We found significant relationships between maternal dietary fat intake and maternal glucose control during each trimester of pregnancy in the participants of the PEN Study. These results are summarized in Table 13. We did not find a significant relationship between maternal glucose control and infant birth weight.

Table 13. Summary of the Relationship between Maternal Dietary Fat Intake and Markers of Glucose Control in Women Participating in the OHSU PEN Pilot Study			
Trimester 1	Trimester 1	Trimester 2	Trimester 3
↑ MUFA ↓ SFA ↓ TFA *associated with* ↑ QUICKI	↑ TFA ↑ SFA ↑ MUFA *associated with* ↑ Fasting Glucose	↑ TFA ↑ SFA ↑ MUFA *associated with* ↑ Fasting Glucose ↑ Fasting Insulin ↑ HOMA-β ↑ HOMA-IR ↓ QUICKI	↑ TFA ↑ MUFA ↑ PUFA *associated with* ↑ QUICKI
$r = 0.72$*	$r = 0.67$*	$r = 0.66$*	$r = 0.65$*
*$r > 0.6$ is considered clinically significant			

CHAPTER 5: DISCUSSION

Summary

The purpose of this study was two fold: 1) to determine the relationship between the types and amounts of maternal dietary fat intake and glucose control during each trimester of pregnancy, and 2) to determine the relationship between maternal glucose control during each trimester of pregnancy and infant birth weight. We also explored the relationship between maternal essential fatty acid intake and the results of the 2-hour oral glucose tolerance test (OGTT). Although patterns were inconsistent, there were

strong relationships between the types and amounts of maternal dietary fat intake and glucose control during each trimester. There was no significant relationship between maternal glucose control and infant birth weight, and there were only weak relationships between maternal essential fatty acid intake and the results of the 2-hour OGTT.

As previously stated, impaired glucose control to any extent during pregnancy leads to adverse health outcomes for both the mother and her fetus, including preeclampsia, delivery complications, and development of type 2 diabetes mellitus for the mother [8, 10-12]. Infants born to mothers with impaired glucose control have an increased risk of neonatal hypoglycemia, macrosomia, high body fat stores, respiratory distress syndrome, poor feeding, and cognitive development issues [4, 8, 13-17, 68]. Severely impaired glucose leads to gestational diabetes mellitus (GDM).

Primary Variables used for Analyses

The measurements of maternal dietary fat intake used for analyses include total fatty acids, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), all estimated from a single Automated Self-Administered 24-Hour Dietary Recall (ASA-24) administered during each trimester. We tested the ASA-24 in this pilot study because it provides high quality dietary intake data with minimal bias [82].

The markers of maternal glucose control used for analyses include fasting glucose, fasting insulin, the homeostatic models of assessment for insulin resistance (HOMA-IR) and beta cell function (HOMA-β), and the quantitative insulin sensitivity check index (QUICKI) measured during each trimester. The results of the 2-hour OGTT performed during the second trimester were also considered.

Maternal Dietary Fat Intake and Glucose Control

Current research shows inconsistent results regarding the relationship between the types and amounts of maternal dietary fat intake and glucose control during pregnancy [21, 28, 67, 76, 99, 100]. We found statistically significant relationships during each trimester between the type and amount of fat consumed and maternal glucose control. During the first trimester, higher intakes of MUFA and lower intakes of SFA were associated with healthier QUICKI scores. Liang, et al. also showed a relationship between maternal SFA intake and glucose control in a rodent model. Rat dams fed an ad libitum high fat diet (60% total fat of total energy and 32.1% from SFA) before pregnancy and during early pregnancy developed insulin resistance by gestational day 10. Dams fed the high fat diet had a 66% increase in plasma insulin concentrations and a 27% increase in plasma glucose concentrations compared to rats fed the chow diet [28]. While one report suggests that maternal MUFA intake does not improve maternal glucose control [99], other research suggests an inverse relationship between maternal intake of SFA and glucose control [21, 67, 100].

Higher total fat, SFA, and MUFA, and lower PUFA intakes during the first trimester were associated with higher fasting glucose values. Current literature suggests that dietary PUFA intake is associated with healthy maternal glucose control [21, 27], however, dietary PUFA intake during the first trimester seems to have little relationship with glucose control compared to dietary PUFA intake during the second and third trimesters of pregnancy [27, 101].

Similar to the first trimester, during the second trimester, higher than average total fat, SFA, MUFA, and lower than average PUFA intakes were associated with less healthy glucose control as indicated by higher than average fasting glucose, fasting insulin, HOMA-β, and HOMA-IR, and lower than average QUICKI values. In a study of

205 women, Ley, et al. showed that women who consumed a lower ratio of PUFA to SFA and higher total fat during the second trimester of pregnancy had significantly higher fasting glucose concentrations ($p \leq 0.04$) after adjusting for pregravid covariates including age, ethnicity, family history of Type 2 Diabetes Mellitus, and pre-pregnancy BMI [21]. Additionally, dogs fed a high fat diet beginning half way through gestation (52% of total energy from fat) developed impaired glucose tolerance as well as GDM compared to dogs fed the control diet (26% of total energy from fat) throughout gestation [25]. In this study, impaired glucose tolerance and GDM were defined with liver and muscle insulin resistance measured by hepatic glucose output as well as non-hepatic glucose uptake [25].

During the third trimester, higher than average total fat, MUFA, and PUFA intakes were associated with higher than average QUICKI values, indicating that high SFA intake results in low QUICKI values. In a study of 227 pregnant women, there was a graded relationship between the severity of third trimester maternal hyperglycemia, serum SFA concentrations, and consumption of SFA [27]. This is consistent with previously mentioned research demonstrating the relationship between maternal intake of SFA and poor glucose control [21, 67, 100].

There are inconsistencies of our results compared to other research results regarding the relationship between maternal MUFA and total fat consumption and glucose control. However, in our results, when MUFA or total fat intake is associated with poor glucose control, it is also associated with SFA. Whenever MUFA or total fat intake is associated with healthy glucose control, it is also associated with PUFA. At each trimester, higher intakes of PUFA are associated with healthier glucose control, and higher intakes of SFA are associated with unhealthy glucose control.

The slightly different relationships between dietary fat intake and glucose control during pregnancy suggest that, in this population, the amount of fat consumed may not

be as important as the type of fat consumed. Only recently has more research focused on the relationship between individual fatty acid intake and glucose control throughout pregnancy [25, 27, 28, 76, 100, 102, 103]. Some research focuses on dietary intake tendencies of women with impaired glucose control during pregnancy, and suggests that these women consume more energy from fat, less omega-3 fatty acids, and significantly more SFA than women with healthy glucose control during pregnancy [76]. Research in a mouse model shows that a high SFA diet (32.1% SFA of total energy) using coconut oil was associated with higher maternal body weight (41%) throughout gestation compared to the control group (19%) [28]. The dams fed the high SFA diet also had significant higher fasting plasma insulin ($p < 0.5$) and glucose ($p < 0.05$) concentrations half way through gestation than those fed the control diet [28]. These findings are particularly relevant to our findings, as average SFA intake exceeded recommended intakes during each trimester, while MUFA, PUFA, DHA, and EPA intakes were lower than recommended intakes for pregnancy.

As previously mentioned, while the implications of impaired glucose control during pregnancy are well studied, the physiological mechanisms behind the relationship between maternal dietary fat intake and glucose control are not well understood. The relationship may be explained in part by the relationship between maternal dietary fat intake and gestational weight gain [14, 22, 24-27, 34] or the impact of dietary fat and fat metabolism on serum and adipose tissue fatty acid profiles [21, 27, 28, 67, 68, 81, 104, 105]. While dietary fatty acid intake is not always reflected in serum or adipose tissue immediately [105], it is possible that the dietary recalls of participants reflect their dietary intakes pre-pregnancy, as well.

Maternal Essential Fatty Acid (EFA) Intake and Glucose Control

The relationship between dietary PUFA intake, specifically the EFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and maternal glucose control has been studied previously [106], but is becoming an even more popular topic in pregnancy research [102, 103, 107]. We found weak correlations between maternal EFA intake in the first trimester and the 2-hour blood glucose concentration after consuming 75 g of glucose during the second trimester. The correlations between maternal EFA intake in the second trimester and the blood glucose concentrations after consuming 75 g of glucose load were stronger, and may be of clinical significance. Most literature supports a strong relationship between maternal EFA intake and glucose control [102, 103, 106, 107]. What is interesting about our results is the inverse relationship between EFA intake during the second trimester and the 2-hour blood glucose concentration. Our results suggest that low maternal dietary essential fatty acid intake during the 2nd trimester is associated with poor concurrent glucose control. These findings are consistent with the results of others. In a study examining maternal glucose control and adherence to the Mediterranean diet, which emphasizes consuming healthy fats including DHA and EPA, good adherence was associated with a lower incidence of GDM (low MedDiet Index with 32.8% GDM incidence, and high MedDiet Index with 24.3% GDM incidence, $p = 0.004$) [102]. Higher adherence to the Mediterranean diet was also associated with better glucose tolerance in women who did not have GDM (as measured by incremental glucose area under the curve 255.6 ± 5.4 and 270.0 ± 7.8, $p = 0.034$; and total glucose area under the curve 793.3 ± 7.0 and 823.1 ± 10.0, $p = 0.016$ in women with high vs. low MedDiet Index, respectively) [102].

Research suggests that women with impaired glucose control during pregnancy tend to consume higher than recommended amounts of SFA compared to women with normal glucose control (14% SFA vs. 12% SFA, respectively) [76, 100]. Healthcare

providers tend to encourage women with impaired glucose control during pregnancy to be cautions of carbohydrate intake in an effort to manage their glucose control. As a result, these women may consume more fat, of all types. It is imperative to educate pregnant women, particularly those with impaired glucose control, about the importance of balancing macronutrient intake, including the amounts and types of dietary fat.

Maternal glucose control and infant birth weight

We found no significant relationship between maternal glucose control, as indicated by QUICKI values, during any trimester of pregnancy and infant birth weight when controlling for gestational weight gain (as a percent of the recommendation), pre-pregnancy BMI, and parity. Research regarding the relationships between maternal glucose control, maternal dietary fat intake, and infant birth weight is inconsistent [6, 23, 78, 88, 89, 91]. One study shows strong correlations between maternal fasting glucose concentration and infant birth weight ($r = 0.61$, $p < 0.01$) and between maternal fasting glucose concentration and infant body fat (as a percent of total weight) ($r = 0.71$, $p < 0.01$) in infants born to women with GDM [88]. Research in an animal model shows a similar relationship, as offspring born to dams with impaired glucose control were significantly heavier than offspring born to control damns [91].

Gnuili, et al found that the offspring of dams fed a high fat diet weighed more at birth than offspring of dams fed the control diet (29.5 g ± 5.3 vs. 27.2 g ± 7.1) [6]. Other animal research [23] and human research [89, 94] shows no relationship between maternal dietary fat intake and infant birth weight. However, research in animal and human models has shown that offspring born to mothers who consumed high fat diets during pregnancy had significantly higher fat mass than offspring whose mothers did not consume high fat diets during pregnancy [23, 91, 94].

Strengths and Limitations

This study assessed multiple components of maternal dietary fat intake as well as multiple components of maternal glucose control to determine the relationship between the two. We used a unique statistical analysis, canonical correlations, to remove redundancy in the results. In addition, we assessed dietary fat intake and glucose control throughout pregnancy, rather than at one time point. We contributed to the few human studies investigating the relationships between maternal dietary fat intake and glucose control and between maternal glucose control and infant birth weight percentile.

The PEN Study was designed to assess the feasibility of a team-based, peer-led curriculum for pregnant women to improve pregnancy outcomes by adopting healthy nutrition and exercise behaviors. There were some limitations with the study design for our purposes of assessing maternal dietary fat intake, glucose control, and infant birth weight. The sample size was small and consisted of well-educated women of medium to high socioeconomic status. The average age of participants, 34 years old, was higher than the 2012 national average age of pregnant women, 26 years old [74]. There was only one blood sample and one dietary recall collected and analyzed during each trimester, limiting data for the present research objectives. One 24-hour recall at each trimester reflects a snapshot in time, and may not capture a participant's usual dietary intake. Additionally, the only OGTT was the routine OGTT performed during the second trimester. Unlike fasting insulin and fasting glucose concentrations, OGTTs describe how efficiently an individual clears a standard load of glucose from concentration. Also, OGTTs are a common marker of maternal glucose control used in research.

Looking forward

If the PEN Study curriculum is tested on a larger, higher-risk sample of women, different dietary recall methods, measurements of glucose control, and additional infant outcomes should be considered. Participants reported that the ASA-24 was difficult to complete due to their inability to find certain foods in the database, and the time it took to complete. An interviewer-led 24-hour recall might be easier for participants to complete, and may result in a better representation of usual dietary intake.

While we did not find that infant birth weight was related to maternal glucose control, it is likely that infant glucose control may be related to maternal glucose control. In further studies, samples of infant blood would allow analyses of infant glucose control. Also, the mechanism between maternal dietary fat intake and glucose control is not well elucidated. Additional maternal blood samples to be used for free fatty acid (FFA) analysis, as composite values and as a FFA profile, may provide more information regarding the relationship between maternal dietary fat intake, circulating FFA, and blood glucose control.

And finally, our study investigated maternal dietary fat intake and glucose control in a low-risk population of mostly healthy women who were well educated and of medium to high socioeconomic status. In the future, investigating these relationships in a high-risk population may produce more significant and novel results.

Our findings contribute to the body of literature that describes the relationship between maternal dietary fat intake and glucose control in pregnant women. Registered dietitians and nutrition professionals need to consider setting more definitive recommendations for dietary fat intake during pregnancy based on various maternal characteristics, including pre-pregnancy BMI, familial history of diabetes, and pre-

pregnancy glucose control values [100]. Improving glucose control during pregnancy will benefit not only the health outcomes of the mother, but also future generations.

Appendix I: Dietary Fat Screener

ID # Place Label Here

NATIONAL CANCER INSTITUTE
QUICK FOOD SCAN

1. Think about your eating habits over the past 12 months. About how often did you eat or drink each of the following foods? Remember breakfast, lunch, dinner, snacks, and eating out. Blacken in only one bubble for each food.

TYPE OF FOOD	Never	Less than Once Per Month	1-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2 or More Times Per Day
Cold cereal	○	○	○	○	○	○	○	○
Skim milk, on cereal or to drink	○	○	○	○	○	○	○	○
Eggs, fried or scrambled in margarine, butter, or oil	○	○	○	○	○	○	○	○
Sausage or bacon, regular-fat	○	○	○	○	○	○	○	○
Margarine or butter on bread, rolls, pancakes	○	○	○	○	○	○	○	○
Orange juice or grapefruit juice	○	○	○	○	○	○	○	○
Fruit (not juices)	○	○	○	○	○	○	○	○
Beef or pork hot dogs, regular-fat	○	○	○	○	○	○	○	○
Cheese or cheese spread, regular-fat	○	○	○	○	○	○	○	○
French fries, home fries, or hash brown potatoes	○	○	○	○	○	○	○	○
Margarine or butter on vegetables, including potatoes	○	○	○	○	○	○	○	○
Mayonnaise, regular-fat	○	○	○	○	○	○	○	○
Salad dressings, regular-fat	○	○	○	○	○	○	○	○
Rice	○	○	○	○	○	○	○	○
Margarine, butter, or oil on rice or pasta	○	○	○	○	○	○	○	○

2. Over the past 12 months, when you prepared foods with margarine or ate margarine, how often did you use a reduced-fat margarine?

○ DIDN T USE MARGARINE ○ Almost never ○ About 1/4 of the time ○ About 1/2 of the time ○ About 3/4 of the time ○ Almost always or always

3. Overall, when you think about the foods you ate over the past 12 months, would you say your diet was high, medium, or low in fat?

○ High ○ Medium ○ Low

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Appendix II: Glossary of Terms

Canonical Correlations: a statistical analysis that extracts the dominant patterns among significant variables of a data set, and represents the variables in a set of fewer, orthogonal variables. The analysis provides simplification, data reduction, modeling, and outlier detection of data sets.

Glucose control: refers to the body's ability to maintain healthy blood glucose concentrations through proper functioning of pancreatic beta cells, insulin, and insulin and glucose receptors

Glucose homeostasis: a healthy balance between postprandial glucose and insulin concentrations, and between postabsorptive glucose and insulin concentrations

Homeostatic model assessment-IR: a calculation representing insulin resistance used to measure an individual's insulin sensitivity

[fasting glucose (mg/dL) x fasting insulin (ulU/mL)]/405

Homeostatic model assessment-β: a calculation representing hepatic beta cell function used to measure an individual's insulin sensitivity

[360 x insulin (ulU/mL)]/[glucose (mg/dL – 63)] %

Insulin sensitivity: refers to how efficiently tissue responds to insulin, i.e. how successfully the tissue's receptor functions to uptake glucose from circulation

Insulin resistance: refers to the body's inability to respond to and use the insulin. Cells are unable to use insulin effectively to transport glucose from circulation, leading to hyperglycemia and hyperinsulinemia.

Quantitative insulin sensitivity check index: a calculation used to measure and individual's insulin sensitivity

1/(log fasting insulin + log fasting glucose)

Appendix III: Evidence Table

Author Name	Journal, Year	Title	Population	Methods/Design	Outcomes
Catalano, PM; Kirwan, JP; Haugel-de Mouzon, S; King, J	The Journal of Nutrition, 2003	Gestational Diabetes and Insulin Resistance: Role in Short- and Long-Term Implications for Mother and Fetus	Pregnant women with and without GDM, non-pregnant women	Review	Differences in insulin sensitivity between women with GDM and without are greatest before and during early pregnancy and less pronounced but still significant by late gestation. Lipid metabolism: cholesterol and triacylglycerol decreases in early gestation then increases progressively until term. Neonatal birth weight is positively correlated with triacylglycerol and FFA concentrations. Increased fetal insulin concentrations suppress FFA concentration and inhibit lipolysis, resulting in increased fat deposition. There is a decreased ability of insulin to suppress FFA with advancing gestation. Maternal insulin sensitivity explains 50% of variance in fetal body composition (fat accretion). Decreased maternal insulin sensitivity with plentiful food + sedentary life likely to manifest to GDM & increase long-term risk for DM & OB in mother & child.

Catalano, PM; Nizielski, SE; Shao, J; Preston, L; Qiao, L; Friedman, JE	American Journal of Physiological Endocrinology Metabolism, 2001	Down regulated IRS-1 and PPAR-gamma in obese women with gestational diabetes: relationship to FFA during pregnancy	4 obese pregnant women with healthy glucose control, 5 obese women with GDM	Glucose control measurements: fasting glucose, fasting insulin, OGTT, hyperinsulinemic euglycemic clamp. Additional outcome measurements: plasma FFA. Abdominal subcutaneous adipose tissue biopsies obtained during C-section delivery from obese pregnant women, obese GDM pregnant women, & non-pregnant controls during gynecological surgery.	Women with GDM had higher basal plasma FFA before pregnancy (p = 0.055). Insulin's ability to suppress FFA concentrations declined from early to late gestation in both groups, and was significantly less in GDM subjects compared to control (p = 0.025). Adipose tissue insulin receptor substrate 1 protein 43% lower in women with GDM (p = 0.02). Lipoprotein lipase 73% lower in GDM participants (p < 0.002)

Chen, X; Scholl, TO; Leskiw, M; Savaille, J; Stein, TP	Diabetes Care, 2010	Differences in Maternal Circulating Fatty Acid Composition and Dietary Fat Intake in Women with Gestational Diabetes Mellitus or Mild Gestational Hyperglycemia	49 pregnant women with GDM, 80 pregnant women with impaired glucose control non-GDM, 98 pregnant women with normal glucose control results	Dietary recall methods: mean of 3 24-h dietary recalls between ~16 weeks gestation and weeks 20 and 28 of gestation Glucose control measurements: hyperglycemic levels Additional outcome measurements: serum FA composition, BMI	Absolute concentrations of all individual FAs and sum of SFAs, MUFAs, and PUFAs showed sig linear trends; the differences between GDM and control were all significant and only significant differences between GDM and impaired glucose control non-GDM groups were palmitoleic acid and DHA concentrations. Palmitic acids and total SFAs were significantly higher in impaired glucose control non-GDM group than control. Relationship between maternal hyperglycemia severity and FA composition was inconsistent. Significant trends for PUFA, linoleic, and DHA intake to be higher in control subjects and SFAs, palmitic acid, and stearic acid intake to be higher in GDM. Serum FA and dietary FA intake correlation only observed between serum PUFA and dietary PUFA.

Elton, CW; Pennington, JS; Lynch, SA; Carver, FM, Pennington, SN	Endocrinology, 2002	Insulin resistance in adult rat offspring associated with maternal dietary fat and alcohol consumption	75 female rats and their offspring	Dietary intervention methods: 35% fat diet w/ ETOH, 12% fat diet w/ ETOH, 35% fat diet w/o ETOH, 12% fat diet w/o ETOH (diets w/o ETOH were pair-fed for calorie amount), chow fed diet, and ad lib diet Glucose control measurements (offspring): muscular and basal insulin-stimulated glucose uptakes, serum glucose assays, serum insulin assays, euglycemic clamp outcomes	HFD had no effect on maternal weight or weight gain, no effect on litter size, no differences in total body fat stores or amount of adipose tissue associated with specific organs in adulthood. Female offspring of pair-fed had higher basal serum insulin levels. Basal glucose uptake by offspring's muscle of 35% fat-fed mother was 1/2 of glucose uptake of offspring born to mothers fed less of 12% fat. Insulin-stimulated glucose uptake by muscle was reduced by > 4 times in pair-fed male offspring of 35% fat mothers.

Frias, AE; Morgan, TK, Evans, AE; Rasanen, J; Oh, KY; Thornburg, KL; Grove, KL	Endocrinology, 2011	Maternal High-Fat Diet Disturbs Uteroplacental Hemodymaics and Increases the Frequency of Stillbirth in a Nonhuman Primate Model of Excess Nutrition	24 young adult Japanese macaques (primates)	Dietary intervention methods: 15 subjects on a HFD (32% kcal from fat) 6 were HFD resistant (R), 9 were sensitive (S). 9 subjects on control diet (14% kcal from fat). Glucose control measurements: GTT, insulin assays Additional outcome measurements: uterine artery volume blood flow, placental histology	HFD-S had 48% increase in weight, 4-fold increase in insulin AUC during GTT, >5-fold increase in leptin levels, and increased fasting insulin compared with control and HFD-R. All HFD had significant increase in triglycerides.

Gallou-Kabani, C; Vige, A; Gross, MS; Boileau, C; Rabes, JP; Ruchart-Najib, J; Jais, JP; Juien, C	American Journal of Physiology - Endocrinology and Metabolism, 2006	Resistance to high-fat diet in the female progeny of obese mice fed a control diet during the periconceptual, gestation, and lactation periods	352 first generation mice (F1) and 191 second generation mice (F2) HFD-R: mothers resistant to HFD HFD-S: mothers sensitive to HFD	Dietary interventions: maternal ad lib control diet (C) of 10% fat or ad lib high fat diet (HFD) of 60% fat Glucose control measurements: OGTT Additional outcome measurements: food consumption, plasma lipids	All F1 HFD mice became hyperphagic and obese. F2 HFD males became obese, hyperglycemic, and hypercholesterolemic. Significantly higher proportion of female offspring was HFD-R. HFD F1 females consumed more food than CD total. Triglycerides not significantly affected. HFD resulted in significant increases in plasma cholesterol, and gradual increases in HDL concentrations between weeks 8 - 24 in F1 HFD females and between weeks 8 - 16 in F2 HFD females. CD had more rapid glucose clearance from peripheral tissues. Glucose intolerance particularly different in F2 HFD-R females. F1 HFD and F2 HFD-S females showed insulin resistance.

Gniulli, D; Calcagno, A; Caristo, ME; Mancuso, A; Macchi, V; Mingrone, G; Vettor, R	Journal of Lipid Research, 2008	Effects of high-fat diet exposure during fetal life on type 2 diabetes development in the progeny	50 female mice, their offspring (F1), and the offspring's offspring (F2)	Dietary intervention: high fat (HF) diet of 60% fat kcal, 20% CHO kcal beginning 2 months prior to breeding. Chow (C) of 10% fat kcal, 60% CHO kcal beginning 2 months prior to breeding Glucose control measurements: offspring's' IPGTT, pancreatic measurements for beta and islet cell sizes, beta cell replication quantity, beta cell neogenesis, islet cell apoptosis	Dietary treatment did not affect litter size or birth weight of both offspring generations. Second generation offspring of HF diet were significantly smaller than other second generation. Results show diabetes may be inheritable from mother's HF diet, notably from B-cell issues during fetal life inducing phenotype of T2DM and transmitting it to progeny even in the absence of further dietary treatment. T2DM onset may be reduced if certain habits begin in early infancy.

Gregerson, S; Dyrskog,SEU; Storlien, LH; Hermansen, K	Metabolism Clinical and Experimental, 2005	Comparison of a high saturated fat diet with a high carbohydrate diet during pregnancy and lactation: effects on insulin sensitivity in offspring of rats	Female wistar rats and their offspring (males on normal chow diet pre-conception)	Dietary intervention: 58.5% SFA diet or 79.6% CHO diet Glucose control measurements: euglycemic clamp outcomes, glucose uptake assays Additional outcome measurements: body fat, lipogenesis tests, glucose oxidation.	No difference in offspring weights at weeks 4 and 16. High fat diet offspring had higher circulating triglycerides. No significant changes in blood glucose/glucose removal. Glucose uptake of white adipose tissue significantly lower in SAF diet mother offspring. Lipid synthesis rates in brown adipose tissue lower in SAF diet mother offspring.
Karamanos, B; Thanopoulou, A; Anastasiou, E; Assaad-Khalil, S; Albache, N; Bachaoui, M; Slama, CB; Ghomari, HE; Jotic, A; Lalic, N; Lapolla, A; Saab, C; Marre, M; Vassallo, J; Savona-Ventura, C; MGSD-GDM Study Group	European Journal of Clinical Nutrition, 2014	Relationship of the Mediterranean diet with the incidence of gestational diabetes	1076 pregnant women in 10 Mediterranean countries	Dietary recall methods: validated 78-question dietary questionnaire administered by trained professional. Mediterranean Diet Index (MDI) was computed. Glucose control measurements: 75-gram glucose dose OGTT at weeks 24-32 of gestation. Results interpreted by both ADA 2010 and IADPSG 2012 guidelines.	Women with GDM (as indicated by both ADA and IADPSG criteria had lower MDI scores (ADA: p = 0.028; IADPSG: $p < 0.001$). Incidence of GDM was lower in subjects with better adherence to Mediterranean Diet (ADA: p = 0.03; IADPSG: p = 0.004). MDI negatively associated with fasting plasma glucose and AUC glucose ($P < 0.001$ for ADA and IADPSG).

Kitajima, M; Oka, S; Yasuhi, I; Fukuda, M; Rii, Y; Ishimaru, T	Obstetrics and Gynecology, 2001	Maternal serum triglyceride at 24-32 weeks' gestation and newborn weight in nondiabetic women with positive diabetic screens	146 pregnant women who screened positively for diabetes during pregnancy but had healthy 75-g glucose dose OGTTs at 24-32 weeks gestation	Glucose control measurements: OGTT Additional outcome measurements: fasting serum triglycerides, free fatty acids, total cholesterol levels at time of OGTT. Infant birth weight.	Infant birth weight correlated with pre-pregnancy BMI, triglycerides, and fasting glucose. Fasting maternal hypertriglyceridemia predicted LGA infants, independent of maternal BMI, weight gain, and plasma glucose concentrations.
Ley, SH; Hanley, AJ; Retnakaran, R; Sermer, M; Zinman, B; O'connor, DL	American Journal of Clinical Nutrition, 2011	Effect of macronutrient intake during the second trimester on glucose metabolism later in pregnancy	205 pregnant women ages 30-40 years. 122 white, 83 non-white	Dietary recall method: FFQ dietary recall. Glucose control measurements: OGGT, GCT.	GDM women had higher fasting glucose, AUC glucose, fasting insulin, and HOMA-IR values. Non-white women had higher rate of GDM. GDM women consumed more total energy from fats and less from CHO during second trimester and a lower ratio PUFAS to SFA. CHO kcal to fat kcal associated with increased fasting glucose. Hyperglycemia associated with SFA and trans fat intakes. Macronutrient variables not associated with insulin resistance based on HOMA-IR.

Liang, C; DeCourcy, K; Prater, MR	Metabolism Clinical and Experimental, 2010	High-saturated-fat diet induces gestational diabetes and placental vasculopathy in C57BL/6 mice	C57BL/6J mice. HFD, n = 16. Control, n = 16.	Dietary intervention: mice fed high SFA diet (20% protein, 60% total fat, 32.1% SFA, 20% CHO) 1 month before conception and throughout gestation Glucose control measurements: blood glucose concentrations and plasma insulin concentrations before and after HFD feeding at gestational day 0, 10, and 19. Additional outcome measurements: oxidative stress, vascular dysregulation, gestational weight gain, placental weight	Maternal body weight increased by 41% by gestational day 19 in the HFD mice compared to 23% in control. HFD dams developed insulin resistance with 66% increase in plasma insulin ($p < 0.05$) and 27% increase in plasma glucose ($p < 0.05$) by gestational day 10. Placental oxidative stress elevated in HFD dams.

Loosemore, ED; Judge, MP; Lammi-Keefe, CJ	Lipids, 2004	Dietary Intake of Essential and Long-Chain Polyunsaturated Fatty Acids in Pregnancy	14 pregnant women with GDM and 31 pregnant women without GDM	Dietary recall method: repeated 24 hour recalls	Women with GDM consumed significantly more total fat energy. Dietary n-3 LCPUFA intake was lower than current recommendations for pregnancy (200-300 mg/d; with a 1:1 ratio to n-6) and SFA intake exceeded recommendations (< 10% total fat).

Masuyama, H; Hiramatsu, Y	Endocrinology, 2012	Effects of a High-Fat Diet Exposure *in Utero* on the Metabolic Syndrome-Like Phenomenon in Mouse Offspring through Epigenetic Changes in Adipocytokine Gene Expression	6 female pregnant mice and their 24 offspring	Dietary intervention: maternal control diet (C) of 12% fat, 28% pro, and 60% CHO; or high fat diet (HFD) of 62% fat, 18% pro, and 20% CHO starting 4 weeks pre-conception. Offspring weaned onto C diet with free access to food and water Glucose control measurements: offspring GTT, insulin tolerance test (ITT), fasting insulin concentrations Additional outcome measurements: maternal weight, total TG, adiponectin, and leptin concentrations	HFD maternal weight greater than C. HFD offspring had significantly greater birth weight than C offspring. No significant difference in litter size. HFD offspring had significantly greater increase in triglycerides and leptin concentrations and decreased adiponectin concentrations, and significantly elevated systolic blood pressure. HFD offspring had greater caloric intake. HFD offspring had significantly worse glucose tolerance and insulin sensitivity at 24 weeks. HFD offspring leptin gene was significantly up regulated and adiponectin gene significantly down regulated in white adipose tissue. HFD offspring had significant increase in leptin expression at 24 weeks.

McCurdy, CE; Bishop, JM, Williams, SM; Grayson, BE; Smith, MS; Friedman, JE; Grove, KL	Journal of Clinical Investment, 2009	Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates	35 adult female Japanese macaques and their offspring	Dietary fat intervention: maternal high fat (HFD) diet of 14.9% kcal fat or a control (C) diet of 5.5% fat. 17 on control diet, 8 HDF-resistant, and 10 HFD-sensitive. Monkeys on diet for 2-4 years pre-conception Glucose control measurements: maternal GTT, offspring immunoblot analysis of liver Additional outcome measurements: offspring TG analysis, liver RNA, plasma hormone measurements, plasma cytokine expression	HFD provoked insulin resistance and hyperlipidemia in pregnant monkeys. HFD-R and HFD-S had greater increase in leptin levels. HFD-S had significant increase in GTT concentrations. No difference in insulin AUC between HFD-R and control. HFD-S significantly elevated glycerol levels during 3rd trimester. HFD resulted in early onset obesity. No difference in fetal serum insulin or FFA concentrations. Total triglycerides and glycerol concentrations in fetus were significantly higher in HFD-S and HFD-R offspring. Insulin, leptin, glucose, and triglycerides were not significantly correlated in fetus. HFD offspring had 2- to 3-fold increase in gluconeogenic genes in liver. Fetal liver triglycerides significantly correlated with gene increase. Hepatic steatosis in fetus attenuated by healthy maternal diet.

Metzger, BE; Phelps, RL; Freinkel, N: Navickas, IA	Diabetes Care, 1980	Effects of Gestational Diabetes on Diurnal Profiles of Plasma Glucose, Lipids, and Individual Amino Acids	Women with severe GDM with fasting plasma glucose >/= 105 mg/dL (n = 6), women with GDM with fasting plasma glucose < 105 mg/dL (n = 7), and pregnant women with healthy glucose control (n = 8)	Dietary intervention: liquid formula standardized diet of 2110 kcal and 275 g CHO in 3 equal feedings. Glucose control measurements: circulating glucose concentrations over 24-hour period. Additional outcome measurements: circulating FFA, triglycerides, cholesterol, and individual AA concentrations over 24-hour period.	Pre-meal, postprandial averages, and overall 24-hour fasting glucose consistently higher in severe GDM women than GDM, and both GDM groups exceeded healthy pregnant women values. Plasma FFA higher in both GDM groups than healthy women. GDM women tended to have higher circulating triglycerides than healthy women. BCAA higher in GDM participants.

Moore, MC; Menon, R; Coate, KC; Gannon, M; Smith, SM; Farmer, B; Williams, PE	Journal of Applied Physiology, 2010	Diet-induced impaired glucose tolerance and gestational diabetes in the dog	12 pregnant dogs, non-pregnant dogs (NP)	Dietary intervention: 6 dogs (P) on chow diet (31% protein, 26% fat, 42% CHO), 6 dogs (P-HFF) on high fat/high fructose diet (22% protein, 52% fat, 26% CHO with ~14% total kcal from fructose) Glucose control measurements: OGTT, hyperinsulinemic euglycemic clamp results, pancreatic islet analysis	OGTT results: pregnant dogs required more time to return to basal concentrations. Basal glucose concentrations in P-HFF dogs were not significantly different than NP and P dogs. P-HFF > 3-fold AUC for post load glucose intolerance than P group. Plasma insulin concentrations not significantly different between P and P-HFF. Clamps: During high insulin P-HFF had low rate of net hepatic glucose output as opposed to net hepatic glucose uptake. During high insulin hind-limb glucose uptake increased only 27% in P-HFF and 72% in P. Non-hepatic glucose uptake reduced in P-HFF during high insulin. Glucose disappearance > in P than P-HFF during high insulin. P-HFF = greater insulin resistance than normal P dogs d/t loss of skeletal muscle insulin sensitivity as well as mild-impairment of liver insulin sensitivity.

Park, S; Kim, MY; Baik, SH; Woo, JT; Kwon, YJ; Daily, JW; Park, YM; Yang, JH; Kim, SH	European Journal of Clinical Nutrition, 2013	Gestational diabetes is associated with high energy and saturated fat intakes and low plasma visfatin and adiponectin levels independent of pre-pregnancy BMI	531 pregnant women without GDM; 215 pregnant women with GDM. Overweight group = pre-pregnancy BMI > 23; normal weight group = pre-pregnancy BMI < 23	Dietary recall method: CAN-PRO version 3; nutrients calculated as percentage of Korean Dietary Reference Intake for pregnant women Glucose control measurements: OGTT, HOMA-IR, and HOMA-beta at 24-28 weeks gestation. Additional outcome measurements: plasma levels of adipokines and gestational hormones.	Normal weight women: GDM gained more weight than non-GDM; GDM status associated with increased insulin resistance in overweight women and decreased insulin secretory capacity in normal-weight women (HOMA-beta). Plasma visfatin and adiponectin lower and progesterone higher in GDM women, independent of BMI. Plasma resistin higher in non-GDM overweight women. Total energy and SFA intakes higher in GDM women.
Radesky, JS; Oken, E; Rifas-Shiman, SL; Keinman, KP; Rich-Edwards, JW; Gillman, MW	Pediatric and Perinatal Epidemiology, 2008	Diet during early pregnancy and development of gestational diabetes	1733 pregnant women – 91 with GDM, 206 with impaired glucose tolerance (IGT)	Dietary recall method: validated food frequency questionnaire Glucose control measurements: glucose tolerance test at 26-28 weeks gestation	Pre-pregnancy BMI was a strong predictor for GDM risk (OR 3.44 for pre-P BMI >/= 30 vs. < 25). OR for GDM risk for total fat = 1.00, SFA = 0.98, PUFA = 1.09, CHO 1.00. Dietary intake of red & processed meat not indicative of glucose control outcome. n-3 FA intake associated with increased GDM risk; OR = 1.11. Pre-P BMI strongest risk factor for GDM.

Strakovsky, RS; Zhang, X; Zhou, D; Pan, YX	The Journal of Physiology, 2011	Gestational high fat diet programs hepatic phosphoenolpyruvate carboxykinase gene expression and histone modification in neonatal offspring in rats	10 obese-resistant, pregnant rats (so mothers cannot develop obesity or diabetes)	Dietary intervention: 5 fed 45% fat diet (HF diet) and 5 fed 16% fat diet (C diet), ad libitum Glucose control measurements: fasting maternal glucose and insulin concentrations Additional outcome measurements: offspring's' weights at birth, liver mRNA expressions related to gluconeogenesis	Gestational dietary intake (g) did not differ between C and HF. There was no difference in maternal body weight throughout gestation but the HF diet did gain significantly more weight in total. Maternal glucose and insulin did not differ. No difference in litter size. Offspring: birth weight of HF diet mothers was significantly heavier. HF diet offspring had significantly higher mRNA expression gluconeogenic genes in liver. HF offspring had elevated glucose levels at delivery.

Taylor, PD; McConnell, J; Khan, IY; Holemans, K; Lawrence, KM; Sare-Anane, H; Persaud, SJ; Jones, PM; Petrie, L; Hanson, MA; Poston, L	American Journal of Physiology: Regulatory, Integrative, and Comparative Physiology, 2005	Impaired glucose homeostasis and mitochondrial abnormalities in offspring of rats fed a fat-rich diet in pregnancy	20 female rats and their offspring	Dietary intervention: maternal standard chow diet (5% fat) or animal fat rich diet (20% fat) beginning 10 days before mating and throughout pregnancy and lactation. Offspring weaned on to standard chow diet ad lib Glucose control measurements in offspring: whole body insulin sensitivity, pancreatic islet cell structure/function Additional outcome measurements: adiposity, leptin assay	No significant difference in birth weights and litter size. Insulin resistance increased in HF offspring compared to control offspring. HF offspring had increased plasma leptin concentrations versus control. At 6 months, HF offspring had significantly increased fasting plasma insulin. At 12 months, HF offspring had significantly increased fasting plasma glucose and triglycerides and significantly reduced HDL. There was no diff in basal insulin release from pancreatic islet cells, but sig reduction in glucose-stimulated insulin secretion in HF offspring. Significantly lower islet insulin content values in HF offspring versus control. HF offspring had sig increase in abdominal fat deposition at 6 months.

van Eijsden, M; Hornstra, G; van der Wal, MF; Vrijkotte, TGM; Bonsel, GJ	American Journal of Clinical Nutrition, 2008	Maternal n-3, n-6, and *trans* fatty acid profile early in pregnancy and term birth weight: a prospective cohort study	3704 pregnant women in Amsterdam	Outcome measurements: blood nutrient analysis (plasma phospholipids) from week 12 of gestation. Infant birth weight.	Low n-3 FA and low 20:3n-6 FA (AA precursor) and high other n-6 FA and high *trans* FA concentrations associated with lower birth weight. With lifestyle adjustments, low n-3 FA, low 20:3n-6 FA, and high 20:4n-6 associated with lower birth weight and higher SGA risk.
Wiendran, V; Bendel, RB; Couch, SC; Philipson, EH; Thomsen, K; Zhang, X; Lammi-Keefe, CJ	American Journal of Clinical Nutrition, 1999	Maternal plasma phospholipid polyunsaturated fatty acids in pregnancy with and without gestational diabetes mellitus: relations with maternal factors	Women with GDM receiving dietary therapy, n = 15; women without GDM, n = 15	Outcome measurements: fasting plasma phospholipid fatty acids at 27-30, 33-35, and 36-39 weeks of gestation	Linoleic acid and arachidonic acid concentrations did not differ significantly between GDM and control. HgA1c was inversely related to plasma AA in control subjects (p = 0.03). Pregravid BMI was negatively associated with plasma phospholipid DHA in control subjects and in women with GDM who had a BMI < 30 (p = 0.007).

Zambrano, E; Martinez-Samayoa, PM; Rodriguez-Gonzalez, GL; Nathanilsz, PW	The Journal of Physiology, 2010	Dietary intervention prior to pregnancy reverses metabolic programming in male offspring of obese rats	15 female Wistar rats and their offspring	Dietary intervention: 5 mothers fed control diet (C) of lab chow. 10 mothers fed an obesity inducing diet (MO) pre-conception of 23.5% pro, 20.0% animal lard, 5.0% fat, 20.2% polysaccharide, 20.2% simple sugars. Glucose control measurements: offspring insulin resistance Additional outcome measurements: mother's weights, offspring birth weights, offspring adipose tissue measurements	Non-pregnant MO rats were 22% heavier than controls 1 month prior to breeding. At breeding MO 16% heavier than controls. No difference in offspring birth weight between groups. MO offspring had more subcutaneous fat tissue, higher serum triglycerides, leptin, and insulin than control. MO offspring had elevated fasting serum glucose and insulin, and insulin resistance. MO offspring had greater amount of body fat, larger fat cell sizes, and higher leptin concentrations than controls.

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