Effects of Poor Maternal Nutrition on Pre- and Post-natal Growth and Metabolism

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Introduction

The human population is expected to reach 9.8 billion by 2050 (Nations, 2017); therefore, it is imperative that we identify methods to improve the efficiency of food production to provide adequate, affordable, and high quality animal protein to consumers. Livestock are huge contributors to the global food supply as milk, meat, and eggs provide approximately 18% of energy and 34% of protein consumed globally (FAO, 2018). Therefore, the identification of methods to improve production efficiency is necessary to increase protein availability for human consumption. Inadequate nutrition during gestation impairs fetal growth and metabolism, which can lead to reduced productivity and quality of the product [e.g., meat, milk, fiber (Du et al., 2010a; Du et al., 2015)] in the offspring. Impaired tissue growth during prenatal development can extend into early postnatal growth and through adulthood, thereby hindering the animal's ability to develop adequate protein (i.e., muscle). Poor maternal nutrition, reduced or excess nutrition, during gestation reduces fetal growth (McMillen and Robinson, 2005; Wu et al., 2006; Reynolds et al., 2010), impairs muscle development (Du et al., 2011; Reed et al., 2014), reduces bone density (Lanham et al., 2008a; Lanham et al., 2008b), increases fat accretion (Du et al., 2010b; Du et al., 2011), alters metabolism (Wu et al., 2006; Reynolds et al., 2010), and impairs stem cell function (Oreffo et al., 2003; Pillai et al., 2016; Raja et al., 2016) in the offspring. Numerous studies in livestock, rodents, and humans have demonstrated that these negative effects can contribute to reduced efficiency of growth and altered metabolism (Du et al., 2010a; Ford and Long, 2011; Long et al., 2012; Hoffman et al., 2014; Reed et al., 2014; Hoffman et al., 2016a). Maternal nutrient restriction and over-feeding during gestation causes metabolic dysregulation and alters key metabolic pathways in offspring which are associated with reduced efficiency of growth and poor health outcomes (Wu et al., 2006; Ford et al., 2007; Ford and Long, 2011; Hoffman et al., 2016a). Current research in the field of fetal programming focuses on identifying mechanisms that contribute to these long-term, persistent negative effects of poor maternal nutrition during gestation.

Fetal Programming

Fetal programming is an important process that occurs during in utero development to ensure proper development and survival of the fetus after birth (Barker, 1995). When adverse events occur during gestation, such as reduced or excess nutrient consumption by the mother, this leads to negative programming effects on the offspring in terms of production, health, and metabolic outcomes. A classic example of the impact of restricted maternal nutrition during gestation is the Thrifty Phenotype Hypothesis proposed by Hales and Barker (Hales and Barker, 2001). Offspring born to mothers

exposed to nutrient restriction during the Dutch famine demonstrated metabolic dysregulation, increased obesity, and insulin resistance in adulthood. These outcomes are likely the result of programming during gestation to survive in an environment with limited nutritional resources. However, when the postnatal environment (adequate or excess nutrition) did not match the fetal environment, the fetal programming led to increased risk of metabolic dysregulation which ultimately reduces efficiency of growth. Specifically, maternal nutrition can negatively impact adipose, muscle, liver, pancreas, brain, and cardiovascular system, all of which can contributed to metabolic dysregulation in the fetus and postnatal offspring (Symonds et al., 2009).

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Models of Poor Maternal Nutrition

Poor maternal nutrition can result from excess or reduced nutrient intake including overall total energy, protein, and/or micronutrients in the diet. These are often practical problems for producers depending on their geographical location. For example, in drought conditions or during winters, forage may be reduced in quantity and/or quality. In addition, certain regions are susceptible to excess or limited micronutrients and therefore proper supplements are necessary. Variations in the quality and quantity of available feed and forage can result in periods of sub-optimal nutrition for livestock. Specifically, a lack of food and/or specific nutrients often occurs for a period of gestation, or often all of it, in many parts of the US. The timing and duration of the nutritional insult also affects the outcomes in the fetus and offspring. In our model of poor maternal nutrition in sheep, we evaluate the effects of restricted and over-feeding based on a total feed deficit or excess. Our control animals are fed a complete feed at 100% of NRC requirements. The restricted animals are fed 60% of control, based on TDN and the over-fed are provided 140% of control. This model has provided us with the advantage to compare the impact of both restricted and over-feeding in the same study.

Growth

The maternal environment can have immediate and long-lasting consequences on offspring fetal and post-natal growth. Poor maternal nutrition is known to impact fetal growth and can lead to reduced body weight at birth, but this is dependent on the timing, duration, and type of nutritional insult (Wu et al., 2006; Du et al., 2010a; Ford and Long, 2011; Reed et al., 2014; Govoni et al., 2019). As we previously summarized (Govoni et al., 2019), nutrient restriction during gestation can lead to intrauterine growth restriction and reduced birth weight; however, several studies of restricted nutrition during gestation also report no effect on offspring body weight at birth (Govoni et al., 2019). Similarly, over-feeding during gestation can lead to increased body weight at birth, but more often does not impact offspring body weight during this time (Govoni et al., 2019). Maternal diet can also impact postnatal offspring growth with compensatory gain occurring in offspring of restricted-fed ewes (Morrison et al., 2010). However, this is not desirable as it often leads to increased adipose tissue and not increased muscle mass (Hornick et al., 2000). Based on the variability in the impact of maternal diet on offspring body weight at birth and

postnatal growth, caution is needed when using birth weight as an indicator of 'healthy' offspring since these offspring can have similar birth weight, but often have differences in body composition and metabolic factors that lead to poor growth, health, and product quality as they mature.

Several proteins in the circulation and local growth factors are associated with altered growth of offspring from mothers consuming a poor diet during gestation. The growth hormone (GH)/insulin-like growth factor (IGF) axis, which is critical for fetal and postnatal development of muscle, adipose, and bone tissue, is altered. Specifically, in offspring that are born small for gestational age due to disease or limited maternal nutrient availability there is reduced circulating IGF-I and IGF binding protein (BP)-3, and increased GH and IGFBP-2 (de Zegher et al., 1997); a hormonal pattern associated with reduced growth or size in cattle (Rausch et al., 2002) and wildlife (Govoni et al., 2010). Furthermore, intrauterine administration of IGF-I in sheep increases fetal growth rate in growth-retarded fetuses (de Boo et al., 2008). Changes in these important circulating growth factors demonstrate one mechanism by which the negative effects of maternal diet alter offspring growth.

Muscle and Adipose

Muscle is the primary product in meat producing animals and adipose tissue is important in product quality. Muscle tissue is not only the end product, but also a key metabolic tissue. In addition, muscle fiber number is set at birth so insults during gestation can lead to persistent effects into adulthood resulting in decreased product quality and quantity, and metabolic dysfunction in offspring. In our sheep model of poor maternal nutrition, nutrient restriction and over-feeding lead to increased muscle fiber cross-sectional area (CSA) in offspring at birth, but at 3 months of age, smaller CSA in both treatment groups relative to control (Reed et al., 2014). These changes in muscle were associated with altered function of satellite cells (e.g., muscle progenitor cells) such that early differentiation and a reduced fusion index may account for the reduced CSA in restricted offspring at 3 months of age (Raja et al., 2016) due to precocial differentiation of myoblasts. Similarly, in cattle, muscle CSA was altered in response to early- and mid-gestation nutrient restriction (Zhu et al., 2004). Within the muscle tissue of restricted- and over-fed offspring there was increased fat accumulation demonstrating a negative impact of both maternal diets on offspring muscle growth and composition. Similarly, others report that nutrient restriction during early or late gestation results in fewer muscle fibers in lambs (Costello et al., 2008) and an increased number of glycolytic fibers (Zhu et al., 2006), which can negatively impact meat tenderness (Oury et al., 2009; Kang et al., 2011). Lambs from obese ewes have decreased abundance of the IGF-I receptor (R) coupled with decreases in Akt, mTOR, and 4EBP1 phosphorylation in the muscle, indicating suppressed signaling for protein synthesis (Yan et al., 2011). Moreover, fetal muscle (gestational day 135) in lambs from obese ewes have decreased muscle fiber diameter and increased collagen content (Huang et al., 2010; Yan et al., 2011), which persist into adulthood (Yan et al., 2011; Huang et al., 2012).

Offspring of mothers that are obese or over nourished during gestation are prone to increased fat deposition and insulin-resistance (Neri and Edlow, 2015; Pankey et al., 2017). In addition to programming the immediate offspring (F1 generation), there is mounting evidence that these effects can pass on to subsequent generations (e.g. F2, F3), even when those F1 offspring consume a normal diet. Specifically, Shasa et al. (Shasa et al., 2015) demonstrated that, despite similar birth weights, F1 and F2 offspring of F0 ewes (mothers) that were over-fed during gestation exhibited increased body fat, decreased insulin sensitivity, increased plasma cortisol, and no increase in early postnatal leptin. Similarly, F0 maternal obesity resulted in increased basal glucose and insulin concentrations in F2 females but not males, resulting in insulin resistance in the females (Pankey et al., 2017). These data demonstrate the multigenerational effects of poor maternal nutrition on offspring metabolism, insulin sensitivity, and growth.

Metabolism

It is well-established that poor maternal nutrition leads to impaired glucose sensitivity, insulin resistance, and leptin resistance in offspring, which likely contribute to increased adipose deposition and inefficient utilization of nutrients (Ford et al., 2007; Gao et al., 2014; Hoffman et al., 2016b). In support of increased adiposity with poor maternal nutrition, leptin synthesis is increased in offspring from mothers that were restricted-fed (Tzschoppe et al., 2011) or over-fed (Hoffman et al., 2014) during gestation. Maternal obesity and/or over-feeding leads to leptin resistance or increased circulating leptin later in life. This may be due to reduced peak of leptin during first week of life as demonstrated in sheep (Shasa et al., 2015). Similarly, maternal restricted feeding increased circulating leptin which was associated with increased body weight and feed intake in offspring (George et al., 2012). Leptin is important in appetite regulation and metabolic activity; therefore, alterations in circulating leptin concentrations or the body's ability to respond to leptin is one example of metabolic dysregulation that persists into adulthood and has been passed to subsequent generations (Shasa et al., 2015).

Both maternal restricted- and over-feeding impair insulin sensitivity in offspring, which can lead to decreased efficiency of growth and poor health due to increased fat accumulation (Ford et al., 2007; Hoffman et al., 2016a). Offspring from restricted- and over-fed ewes demonstrate increased insulin:glucose during an in vivo glucose tolerance test (Hoffman et al., 2016a). Maternal obesity and nutrient restriction are associated with increased type II diabetes in humans demonstrating the programming of offspring insulin production and/or response. Based on the insulin resistance in offspring, we and others have further explored the impact on pancreas development in the offspring. Restricted- and over-feeding decreased pancreatic islet number and increased islet size with reduced beta-cell proliferation (Peterson et al., 2021). Further, these changes were associated with sex-specific differentially methylated regions in response to diet. DNA methylation is a mechanism that controls gene expression. Altered methylation will impact the gene and proteins expressed and ultimately cell function, but not alter the DNA sequence. Specifically, there was a greater increase in differentially methylated regions in offspring of restricted-fed ewes and fewer in over-fed offspring. In the male offspring, there was a greater decrease in differentially methylated regions in both the restricted and over-fed

groups relative to female offspring (Peterson et al., 2021). These findings are consistent with previous sex-specific effects of poor maternal nutrition on insulin sensitivity in F2 offspring (Pankey et al., 2017). In addition, this highlights the importance of including both sexes when evaluating impact of poor maternal nutrition.

In addition to changes in circulating metabolic factors, we used metabolomic and proteomic analyses to identify metabolic changes at the tissue level in muscle and liver, two highly metabolic tissues. In a study evaluating maternal nutrient restriction effects on fetal development, we demonstrated a change in lipid abundance of cholesterol esters, ceramides, diacylglycerols, free fatty acids, sphingomyelin, and triacylglycerols in offspring blood, liver, and muscle at day 130 of gestation (Smith et al., 2022). Consistent with the changes observed in metabolite abundance, proteomics analysis demonstrated similar changes in proteins involved in glucose metabolism and glycogen synthesis in liver of fetal offspring (Smith et al., 2022). In offspring longissimus dorsi from nutrient restricted mothers, we observed changes in lipid and amino acid metabolites as early as day 90 of gestation using global metabolomics analysis. At day 135 of gestation, we see a shift such that glutamate, which was increased at day 90, is reduced at day 135, and ceramides which were decreased at day 90, are increased at day 135 (Martin et al., 2019), demonstrating a response to maternal diet that is specific to the stage of gestation. In the same analysis in offspring of over-fed ewes, we observed increases in several amino acids at day 90 of gestation, whereas at day 135 fatty acids increased; again, demonstrating stage of gestation and diet-specific responses of muscle metabolites (Martin et al., 2019). Based on changes in skeletal muscle growth, lipid composition, and metabolite abundance in response to maternal nutrient restriction and over-feeding, we further explored changes in protein abundance using proteomics. In offspring of over-fed ewes, protein synthesis was repressed at day 90 of gestation and there was a decrease in protein degradation at day 90 of gestation and at birth (Reed et al., 2022). Maternal nutrient restriction decreased protein degradation at day 90 of gestation, while increasing protein turnover (Reed et al., 2022). These findings are consistent with delayed secondary myogenesis observed in these fetuses (Gauvin et al., 2020), and our previous report that both restricted and over-feeding decrease muscle fiber growth (Reed et al., 2014); demonstrating changes in key protein pathways in fetal development.

Summary

Proper nutrition is a critical part of livestock management and production. The evidence that poor maternal nutrition (too much or too little) during gestation negatively impacts not only fetal development but can persist into adulthood and subsequent generations highlights the critical need to understand the mechanisms. Our recent metabolomics and proteomics analyses demonstrate the potential programming of key pathways involved in lipogenesis, glucose and glycogen metabolism, and protein synthesis and degradation contribute to altered tissue growth and metabolism in offspring. More importantly, these negative outcomes can occur even following a short duration of poor nutrition and with proper feeding after birth. Based on persistent effects into adulthood and subsequent generations, we and others are actively investigating the programming occurring at the tissue level (e.g., muscle, liver, pancreas, gut) to fully

understand how maternal diet programs offspring growth and metabolic dysregulation. Ideally producers would reach target feeding programs; however, this is not always realistic so there is a critical need to identify the mechanisms involved and ideal management of offspring subjected to poor maternal nutrition during gestation.

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