CELL BIOLOGY SYMPOSIUM: METABOLIC RESPONSES TO STRESS: FROM ANIMAL TO CELL: Poor maternal nutrition during gestation: effects on offspring whole-body and tissue-specific metabolism in livestock species^{1,2}

Kristen E. Govoni,³ Sarah A. Reed,[•] and Steven A. Zinn

Department of Animal Science, University of Connecticut, Storrs, CT

ABSTRACT: Poor maternal nutrition, both restricted-feeding and overfeeding, during gestation can negatively affect offspring growth, body composition, and metabolism. The effects are observed as early as the prenatal period and often persist through postnatal growth and adulthood. There is evidence of multigenerational effects demonstrating the long-term negative impacts on livestock production. We and others have demonstrated that poor maternal nutrition impairs muscle growth, increases adipose tissue, and negatively affects liver function. In addition to altered

growth, changes in key metabolic factors, increased glucose concentrations, insulin insensitivity, and hyperleptinemia are observed during the postnatal period. Furthermore, there is recent evidence of altered metabolism in specific tissues (e.g., muscle, adipose, and liver) and stem cells. The systemic and local changes in metabolism demonstrate the importance of determining the mechanism(s) by which maternal diet programs offspring growth and metabolism in an effort to develop novel management practices to improve the efficiency of growth and health in these offspring.

Key words: livestock, metabolism, nutrition

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INTRODUCTION

The livestock industry is a \$194.9 billion industry in the United States (USDA, 2017). Therefore, it is important to identify ways to

improve the efficiency of production thereby reducing costs for producers and maintaining affordable and healthy food for consumers. In addition, the estimated increase in the human population from 7.6 billion in 2017 to 9.8 billion in 2050 (Nations, 2017) demands an increase in food production to ensure an adequate food supply. Therefore, in addition to providing an affordable product, it is important that we also identify management practices and novel methods to improve the efficiency of production to increase the availability of animal protein sources of food worldwide. Several factors contribute to livestock production including genetics, management practices, nutrient availability, and health status. In particular, our laboratory, along with others, has focused on the role of the maternal nutritional environment and its effects on offspring fetal and postnatal growth and development. Gestation is a period of rapid growth and development of organs critical for survival, future growth, and metabolism of offspring. The

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³Corresponding author: kristen.govoni@uconn.edu

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importance of this period is emphasized by the recent increased research focus, in both livestock and human models, on fetal programming and the role of maternal nutrition. 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 poor nutrient consumption by the mothers, this can lead to negative programming effects on the offspring in terms of production, health, or metabolic outcomes. A classic example of the impact of poor maternal nutrition during gestation is the thrifty phenotype hypothesis proposed by Hales and Barker (2001). This hypothesis was developed based on the study of children born to mothers exposed to nutrient restriction during the Dutch famine. These offspring were followed into adulthood and demonstrated increased risk of metabolic syndrome-related diseases such as obesity, cardiovascular disease, and diabetes. This was probably the result of programming during gestation to survive in an environment with limited nutritional resources. However, when offspring gained access to adequate (or excess) nutrition, altered growth and metabolism led to increased risk of metabolic dysregulation. These early epidemiological studies also led to the development of the Barker hypothesis and developmental origins of disease hypothesis (Hales and Barker, 2001; Barker, 2004). There are several models used to study the negative effects of maternal nutrition on offspring growth and health. Livestock species have become well-accepted models for human biomedical research, including the impacts of the maternal environment on offspring (Ireland et al., 2008). Many previous reviews have provided excellent overviews of the impacts of insults to the maternal–fetal environment on offspring growth and health (McMillen and Robinson, 2005; Wu et al., 2006; Du et al., 2010; Reynolds et al., 2010; Yates et al., 2012; Sinclair et al., 2016). For the purpose of this symposium review, we will focus on recent work in our laboratory and others on the negative impacts of poor maternal nutrition on offspring metabolism.

There are several models of poor maternal nutrition during gestation, including excess or limited energy (Ford et al., 2007; Long et al., 2009, 2010, 2011; Meyer et al., 2010; Ford and Long, 2011; Vonnahme et al., 2015), protein (Liu et al., 2015), and/or specific vitamins and minerals (Reed et al., 2007; Ward et al., 2008; Lekatz et al., 2011; Meyer et al., 2011). Specifically, several laboratories have developed models of overfeeding and/or restricted-feeding (total energy or total nutrients)

during different stages of gestation and demonstrated negative impacts on maternal health and reproductive organs, including placental development and fetal growth and development (Scheaffer et al., 2004; Vonnahme et al., 2007; Caton et al., 2009; Long et al., 2010). Our laboratory has used similar models of overfeeding (140% of control) and restricted-feeding (60% of control) from early gestation in the same experiments (Hoffman et al., 2014, 2016a,b; Reed et al., 2014; Pillai et al., 2017). Using this model, we have demonstrated negative impacts of poor maternal nutrition on both prenatal and postnatal growth, and metabolism in offspring. There is increasing evidence that poor maternal nutrition during gestation not only alters offspring growth, decreases muscle, and increases fat, but also alters circulating and local metabolic factors. These changes in metabolism not only affect growth, but have long-lasting effects on the health of the offspring, leading to decreased production efficiency and increased costs of production. This review focuses on work in our laboratory and others on the effects of maternal diet on offspring systemic and local metabolic factors.

EFFECTS OF MATERNAL NUTRITION ON TISSUE GROWTH AND METABOLISM

Muscle

Skeletal muscle comprises approximately 40% of mature body mass, and although its metabolic rate per gram of tissue is relatively low, its abundance makes it a primary driver of whole-body metabolism (DeFronzo et al., 1985; Baron et al., 1988; Zurlo et al., 1990). Furthermore, skeletal muscle is the main source of glucose uptake in the body and thus contributes significantly to glucose and insulin dynamics (DeFronzo et al., 1985; Baron et al., 1988; Zurlo et al., 1990). Proper muscle development, therefore, is crucial to optimal postnatal metabolic status and efficient growth. In livestock, muscle fibers are formed during prenatal development, such that the full complement of muscle fibers are in place at birth, and no new muscle fibers are formed postnatally (Wigmore and Stickland, 1983). Thus, maternal diet during fetal development can positively or negatively affect the potential for postnatal growth and efficiency. Furthermore, exposure to nutrient restriction or excess during gestation programs the offspring for that environment postnatally, and when the expectation does not match the reality (e.g., when feed restriction or excess is not continued after parturition), the

mismatch between the existing metabolism and nutrient intake results in increased propensity for metabolic diseases (Barker, 2004).

Our group and others have demonstrated that restricted-feeding (60% of control) and overfeeding (140% of control) during gestation (beginning at day 30) alters muscle development and structure. Specifically, maternal nutrient restriction and overfeeding during gestation result in larger muscle fibers at birth that experience less hypertrophy postnatally in sheep (Reed et al., 2014). This is coupled with alterations in muscle lipid content, in which the offspring of restricted-fed and overfed ewes had increased lipid content in muscle at birth (Reed et al., 2014). This was maintained to 3 mo of age in offspring of overfed ewes, but reduced compared with control in offspring of restricted-fed ewes (Reed et al., 2014). Similarly, dams who faced reduced nutrient intake (60% of control) during pregnancy produced lambs that were fatter with reduced lean-to-fat ratios (Tygesen et al., 2007). Furthermore, nutrient restriction (40% to 50% of control) during early or late gestation results in fewer muscle fibers in lambs (Costello et al., 2008) and an increased number of glycolytic myofibers (Zhu et al., 2006). Moreover, fetal muscle (gestational day 135) in lambs from obese ewes have decreased diameter of primary muscle fibers and increased collagen content (Huang et al., 2010; Yan et al., 2011), which persist into adulthood (Yan et al., 2011; Huang et al., 2012). In cattle, nutrient restriction (50% of control) during early gestation and midgestation resulted in altered offspring muscle fiber cross-sectional area (Zhu et al., 2004). Overall, poor maternal nutrition during gestation reduces muscle hypertrophy and increases lipid accretion in the offspring.

The phenotypic changes in muscle are often accompanied by changes in gene transcription. Low-protein diets during gestation decreased expression of sirtuin (SIRT)-3, the predominant NAD⁺ deacetylase in mitochondria, in adult male rodent offspring (Claycombe et al., 2015). Reduced SIRT-3 protein in murine mitochondria is associated with the development of insulin resistance (Hirschey et al., 2011), and the absence of SIRT-3 decreased pyruvate dehydrogenase activity, impairing glucose oxidation (Sugden and Holness, 2003). Kalbe et al. (2017) demonstrated decreased mRNA expression of myogenin, insulin-like growth factor (IGF)-1, and IGF-1R in fetal pigs exposed to low-protein maternal diets at day 64 of gestation. These changes in gene expression were identified in the absence of any morphological changes to the muscle. Similarly,

maternal obesity during gestation in ewes impaired myogenesis in the semitendinosus by downregulating myogenic markers including MyoD, myogenin, and desmin in offspring from obese mothers compared with controls at birth (Tong et al., 2009). Gene expression of myogenin, myogenic regulatory factor 4, and creatine kinase was decreased at days 55 and 90 of gestation in fetal offspring of sows fed a high-energy diet during early gestation to midgestation compared with control offspring (Zou et al., 2017). Transcriptome analysis of the semitendinosus muscle within 24 h of birth identified 15 differentially expressed genes between lambs of control-fed and overfed (140% of control) ewes (Hoffman et al., 2016a). Notably, myostatin transcript expression was increased 1.96-fold in offspring of overfed ewes compared with control lambs. Myostatin is a negative regulator of muscle mass and may contribute to the altered body composition observed in these offspring. Expression of peroxisome proliferator-activated receptor (PPAR)- γ coactivator-1 α (PGC-1 α , a master regulator of mitochondrial biogenesis) was decreased 2.31-fold in lambs of overfed ewes compared with control lambs. This may indicate that maternal overfeeding during gestation contributes to alterations in offspring muscle metabolism. Together, these data suggest that poor maternal diet (overfeeding and restricted-feeding) may alter muscle morphology, gene transcription, and mitochondrial function.

In addition to changes in phenotype and gene transcription, poor maternal nutrition during gestation can alter muscle metabolism, much of which, to date, has been associated with mitochondrial number and/or function. Importantly, skeletal muscle hypertrophy is associated with increased mitochondrial function and biogenesis, suggesting that appropriate mitochondrial function is critical for optimal muscle growth and metabolism. Specifically, increased mitochondrial DNA (mtDNA) copy number, mitochondrial mass, and mitochondrial respiration have been demonstrated during the differentiation of C2C12 myoblasts (Remels et al., 2010). Furthermore, inhibiting mitochondrial function impairs myoblast differentiation (Rochard et al., 2000). Thus, it is reasonable to consider changes in mitochondrial mass and/or function as a potential contributor to altered muscle development in offspring exposed to poor maternal nutrition. In support of this, offspring of sows fed obesogenic diets had reduced mtDNA copy number, coupled with decreased gene expression of PGC-1 α , SIRT-1, nuclear respiratory factor (NRF)-1, mitochondrial transcription factor a (TFAM),

cytochrome c, and citrate synthase compared with offspring of control-fed sows (Zou et al., 2017). Gene expression of γ DNA polymerase and single-strand DNA binding protein (SSBP1), which are responsible for mtDNA replication, was also decreased. Similarly, in adult male rats of dams fed high-fat diets during gestation, TFAM and NRF-1, mtDNA copy number, and gene expression for mitochondrial respiratory complexes I, II, III, IV, and V were decreased compared with control offspring (Pileggi et al., 2016). Furthermore, the functional capacity of complex I + III was reduced in offspring of high-fat-fed dams, demonstrating that mitochondrial mass and function were altered in these animals. In contrast, male offspring of rats fed a low-protein diet during gestation had similar mitochondrial number and PGC-1 α mRNA expression compared with offspring of control rats (Claycombe et al., 2015). However, the low-protein diet during gestation decreased state 3 and state 4 mitochondrial respiration and decreased expression of SIRT-3 mRNA, suggesting that despite similar mitochondrial mass, there were negative changes to mitochondrial function as a result of poor maternal diet during gestation. Similarly, restricted-feeding (50% of control) during late gestation resulted in no observed difference in mitochondrial density, but decreased VO_{2max} , state 4 respiration, and respiratory coupling ratio in ovine offspring muscle at 24 mo of age (Jørgensen et al., 2009).

Changes at the cellular level in muscle are very likely reflected in whole-body metabolism and growth efficiency. Residual feed intake (RFI) is defined as the difference between the actual feed intake and the predicted feed intake of each animal, and is phenotypically independent of growth rate (Herd and Arthur, 2009). Low RFI indicates increased feed efficiency; that is, an animal that requires fewer nutritional inputs to achieve similar growth. Importantly, sheep with low RFI reach similar final BW and have similar ADG but have reduced DMI (Zhang et al., 2017) compared with sheep with high RFI. Less-efficient animals tend to have increased adiposity (mainly backfat) and leptin concentrations, and decreased markers of protein accretion, such as urea and creatinine (reviewed in Herd and Arthur, 2009). These changes are similar to the differences in phenotype resulting from poor maternal nutrition, suggesting that offspring of poorly nourished animals may be less efficient (greater RFI). However, there are limited data available assessing the effects of poor maternal diet on offspring RFI. Offspring of primiparous beef heifers supplemented with

rumen-undegraded protein during late gestation demonstrated decreased RFI (increased efficiency) compared with offspring of unsupplemented dams during the feedlot period (Summers et al., 2015). However, Meyer et al. (2014) found no differences in RFI, DMI, G:F, or ADG during finishing in steers or heifers born to cows that were nutrient restricted (70% of control) during early gestation and midgestation. Similarly, late gestational protein supplementation did not affect heifer or steer offspring ADG or G:F in the feedlot (Stalker et al., 2006; Martin et al., 2007). In sheep fed adequate concentrations of selenium, increased nutrient intake (140% of control) during midgestation and late gestation in the dam tended to decrease ADG and G:F of the offspring on growing and finishing diets (Neville et al., 2010). However, many of the studies have assessed feed efficiency during the finishing phase, when animals have had opportunities for compensatory growth. To our knowledge, there has been no measurement of RFI in early postnatal growth in lambs as a result of poor maternal diet, nor has RFI been investigated in the F2 generation. This is a critical period of growth for market lambs, and one which often requires significant producer input in the form of feed costs.

Adipose

Using livestock, human, and rodent models, it has been well established that poor maternal nutrition during gestation leads to increased adipose tissue and often obesity later in life. Although adequate amounts of intramuscular fat are desirable for meat products, excess subcutaneous fat is not desirable and associated with negative metabolic consequences. Specifically, high-fat diets fed to ewes increased subcutaneous fat 100% in lambs at birth (Ford et al., 2009). Similarly, maternal obesity in sheep increased perirenal, omental, and subcutaneous adipose in adult offspring (Long et al., 2015). The negative effects of maternal diet on offspring fat deposition can have multigenerational effects as demonstrated by Shasa et al. (2015) in which granddaughters of obese ewes, even when F1 were fed a control diet, had increased adipose at birth and throughout life. Several studies using an over nutrition model in sheep did not observe an effect during fetal and early postnatal growth (Meyer et al., 2010; Hoffman et al., 2014, 2016a; Kleemann et al., 2015; Pillai et al., 2017), suggesting that there are potential metabolic changes in the offspring that make them more susceptible to fat deposition as an adult. This can have negative impacts on product quality,

animal health, and animal reproduction. The effect of maternal nutrient restriction during gestation on offspring adipose is variable and depends on age of offspring. Maternal nutrient restriction (60% to 70% of control) reduces offspring adipose at early age (birth to 3 mo; Meyer et al., 2010; Hoffman et al., 2014, 2016a; Kleemann et al., 2015). However, when followed to maturity, increased subcutaneous and carcass fat are observed (Ford et al., 2007). Wallace et al. (2015) demonstrated altered mRNA expression in offspring perirenal adipose beginning at midgestation in restricted-fed ewes. This is consistent with the thrifty phenotype hypothesis in which offspring from nutrient-restricted mothers are programmed during gestation to survive in a similar nutrient-restricted environment (Hales and Barker, 2001). However, if these offspring are then provided adequate or ad libitum feed, they are likely to develop increased deposition of adipose and/or obesity. Again, these studies confirm that poor maternal nutrition, both restricted-feeding and overfeeding, leads to increased adipose in offspring, and these changes are often associated with metabolic dysregulation such as altered glucose, insulin, and leptin, which are discussed later in this review.

Liver

Despite its critical role in the regulation of growth and metabolism, as it is not a primary product for consumption, the liver has not been as well studied as muscle in livestock species as other tissues. The effects of nutrient restriction on fetal liver size are variable depending on the severity and length of restriction. For example, in cattle, nutrient restriction (60% of control) during the first one-half of gestation decreased liver size in mothers (Camacho et al., 2014), whereas realimentation later in gestation increased offspring liver size (Prezotto et al., 2016). However, maternal nutrient restriction and realimentation did not affect offspring liver oxygen consumption (Prezotto et al., 2016). In sheep, nutrient restriction (60% of control) beginning at day 30 of gestation increased liver size in offspring at day 45 of gestation, but was similar mass to controls at birth (Pillai et al., 2017). It is well established that during postnatal growth and adulthood, obesity and metabolic disorders lead to increased lipid and collagen accumulation in the liver in multiple species, including sheep, humans, and rodents (Brighenti et al., 2011; Hyatt et al., 2011; George et al., 2012). Fifty percent nutrient restriction during early gestation leads to obesity, greater liver triglyceride accumulation, and increased expression of

fatty acid oxidation genes, PPAR- γ and PGC-1 α in sheep (Hyatt et al., 2011). These findings demonstrate a negative effect of poor maternal nutrition during gestation on offspring liver growth and metabolism. Postnatally, maternal nutrient restriction (50% of control) has been shown to increase liver size in adult males, but reduce mRNA expression of growth hormone (GH) receptor, which is critical for optimal animal growth (Hyatt et al., 2011). Overfeeding ewes during gestation decreased expression of IGF-IR and insulin receptor in offspring liver during postnatal growth (Peel et al., 2012). Changes in liver size, growth factors, and metabolic function of offspring could alter gluconeogenesis and fatty acid oxidation leading to altered metabolism and impair growth and health. In fetal sheep, nutrient restriction (50% of control) of the mother reduced phosphoenolpyruvate carboxykinase (PEPCK) mRNA, the rate-controlling enzyme in gluconeogenesis, but did not alter expression later in life (Poore et al., 2014). However, nutrient restriction during early gestation increased the capacity for glucose production, demonstrated by increased PEPCK in aged ewes, increased feed intake and BW gain, and decreased insulin sensitivity (George et al., 2012). In addition, these aged offspring had increased hepatic lipid and glycogen content. The authors concluded that these offspring may be programmed for metabolic thriftiness, but are prone to overeating and metabolic dysregulation when fed according to guidelines. Further studies are needed to elucidate the mechanisms by which poor maternal diet programs the offspring liver metabolism and long-term consequences of altered liver function.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) are the key progenitor cells for several tissues including bone, muscle, and adipose. There is evidence that factors, such as maternal diet, negatively affect MSC metabolism and function (e.g., proliferation and differentiation; Boyle et al., 2016, 2017; Pillai et al., 2016), which are implicated in increased obesity or incidence of osteoporosis (Devlin and Bouxsein, 2012; Chen et al., 2016b). Mesenchymal stem cells are multipotent stem cells found in the bone marrow, as well as other tissues, including adipose. Mesenchymal stem cells can differentiate into several tissue-specific cell types of mesenchyme origin including bone, adipose, muscle, and cartilage. Therefore, these cells are critical for tissue growth, maintenance, and repair from fetal development through adulthood. Mesenchymal stem cells are key components of the bone marrow

niche, which is responsive to hormonal and metabolic changes in the whole body (Reagan and Rosen, 2016). In addition, there is evidence that factors, such as maternal diet, may cause MSC to favor differentiation into one lineage (adipose) vs. another (bone) contributing to obesity and/or bone loss (Devlin and Bouxsein, 2012). This diversion could be a potential mechanism by which poor maternal diet alters offspring growth and body composition (e.g., muscle, bone, and adipose; Devlin and Bouxsein, 2012) and metabolism. In offspring from both restricted-fed (60% of control) and overfed (140% of control) ewes during gestation, MSC proliferation was reduced by 50% (Pillai et al., 2016). In addition, MSC mitochondrial basal respiration and ATP production were decreased, suggesting a decreased basal metabolic activity. Maximal respiration and spare respiratory capacity were reduced in offspring from overfed ewes, and maximal respiration was reduced in offspring of restricted-fed ewes (Pillai et al., 2016). This suggests that the poor maternal diet restricts the ability of MSC to upregulate oxidative phosphorylation to meet any increase in energy demands. These findings demonstrate that poor maternal nutrition reduces mitochondrial function in MSC of offspring. In humans, maternal obesity during gestation altered Wnt-beta-catenin signaling, causes MSC metabolic perturbation, and stimulates hypermethylation of factors involved in fatty acid oxidation in umbilical cord MSC, which was correlated with increased infant adiposity (Boyle et al., 2016, 2017). Similarly, Chen et al. (2016a) demonstrated reduced osteogenic potential, increased cell senescence signaling, decreased glucose metabolism, and insulin resistance in human umbilical cord MSC from obese mothers. In the case of intrauterine growth retardation (IUGR) in rats, bone marrow MSC demonstrated increased adipogenic profile including increased expression of genes and proteins involved in adipogenesis (Gong et al., 2016). The negative effects of maternal diet on offspring MSC metabolism probably contribute to reduced cell function and metabolism, thereby impairing long-term tissue growth and overall metabolism in offspring. This can have negative implications in livestock growth, muscle development, and adipose deposition in livestock species as well.

OFFSPRING CIRCULATING GROWTH AND METABOLIC FACTORS

Several proteins in the circulation and local growth factors, including the GH/IGF axis, insulin, and leptin, have been associated with altered growth and metabolism of offspring from mothers

consuming a poor diet during gestation. As described earlier, poor maternal nutrition results in alterations in protein and adipose accumulation, as well as changes in metabolic hormone secretion and sensitivity in the offspring.

Leptin is a hormone secreted by white adipose tissue involved in energy homeostasis, insulin sensitivity, and appetite regulation (Dube et al., 2007). We and others have reported increased circulating concentrations of leptin in offspring from poorly fed dams during gestation, suggesting hyperleptinemia and reduction in leptin sensitivity (Krechowec et al., 2006; Muñoz et al., 2009; Long et al., 2010; Hoffman et al., 2016b). However, leptin concentrations in offspring from restricted-fed sows were not different at 120, 180, or 290 d of age (Barbero et al., 2014). These apparent conflicting results may be due to species differences or due to the timing of sampling. For example, Long et al. (2011) reported that feeding an obesogenic diet before conception can reduce the early postpartum (days 6 to 9 of age) leptin surge in offspring of overfed ewes. The reduction in this early postpartum leptin surge is maintained in F2 lambs, even though F1 animals were fed a control diet (Shasa et al., 2015). Given that the reduction in the postpartum leptin surge is preceded by an increase in cortisol concentrations at birth in offspring from overfed ewes, Shasa et al. (2015) hypothesized that this increase in cortisol at birth is, in part, responsible for the lack of the postpartum leptin surge. More recently, Lewis et al. (2019) demonstrated that administration of exogenous glucocorticoids to pregnant cattle suppresses neonatal leptin in calves. Therefore, poor maternal nutrition during gestation may predispose these offspring to obesity later in life, and for multiple generations, due to altered temporal changes in circulating leptin.

Poor maternal nutrition has been shown to alter circulating concentrations of glucose and/or insulin as well as increase insulin resistance in the offspring (Wu et al., 2012). Specifically, we reported increased circulating concentrations of insulin, as well as, increased insulin:glucose in offspring born to both restricted-fed and overfed ewers during early postnatal growth (Hoffman et al., 2016a). In agreement with our data, Long et al. (2015) reported reduced insulin and increased glucose concentrations in lambs born to overfed ewes following glucose tolerance tests. Similar to leptin, differences in insulin, glucose, and cortisol concentrations were observed in the very early postpartum period (before day 3 of age) in F2 lambs born to grand dams fed an obesogenic diet (Shasa et al., 2015). Similar

to leptin, alterations in insulin sensitivity due to maternal diet may be multigenerational influencing the F1 and F2 generation (Tarry-Adkins et al., 2018). These data, as well as findings from other species, demonstrate that maternal diet during gestation can lead to hyperglycemia, hyperinsulinemia, and insulin resistance in offspring.

The somatotrophic axis, including GH, IGF-I and -II, and IGF binding protein (IGFBP)-1 to -6, have important roles in growth and development (LeRoith, 2000). In addition, circulation concentrations of these hormones are responsive to alterations in nutritional status (Bauer et al., 1998) and may be predictive of nutritional status (Freake et al., 2001). For example, in poorly fed individuals, GH and IGFBP-2 increase, whereas IGF-I and IGFBP-3 decline (Breier, 1999; Harrell et al., 1999; Rausch et al., 2002). Therefore, to investigate the potential role of the somatotrophic axis in growth and development of offspring born to poorly nourished dams, we and others have quantified components of the somatotrophic axis during postnatal growth of the offspring in livestock (Bauer et al., 1995; Rehfeldt et al., 2004; Hoffman et al., 2014) and rodents (George et al., 2012; Sferruzzi-Perri, 2018). Similar to the changes in nutritional status, we reported reduced concentrations of IGF-I and IGFBP-3 that were associated with reduced BW in offspring born to restricted-fed mothers (Hoffman et al., 2014). However, increased concentrations of IGF-I and IGFBP-3 were associated with increased BW of lambs born to overfed ewes (Hoffman et al., 2016a). As hypothesized by Sferruzzi-Perri (2018), the role of the somatotrophic axis in fetal and postnatal development in the offspring of poorly nourished dams may be related to the regulation of resource allocation during gestation across the placenta.

These changes in concentrations and sensitivity of these circulating factors are evidence of developmental programming in the offspring born to poorly nourished dams that can alter growth and metabolic activity during postnatal development of the offspring. Additional circulating factors may be altered in the prenatal and postnatal period that can cause long-term negative postnatal development in the offspring and across multiple generations.

CONCLUSION

Poor maternal nutrition during gestation, both restricted-feeding and overfeeding, negatively affect multiple systems in offspring such as organ and tissue growth, local and systemic metabolism, and

ultimately product quality and health of offspring. Therefore, a whole systems approach is needed to fully understand the impact of maternal diet on offspring prenatal and postnatal growth and metabolism. In addition, identification of local and systemic factors at both the protein and metabolic levels will allow for the identification of novel management practices to alleviate the effects of poor maternal nutrition and/or improve growth and metabolism in offspring. Based on the evidence of multigenerational impacts, additional studies to further characterize epigenetic regulation and impacts on future generations of both males and females are critical to improve the efficiency of production, product quality, and animal welfare.

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