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Epigenetic Modifications Due to Maternal Diet

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Abstract

Obesity is a growing exponentially to be a health issue globally. Worldwide the rate of obesity has nearly doubled since 1980, with approximately 200 million adult men and 300 million adult women now being considered obese. We are also seeing growing percentages of woman of reproductive age being considered obese (BMI>30). Maternal obesity is known to increase the likelihood of developing complications during the pregnancy such as gestational diabetes and pre-eclampsia. These conditions create the environment for the growing fetus that are more difficult than that of a healthy pregnancy. The Developmental programming hypotheses links the environment of development to the development of chronic disease later in the offspring's life. Nutritional intake also is a component of the environment that influences the epigenetic markers on the fetal genome. Both under and over nutrition have observed results in epigenetic changes in both human and animal studies. The maternal high fat diet, effect, and implications will be overviewed in this review. As well as suggested routes for future studies involving humans.

Once Sentence Summary: This review discusses animal and human studies that show the implications of changes in maternal diet from a base line "normal," nutriton, primarily focused on high fat diet effects to the epigenetic marks of the offspring.

Methods

Research databases were utilized to find the most relevant information and experimental studies with the search terms used were maternal diet, epigenetic modifications due to diet, fetal changes

due to inflammation. Databases were searched for six months with continual reassessment of information. Date was then organized and summarized to the review research paper.

Introduction

Over the recent decades the rate of obesity has dramatically increased for many nations, becoming a healthcare pandemic. Worldwide the rate of obesity has nearly doubled since 1980, with approximately 200 million adult men and 300 million adult women are now considered obese [*1,3]*. Obesity has a growing prevalence both developed and underdeveloped society, the World Health Organization (WHO) declared it to be one of the top ten adverse health risks worldwide. Obesity is a known risk factor for numerous non-communicable diseases such as hypertension, type 2 diabetes, cardiovascular disease, and certain types of cancer [3,4]. In the case of pregnancy, obesity can have health effects on more than just the individual.

As of 2015, approximately 17% of adolescents and children in the United States were considered obese [16]. Billions of dollars have been spent in finding commonalities in the cause to obesity including the child's nutrition, the guardian's education level, the child's birth weight, and familial metabolic disorders.

Within the research community there is growing interest to the connection of early life environment and later development of chronic disease. The Developmental Origins of Health and Disease (DOHaD) hypothesis was formed in 1990 by David Backer to encompass the belief that development of disease in adulthood is related to nutritional environment during periconceptual, fetal, and early infant phases of life [2,6, 22]. DOHaD model postulates the following the fetus is capable of modifying epigenomic expression in a predictive manner in response to over and under maternal nutrition, and the nutritional intake prior to conception can alter the methylation pattern of the fetus epigentics [2]. Unfortunate, the prenatal predictive

adaptations that occur can be counterproductive to the true postnatal life and true nutritional intake the child will encounter. These predictive adaptations are often seen in the form of up or down regulation via epigenetic modifications. There are expected epigenetic modifications predominantly occurring on imprinted genes [9]. One such example of an imprinted gene is insulin-like growth factor 2 (IGF-2). IGF-2 is a gene normally only expressed by the paternal copy, and characteristically can easily be altered by methylation in the response to the over and under nutritional stimulus during early life development [2,9,10]. A number of studies have shown both environments of undernutrition and over nutrient cause epigenetic modifications in a predictive manner that was intended to give the fetus the greatest metabolic advantage in postnatal life. The results of these environments typically are counter intuitive results predisposition the fetus for metabolic disorders such as hyperinsulinemia, hyperlipidemia, hypertension, and obesity by. [5-8]

What are epigenetic changes?

The primary DNA sequence exhibits minimal changes post fertilization and the formation of diploid chromatin [5] Due to this observed lack of change, the search began for alternative shifts around the primary DNA sequence. Researchers studied the chromatin, down to the histones, and observed alterations occurring outside the primary sequence that caused the change in protein expression. Epigenetic changes are enzyme-medicated chemical modifications that alter the expression of the DNA but do not alter the primary DNA sequence [2]. The current mechanisms known so far for mediating epigenetic effects are DNA methylation, histone modifications, chromatin modifications, and small and long non-coding RNAs (ncRNAs) [5,11]

The gametes are highly methylated when compared to paternal and maternal somatic cells, but upon fertilization the newly formed zygote undergoes a global demethylation with an immediate follow up of genome wide methylation [30]. These new methylation patterns are expressed in pluripotent cells, with changes in the gene expression leading to differentiation for the cells. Methylation is a critical aspect to development of the fetus, but the controlling aspect to where and how long a chromosome is methylated remains to be discovered but it is thought the mechanism is combination of inheritance and stochastics [31].

1. DNA Methylation

DNA methylation is mediated by an enzyme called DNA methyltransferase. Methylation is a common modifications in eukaryotic organisms either at the DNA level on the 5' position of cytosine found in CpG sites, CpG islands, and on the Histone tails [2,3,15] . CpG islands are areas of high frequency of CpG dinucleotides, and are commonly found near gene promotor regions. 70% to 90% of CpG sites are methylated, and this CpG methylation largely occurs during embryogenesis or in early postnatal life [29]. But, CpG islands are found to be unmethylated. Increased levels of methylation on or near a gene's promotor region, CpG islands, is associated with gene silencing. A classic example of silencing if found with the X chromosome of woman, where the genome is not expressed by one of the two X chromosomes. While, low levels of methylation is associated with transcriptional activity [3] or upregulation.

It is reasonable to question how methylation continues to be present on the primary DNA CpG islands after the synthesis of a new strand. Methylation concentration is heritable from one cell generation to the next through the protein methyltransferase, DNMT1 [5]. DNMT1 is an enzyme capable of reading the methylation pattern of the parental DNA strand, and proceeded to methylate the CpG dinucleotides on the new synthesized, "daughter," strand [5]. DNMT1 attaches methyl

groups from S-adeosyl-L-methinine (SAM). SAM is created via an ATP reaction with methionine derived from micronutrients in the diet (such as folate, choline, Pyridoxine, mthylcobalamin, methionine) and is considered the universal methyl doner [9]. Full gestation of a zygote was unsuccessful in mice with homozygous knockout for DNMT1 protein, this is evidence of the importance of DNA methylation for successful embryonic development [20].

2. Histone Modifications

A histone is an evolutionarily conserved octamer protein made up proteins named H1A, H2B, H3, and H4. There are two of each of the proteins to produce the positively charged octamer, that all have a flexible amino terminal tail. The positive charge on the octomer complex allows for approximately 147 bp of the negatively charged DNA to tightly wrap twice around in a left-handed super-helical turn. [5]. The amino N-terminal tail of H3 and H4 proteins are the primary location of Histone modification. These modifications include acetylation, methylation, phosphorylation, ubiquitinoylation, and SUMOylation [3,9,15, 17]. The chemical modifications made to the H3 and H4 tails contributes to genomic stability and expression of genes [9].

Histone tail acetylation is known to cause transcriptional activation. The acetyl groups attaching to the H3 and H4 tails are capable of decreasing the positive charge of the histone octamer. This decrease in positive charge on the histones lessens the interaction with the negatively charged phosphate groups on DNA allowing for the once tightly held genes in the primary DNA to be accessed [9,18]. The protein histone acetyltransferases (HATs) adds acetyl groups, while the protein deacetylases (HDACs) remove acetyl groups [3,19].

Histone tail methylated on the lysine and arginine residues of H3 and H4. Methylation of the histone tails can be either an active or repressive mark, depending on the specific residue involved. The methylation of arginine (R) on sites H3R2, H2R8, H2R17, H3R26, and H4R3 and the lysine (K) on sites H3K4, H3K9, and H3K27 are established by several proteins under the family Histone

methyltransferases (HMT). An example of the activating and inhibitory impact of methylation can be found in the H3K4 and H3K9 sites. H3K4 methylation is associate with gene activation, while H3K9 is associated with gene silencing [18].

These means of epigenetic markers DNA and on the histone tails can function cohesively to further establish gene silencing or upregulation. Methylation occurring on the primary DNA CpG islands are capable of recruiting both histone deacetylases (HDACs) and histone methyltransferases, these combined enzymatic reactions work to tighten the chromatin and repress gene expression.

3. One Carbon Metabolism

Knowing the implications of methylation is one component to understanding epigenetics, but it is critical to know where the methyl groups come from that are added to the Primary DNA and histone tails. Evidence of methylation on the primary DNA from nutrition can be found in the Folate-mediate one carbon metabolism. As said above, S-adeosyl-L-methinine (SAM) is created via an ATP reaction with methionine derived from micronutrients in the diet such as choline, Pyridoxine, mthylcobalamin, methionine [9]. The major contributors of methyl groups in human intake come from primarily methionine and choline containing food, seen in Figure 1.

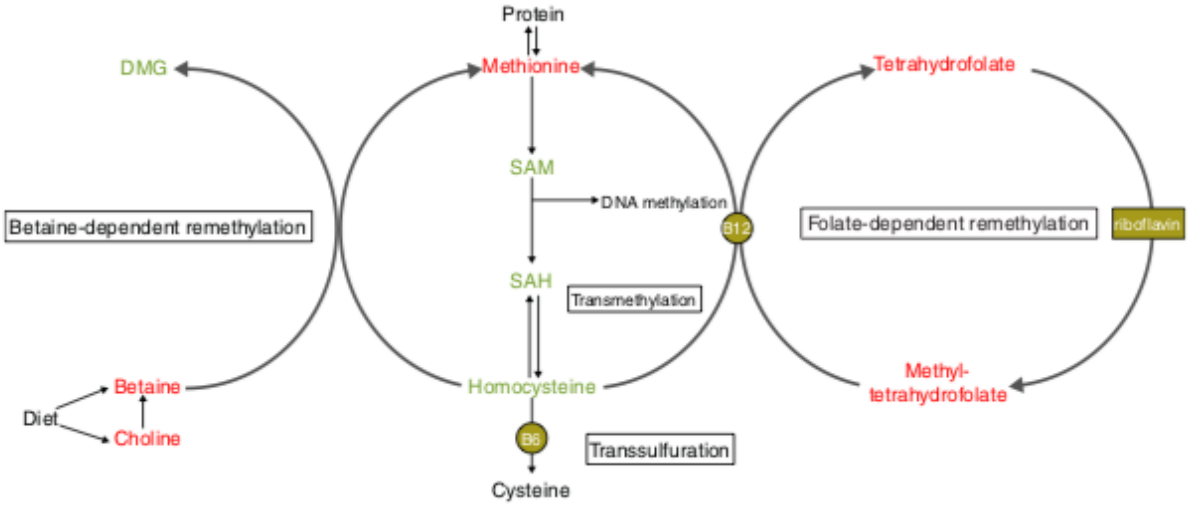

Figure 1. Diagram of C_1 metabolism. Methyl donors are shown in orange. In green are the functional bio-markers, and encircled are the cofactors. **SAM**: S-adenosyl-L-methionine; SAH: S-adenosylhomo- cysteine; DMG: dimethylglycine.

Major contributing foods include eggs, fish, sesame seeds for methionine [27], and for choline foods continuing phosphatidylcholine such as eggs, liver, cauliflower, and salmon [28]. Our nutritional intake influences the supply of methyl groups for the formation of SAM and therefore influences the formation of epigenetic markers thorough our lifetime.

Early Life and the Epigenome

Alterations in epigenetics was found in 1998 study of mice and the expression of the agouti gene. Wolff et al. reported that feeding homozygous (a/a) black dams a diet rich in methyl-donating nutrition, such as folic acid, vitamin B12, betaine, and choline, changed the epigenetic markers on the expression of genes responsible for agouti in their offspring [21] In mice, coat color is determined by the methylation of an intracisternal-A partial (IAP) in the 5' upstream region of the agouti gene, which regulates the paracrine signaling that induce follicular melanocytes. The increased methylation to the IAP region induced a change in the expression of the agouti gene to switch from producing the black coat seen in the first generation to be yellow and brown [21, 24]. The study shows that maternal nutrition has a direct effect on the epigenetic marks.

Deficiency in methyl donating groups can also contribute to metabolic disorders. Methyl group deficiency can result from restricted diet, a diet low in methyl donating foods, or lifestyle factors such as smoking, consumption of alcohol or large amounts of stress during periconceptual and fetal phases [2]

Further studies suggest maternal overnutrition, gestation diabetes and obesity play a role in increased in risk of non-communicable diseases (NCD) later in life [16, 22, 23]. It cannot be negated that other environmental stressors play a critical role in the changes to epigenetic markers for the fetus such as environmental pollutants (smoking/second hand smoke), physical illness, toxins (alcohol), or

pregnancy complications that result in increased inflammatory markers. A long-term cohort study of individuals conceived during the Dutch Famine that occurred after WWII was conducted in 2008. During this time food rations caloric value was gradually decreased from approximately 1,800 calories in December of 1943 to approximately 400 to 600 calories at the height of the famine in November of 1944 [32]. In 2006, the phenotypic observed differences in this cohort of individuals, was higher BMI, impaired glucose tolerance and increased risk for insulin resistance when compared to the general population. Genotypic observation on this cohort were made as well, specifically focusing on the methylation pattern in the functional loci of the imprinted gene IGF-2. The genotypic study conducted in 2008 compared the cohort to their siblings of the same sex born either prior to or post the Dutch Famine. It was found an average decrease of 5.2% in DNA methylation at IGF-2 loci in the cohort when compared to their siblings [32,33] This hypomethylation being seen 60years after the famine ended, suggest that environmental conditions such as maternal undernutrition display persistent changes in the epigenome of the fetus. The timing of caloric restriction also had association, as hypomethylation in the IGF-2 loci was only found when undernutrition was periconceptional but not later in gestation [33].

Maternal High Fat Diet

Generally, one of three nutritional diets followed for non-human studies are low-protein diet, a complete dietary restriction, or the high fat/ high junk food diet before pregnancy and through lactation. The "Western diet," has been classified as cheap and one of high caloric intake. The Western diet is growing in popularity due to Westernization, and the globe's growing populations' needing food demands a cheap source. It is not a surprise that globally there has been an increase in obesity rates, accounting for 60% of all deaths [22, 23,26].

Center for Disease Control and Prevention (CDC) shows there was little change to the prevalent of obesity in woman of reproductive age, 20- 39,from 2011-2012, but from 1990 to 2001 the prevalence

of obesity in woman of reproductive age increased from 28.4% (CI 95%, 24.4-32.4), to 34.0% (CI 95%, 29.0-39.1) [25]. Obesity in pregnancy is known to increase the odds of developing complications such as preeclampsia, gestational diabetes, and elevated VLDL-triglycerides in the blood plasma [22].

1. Animal Studies—

The Developmental Origins of Health and Disease (DOHaD) hypothesis is supported in feeding non-human subjects a high fat diet (HFD) during periconceptual, fetal, and lactation phases. As stated before the environmental factors can induce epigenetic changes in a predictive manner to allow the fetus to have the most advantage for survival once born. Some of these adaptations can be counter intuitive and lead to metabolic dysfunction.

In a number of mouse studies maternal HFD causes increases in fat mass and therefore body weight [24, 4], increase blood glucose [4,35], and development of fatty liver [24,34,35] The liver, a massive and important organ in lipid regulation in the body, undergoes epigenetic adaptations to prepare the fetus for a nutritional environment that is high in fat. This can be supported by the changes in expression to the PPARs. *PPAR* is a regulator of lipid and glucose homeostasis [36] It should also be noted that *PPAR* is also a regulator of genes involved in cell differentiation and proliferation during development.

There are three isoforms of the PPAR protein, PPARα, PPARβ/δ, and PPARγ, that all function as ligand activated transcription factors. PPARα is a nutritional sensor that adapts the amount of fatty acid oxidation and gluconeogenesis occurring by the liver [35]. These transcription factors from heterodimers with retinoid X receptor (*RXR*), that then bind to the peroxisome proliferator

response elements (PPRP) of the promoters of target genes that control metabolic function, and allow for transcription to occur [36]. High fat, high energy diets cause the hypermethylation to occur in the liver (Figure 1), and *PPAR* and *RXR* hepatic genes to be inhibited (Figure 2) in male mice specifically [6, 23, 35, 36]. Male offspring also have higher expression to the *Fasn* gene when exposed to a high fat diet during development and post-weaning [6]. Fasn is responsible for fatty acid synthesis.

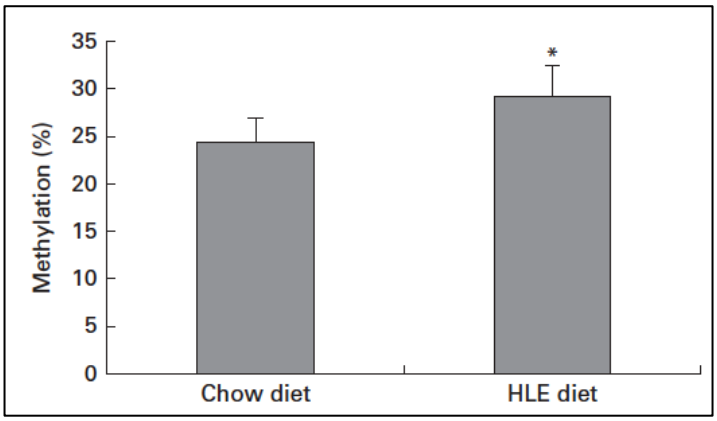

Figure 1. Liver methylation in adult male offspring from dams fed either a Chow diet or a high lipid energy (HLE) diet. During pregnace and lactation. [9]

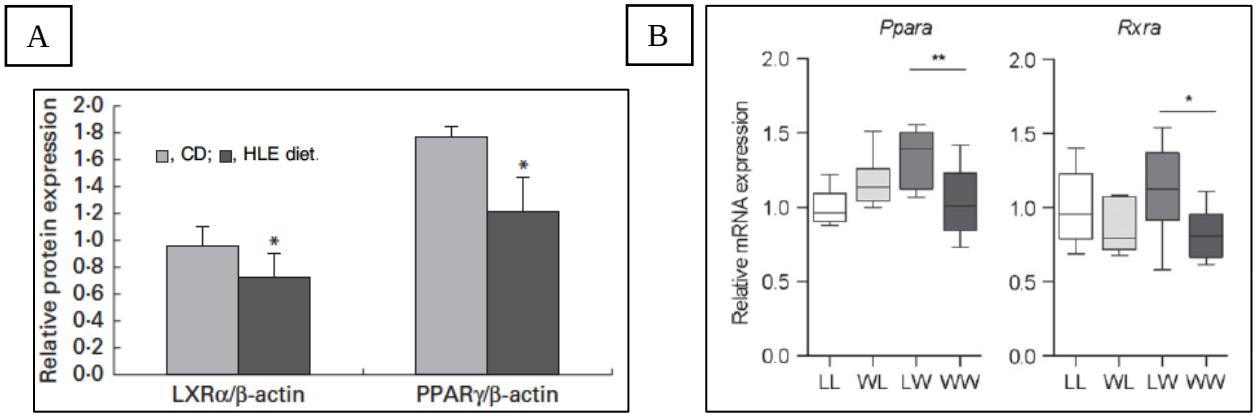

Figure 2. Shows the decrease in mRNA expression levels in both A and B. (A.) represents a study in which the male offspring were exposed to a either a Chow diet (CD) or a high lipid energy (HLE) diet during the dam's pregnancy and through lactation[9]. (B) show changes in expression due to low-fat control (L) or western/high fat (W) diet. LW- the first intial represents the diet the dams followed through weaning and the second initial represents male offspring being fed after weaning [6].

The repression of *PPAR* and upregulation of *Fasn*, suggests that a larger amount fatty acid will be synthesized with little hemostasis maintained by PPAR. PPARα normally is activated to break down the fatty acids his suggesting is supported by A.L. Burgueno et al study comparing the storage of male and female. Male mice feed a high fat diet were found to be hyperleptinemic and accumulated larger amounts of abdominal fat (Figure 3) [35].

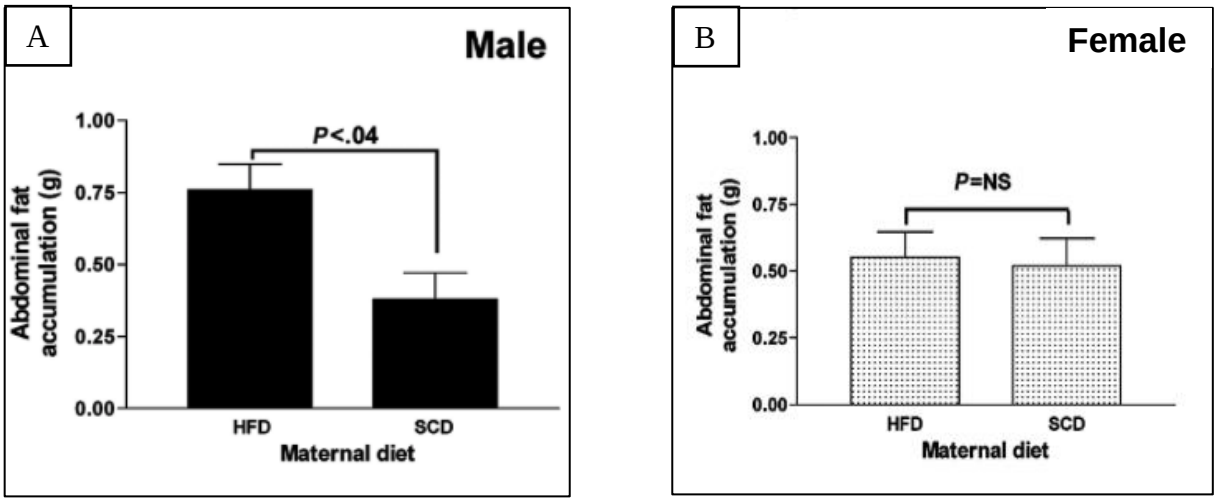

Figure 3. Abdominal fat accumulation in (A) male and (B) female mice. Nonsignificant (NS) p value is observed in the female mice when comparting offspring from dams feed either Hight fat diet (HFD) or a standard chow diet (SCD)

Female offspring born to dams feed a high fat diet demonstrated an upregulation in PPAR and exhibit an increase in insulin resistance in both mice and rats, [35, 37]. Some evidence suggest the sex-specific outcomes are due to the expression of sex-specific hormones. Estrogen is suggested to protect the offspring from HFD induced insulin resistance and glucose intolerance in mice [38] This is supported by Ppargc1a's positive and negative feedback controls with Estrogen-related receptors (ERR) for gene expression [39]. ERR's control expression of genes involved in lipid metabolism at the organismal level [39]

Changes to hepatic function were also seen in non-human primate studies. Chronic maternal HFD induced a fatty liver that persistent into the postnatal period, and reprograming of the gluconeogenic pathway. This is supported by a two-fold increase in mRNA in PPARγ, Glucose 6 phosphatase (G6P), Fructose 1,6-bisphosphataes 1 (FBP1), and Phosphoenolpyruvate carboxykinase 1 (PCK1) [41]. Presently, there are a number of findings indicating maternal HFD the excess release of inflammatory factors [6,41,42]. Oxidative stress markers such as 8-hydroxy-deoxyguanisine (a marker for DNA oxidation) and 4-hyroxy-2noneal (a marker for oxidized fatty acids in the cytosol) along with inflammatory marks were found to be elevated in the fetal liver of non-human primate livers [41]. In the study conducted by Fias et al. 24 macaques, similar in age, were fed a high fat diet for at the minimum of four years prior to pregnancy and compared to a control group. They found the HFD group to have higher insulin secretion, higher adiposity gain, increase triglyceride levels and a decrease uteroplacental profusion when compared to the control. Surprisingly placental weight and size were not significantly different that the control but due to the decreases profusion, the HFD had a greater rat of still births [42] The Furthermore, retinoid X receptor (*RXR*) and *PPAR* gene silencing seen in Mousa AA, et al. human study of several preeclampsia effected woman noted the decrease in RXR/PPAR protein dimers has a direct proinflammatory effect specifically in the epithelia cells and vascular smooth muscle of the blood vessels [44]. In addition to metabolic hemostasis the isoform PPARγ has a critical role in establishing the placenta via trophoblast cell invasion intrauterine wall and differentiation into syncytiotrophoblast [49]

Increases in inflammatory markers such as Tnf-α, MPC1 (a chemokine fore monocytes), and IL-1β are also found in the fetal livers and adipose tissue of male mice [6, 4] leading to the development of larger livers (Figure 4).

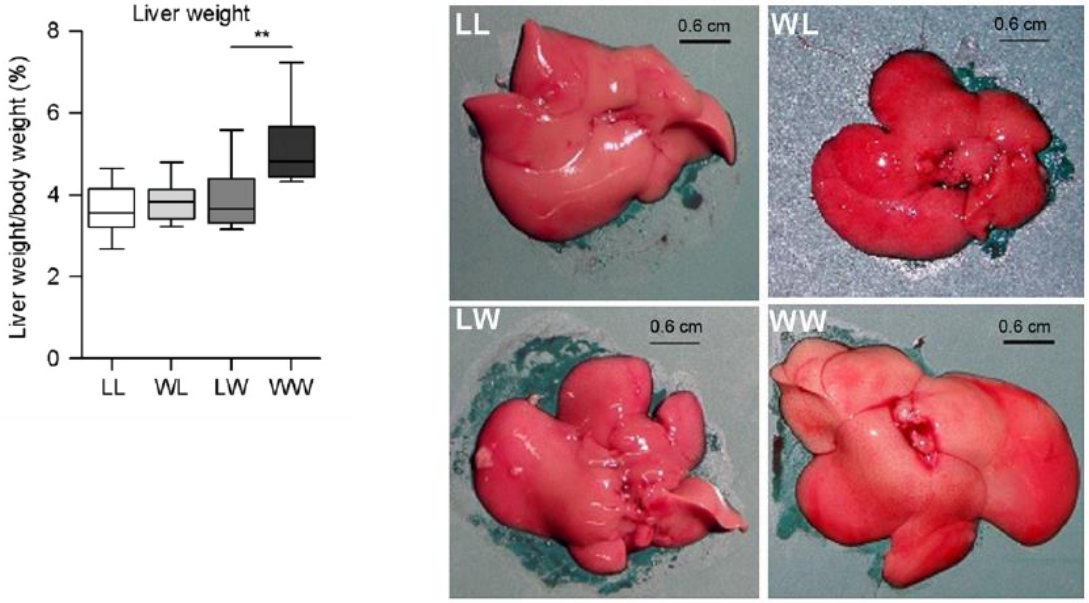

Figure 4. (A) displays the mean weigh of each group Low fat (L) or western/high fat (W) diet. The first intial represents the diet the dams followed through weaning and the second initial represents male offspring being fed after weaning ie LW= maternal low fat diet follower through weaning, Western diet followed by the offspring [6]. (B) is the harvest livers from the cohort where WW had the highest inflammatory mRNA expression and highest in weight.

It seems, a high fat maternal diet has a profound, largely sex-specific effect on the fetus. The maternal diet has the capability in altering the methylation of the genome of result in small protein expression quantity changes intended for advantage in the postnatal environment but do not correlate with the true nutritional environment resulting in a counterintuitive phenotype.

2. Human Studies of Maternal Obesity

Currently the United States, 38% of normal weight, 63% of overweight, and 46% of obese women gain weigh in excess to the recommendations published by the Institutional of Medicine (IOM) [16]. Maternal obesity early in pregnancy doubles the risk of obesity in the offspring [44]. If similar modifications occur humans that occur in animals, the scientific and medical community can use the information to their advantage in reducing the chances development of chronic diseases by educating the population on appropriate nutritional intake during pregnancy. Human studies are often difficult and a number of factor need to be included and calculated for such as weight, and BMI of the mother, education level (0–6, 7–12, and 13–16 years), socioeconomic level (low, medium, high), maternal and paternal smoking status during pregnancy, offspring sex, offspring birth weight, and weeks of gestation.

One similarity can be found in regards to importance of RXR in the human genome just as it is in the rat and mouse studies. In two independent cohorts Godfrey et al. observed the methylation of a single CpG site on *RXRA* promoter region and the single methylation at this site correlated to childhood obesity in both boys and girls [46] In a number of studies, Omega 3-fatty acid supplementation during pregnancy with docosahexaenoic (DHA) and/or eicosatetraenoic (EPA) acids was associated with changes in methylation quantities in various genes within the offspring. These genes includ genes coding for inflammatory mediators [41,46,47].
Most studies are epidemiological in nature, and there are few ways to track nutritional intake and adverse effects during development.
The importance of the PPARγ gene in humans is also evident in women with rare dominant-negative PPARγ mutations. These women have symptoms such as dyslipidemia, early-onset

insulin resistance, gestational diabetes, hypertension, and polycystic ovarian syndrome but also preeclamptic pregnancies [51]. Complete deletion of PPARγ or RXR in mice results in results in loss of the fetus between at embryonic days 9.5 and 10.5 [50]

Discussion

High fat diet in mouse models is shown to have sex-specific effects. The high fat diet effects the male mice predominantly more than females, in excessive lipid storage in the abdomen, decreased expression of PPAR proteins, and increased expression of inflammatory cytokine genes. It cannot be negated that increased inflammatory factors are observed in female mice born from dams of a high fat diet as well. Non-human primate studies show similar results in down regulation of PPAR proteins and inflammation, but seems to be less sex specific than mice. Female non-human primates that consume a high fat diet have an increase in still births. Dyslipidemia and chronic inflammation are common signs of non-alcoholic fatty liver disease (NAFLD), which are seen in our mouse, rat, and non-human primate models. This evidence suggests maternal diet's effect on the epideictic markers for *PPAR*, *RXR* and *Fasn* dysregulate the fat metabolism and hemostasis therefore predispositioning the offspring for NAFLD.

Future Work

Knowing that the HFD causes *PPAR* down regulated in mice, and the role of PPARγ beyond glucose hemostasis is to the primary development in establishing implantation and placental development, and HFD increases the rate of still births in primates, it is clear that further study of *PPAR*, *RXR*, *Fasn*, and inflammatory genes should be conducted. If woman consuming the Keto diet decides she would like to become pregnant, a normal diet should be followed for a few

months prior to her ideal conception. This idea is supported by Summerfield et al. mouse study in changing from a high fat diet to a normal diet at one, five, and 9 weeks prior to pregnancy. It was found that long-term not medium or short term diet transition is best for: 1) the reducing pro-inflammatory expression in the offspring, 2) recovery of normal expression of genes, and 3) reduces macrophage infiltration caused by oxidative damage to adipocyte cells [4].

It would be advantage to understanding the epigenetic markers to use them as predictors for chronic diseases by utilizing samples from blood, buccal swab, and placenta tissue when the offspring is born and later in age blood and buccal to observer for methylation patterns. One such protein to be tested for is adiponectin. Adiponectin and leptin are hormones sectored by the adipocyte that help to regulate energy hemostasis and metabolism in both children and adults [49] In the third trimester, insulin resistance is highest (Figure 5), leptin is high and adiponectin should be low.

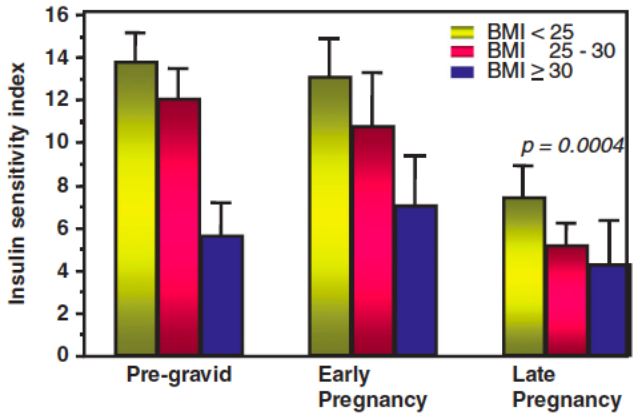

Figure 5. Insulin resistance changes prior to, early, and late pregnancy in the various BMIs. BMI that is greater than 30 is considered obese, and this population has increased insulin reistance.

Furthermore, the placenta cannot create adiponectin and amounts present are entirely contributed by the mother with adiponectin amount being lower in those who consume the Western/ high fat diet [16]. Mantzoros et al in Project Viva from 1999-2003 created a 2128 cohort of woman

following primarily a Mediterranean diet and collected cord blood from 1622 deliveries. The study found for every 1% increase in caloric intake the lower the blood adiponectin was found to be (-0.25μg/mL with 95% CI (-0.48,-0.02)). Low adiponectin in associated with a healthy pregnancy, while higher adiponectin indicates an unhealthy pregnancy, typically found in obese mothers, and likely increase in inflammatory markers being expressed [4, 16, 48]. As seen in the mouse model, inflammatory markers are expressed in the presence of a high fat maternal diet leading to adverse phenotypic outcomes. More research can be done following these inflammatory markers such as Tnf-α, IL-1β, and IL-6. Measuring the markers in the cord blood and periodically at checkup can be used to in studies to better understand if inflammation present during development is correlated to adverse development later such as non-alcoholic fatty liver disease, hypertension, or type 2 diabetes.

A human diet should be balances in it macronutrients to be a healthy caloric intake fitting of that person basal metabolic rate. Cutting out as well as over consumption of specific food groups can result in tissue inflammation and inflammatory markers. This effect happens for the developing fetus as well, if the maternal diet is not balanced. With or without risk factors of obesity, it would stand to include nutritional consultation with perinatal care, as lean, normal, and obese woman gain above the recommend amount during gestation. Such consultation can later be effective in mediating the development of chronic diseases in future generations.

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