

## BOARD INVITED REVIEW

# Maternal periconceptual nutrition, early pregnancy, and developmental outcomes in beef cattle

Joel S. Caton,<sup>†,1</sup> Matthew S. Crouse,<sup>‡</sup> Kyle J. McLean,<sup>||</sup> Carl R. Dahlen,<sup>†</sup>  
Alison K. Ward,<sup>†</sup> Robert A. Cushman,<sup>‡</sup> Anna T. Grazul-Bilska,<sup>†</sup>  
Bryan W. Neville,<sup>§</sup> Pawel P. Borowicz,<sup>†</sup> and Lawrence P. Reynolds<sup>†</sup>

<sup>†</sup>Center for Nutrition and Pregnancy, and Department of Animal Sciences, North Dakota State University, Fargo, ND 58108-6050, <sup>‡</sup>USDA, ARS, U.S. Meat Animal Research Center, Clay Center, NE 68933, <sup>||</sup>Department of Animal Science, University of Tennessee, Knoxville, TN 37996, <sup>§</sup>Carrington Research Extension Center, Carrington, ND 58421

<sup>1</sup>Corresponding author: [joel.caton@ndsu.edu](mailto:joel.caton@ndsu.edu)

ORCID numbers: 0000-0003-4579-2737 (M. S. Crouse); 0000-0002-4556-4315 (C. R. Dahlen).

## Abstract

The focus of this review is maternal nutrition during the periconceptual period and offspring developmental outcomes in beef cattle, with an emphasis on the first 50 d of gestation, which represents the embryonic period. Animal agriculture in general, and specifically the beef cattle industry, currently faces immense challenges. The world needs to significantly increase its output of animal food products by 2050 and beyond to meet the food security and agricultural sustainability needs of the rapidly growing human population. Consequently, efficient and sustainable approaches to livestock production are essential. Maternal nutritional status is a major factor that leads to developmental programming of offspring outcomes. Developmental programming refers to the influence of pre- and postnatal factors, such as inappropriate maternal nutrition, that affect growth and development and result in long-term consequences for health and productivity of the offspring. In this review, we discuss recent studies in which we and others have addressed the questions, “Is development programmed periconceptually?” and, if so, “Does it matter practically to the offspring in production settings?” The reviewed studies have demonstrated that the periconceptual period is important not only for pregnancy establishment but also may be a critical period during which fetal, placental, and potentially postnatal development and function are programmed. The evidence for fetal and placental programming during the periconceptual period is strong and implies that research efforts to mitigate the negative and foster the positive benefits of developmental programming need to include robust investigative efforts during the periconceptual period to better understand the implications for life-long health and productivity.

**Key words:** developmental programming, early pregnancy, maternal nutrition, offspring outcomes, periconceptual period

## Introduction

Animal agriculture faces immense challenges. The Food and Agricultural Organization of the United Nations (FAO) reports that livestock contribute 15% of total food energy, 25% of dietary protein, and provide essential micronutrients not easily

obtained from plant-based food products (FAO, 2018). Production of animals for food and fiber is a multi-billion-dollar industry in the U.S. alone. Currently, livestock contribute to 40% of the global value of agricultural production and support the livelihoods and food security of over 1.3 billion people (FAO, 2018). However,

**Abbreviations**

ADG	average daily gain
IFN- $\tau$	interferon- $\tau$
IVF	in vitro fertilization
NADPH	nicotinamide adenine dinucleotide phosphate
NASEM	National Academies of Science Engineering and Medicine
PGF2 $\alpha$	prostaglandin F2 $\alpha$

the world needs to significantly increase its output of meats by 2050 and beyond to meet the projected requirements of the rapidly growing population (Elliot, 2013; FAO, 2018). Additionally, livestock are critical components of sustainable agricultural systems (Lardy and Caton, 2012; Reynolds et al., 2015b). Consequently, efficient and sustainable approaches to livestock production are essential to food security and agricultural sustainability in humans.

Feed costs are the largest economic burden for beef cattle producers. For beef cattle, more feed resources are dedicated to the parent population (cow herd) than to market-bound offspring (Webster, 1989). In mature beef cows, ~70% of dietary energy is consumed by maintenance functions (Jenkins and Ferrell, 1983; Ferrell and Jenkins, 1985; Ferrell, 1988; NASEM, 2016). Maintenance energy is consumed extensively by visceral tissues and muscle (Ferrell, 1988; Baldwin and Donovan, 1998; Caton et al., 2000). Small changes in efficiency of energy use for maintenance equate to considerable energy savings and represent opportunities for enhanced production efficiencies (NASEM, 2016).

Metabolically and otherwise compromised animals are major detriments to efficient and sustainable livestock production systems (Reynolds and Caton, 2012). Muscle and visceral tissues are key drivers of efficient utilization of feedstuffs. Furthermore, efficient reproductive outcomes are critical to successful production systems. Therefore, improvements in fetal development that lead to enhanced efficiency of feed use and improved reproductive outcomes postnatally would have a significant impact on the competitiveness, sustainability, and profitability of animal agriculture in the United States and elsewhere.

The concept of developmental programming, sometimes referred to as fetal programming, is the idea that maternal stress, particularly nutritional stress in this case, during critical windows of development can have short- and long-term consequences for the offspring. This concept arose about 30 years ago based on human epidemiological studies (Barker, 1992, 2004). Developmental programming occurs during normal developmental process and during times of stress, like inappropriate maternal nutrition, the consequences can be negative developmental outcomes. However, programmed events can also hold positive outcomes for offspring by preparing them for the postnatal environment they will encounter after parturition. Research with various animal models, including livestock, has confirmed the occurrence of developmental programming, with consequences for the offspring likely being greater than previously thought (Wu et al., 2006; Caton and Hess, 2010; Funston et al., 2012; Reynolds and Caton, 2012; Vonnahme et al., 2013; Cushman et al., 2016; Greenwood et al., 2017; Hoffman et al., 2017; Reynolds et al., 2017, 2019; Caton et al., 2019; Cushman and Perry, 2019).

Ruminants (cattle, sheep, deer, goats, giraffes, and their relatives) develop primarily within extensive grazing systems,

which, by their very nature, provide wide seasonal variations in nutrient quantity and quality (NASEM, 2016). Beef cattle, sheep, and other domesticated and wild ruminants often experience a poor or compromised nutritional environment during gestation (Krysl et al., 1987; Wu et al., 2006; NASEM, 2016; Caton et al., 2019). Consequently, the offspring from dams experiencing compromised nutrition may exhibit altered metabolic, energetic, and body composition outcomes at various points during their postnatal growth curves (Du et al., 2017; Greenwood et al., 2017; Reed and Govoni, 2017; Reynolds and Vonnahme, 2017; Caton et al., 2019).

Evidence suggests that biological mechanisms regulating normal growth, development, and nutrient utilization are programmed in utero and affect postnatal growth and physiological function into adulthood (Godfrey and Barker, 2000). Perturbed maternal nutrition during critical windows of time during gestation may negatively affect fetal growth and development through epigenetic modifications such as altered patterns of DNA methylation and histone modifications that ultimately lead to impaired growth and metabolism of the conceptus (Wu et al., 2006; Caton and Hess, 2010; Meyer et al., 2012; Greenwood et al., 2017; Hoffman et al., 2017; Reynolds et al., 2017, 2019).

Interactions between the developing mammalian embryo or fetus and its environment involve the process of developmental plasticity (Gluckman et al., 2005). Developmental plasticity is defined as a process that evolved to adjust the pattern of development such that a phenotype is produced that is matched to the anticipated environment (West-Eberhard, 2005). However, when the prediction of the future environment is inaccurate, or when the environment changes between generations, a mismatched phenotype may result, and the consequences of developmental plasticity may be maladaptive (Bateson et al., 2004). Thus, the maternal environment during pregnancy can have a large impact on fetal development that leads to subsequent impacts on postnatal growth and production efficiency of the offspring.

Most of the research investigating developmental programming in ruminants has focused on the last two-thirds of gestation. A smaller set of published literature focuses on initiation of maternal nutritional treatments and developmental programming paradigms between days 30 and 60 of gestation; however, these nutritional treatments are initiated after pregnancy is confirmed and therefore misses a critical window of programming. Detailed studies investigating developmental programming in response to maternal nutritional challenges during the periconceptual period, including very early pregnancy (days 0 to 50 or so; the embryonic period), are limited (Crouse et al., 2016ab; McLean et al., 2016ab; Copping et al., 2020) and thereby create a critical research need, which our laboratories have been addressing (Crouse et al., 2016a, b, 2017, 2019a, b,c,d, 2020b,c; Greseth et al., 2017; McLean et al., 2017a, b, 2018; Diniz et al., 2020; Menezes et al., 2020).

The periconceptual period has been defined differently depending upon species and research group (Padhee et al., 2015; Van Eetvelde et al., 2017; Velazquez et al., 2019; Copping et al., 2020). In essence, the periconceptual period is the time immediately preceding and after conception. Broad definitions in ruminants usually range from around 60 d pre- to 60 d postbreeding, with numerous variations within these ranges. During the periconceptual period, the conceptus is influenced by both maternal (ovarian, oviductal, uterine, and developing placenta) and paternal (testicular and seminal fluid) nutrient supplies and other factors including metabolic substrates such

as those in seminal, oviductal, and uterine fluids. The focus of this review is on maternal nutrient supply to the conceptus during the periconceptual period and its influence on outcomes in the developing offspring, with an emphasis on the first 50 d of gestation; that is, the embryonic period, in beef cattle.

## Maternal Nutrition and Developmental Programming

Maternal nutritional status is a major factor that leads to developmental programming and thereby affects offspring outcomes (Wu et al., 2006; Reynolds et al., 2010b; Funston et al., 2012; Vonnahme et al., 2015; Reynolds and Vonnahme, 2016, 2017; Wallace, 2019). Prenatal growth trajectory is responsive to maternal nutrient intake from the earliest stages of embryonic life, when nutrient requirements for conceptus growth are reported to be negligible (NRC, 1996; Robinson et al., 1999; NRC, 2007; NASEM, 2016). In ruminants, which are grazers/foragers, seasonal changes in forage quantity and quality substantially affect nutrient supply (NASEM, 2016) and contribute to compromised maternal nutrient intake, which is a major contributing factor to developmental programming (Reynolds et al., 2017, 2019). For example, in the Intermountain West and Great Plains of the United States, forage quantity and quality are often severely reduced during pregnancy, which normally occurs in the late summer or fall (Krysl et al., 1987; Cline et al., 2009; NASEM, 2016). In contrast, when livestock are exposed to periods of lush forage growth or when overconsumption occurs, nutritional excess may also result in developmental programming (Wallace et al., 2006; NASEM, 2016; Reynolds et al., 2017, 2019). In addition to general nutrient restriction or excess, specific nutrient imbalances in the maternal diet can also have negative consequences for the developing offspring (Wu et al., 2006; Caton and Hess, 2010; Reynolds and Caton, 2012; Reynolds and Vonnahme, 2017; Reynolds et al., 2019; Wallace et al., 2020). Specifically, maternal selenium supply during gestation can alter offspring small intestinal development during both the fetal and postnatal (days 20 and 180 of life) phases of life (Meyer and Caton, 2016). Protein supply and specific amino acids, like arginine, are also critical to developmental outcomes (Herring et al., 2018; Peine et al., 2018; Prezotto et al., 2018). Because of differential patterns of fetal and placental growth, the effects of compromised maternal nutrition during pregnancy may depend

on the timing, severity, and (or) duration (Caton et al., 2019; Reynolds et al., 2019).

## The Periconceptual Period and Programming of Offspring

Maternal nutrition during the periconceptual period has dramatic effects on fertility and conceptus development. Likewise, a growing body of literature supports the idea that paternal nutrition influences sperm development and seminal fluid composition (Lucas and Watkins, 2017); however, the impacts of paternal nutrition on periconceptual programming of offspring are beyond the scope of this review.

The periconceptual period in cattle and sheep is ~60 d before to 60 d after breeding (Padhee et al., 2015). Inappropriate maternal nutrient supply during the periconceptual period in livestock affects oocyte quality, which is important for fertilization and early embryonic, fetal, and placental development, and consequently, pregnancy outcome and offspring health in various species (Robinson, 1990; Krisher, 2004; Kakar et al., 2005; Kumarasamy et al., 2005; Borowczyk et al., 2006; Grazul-Bilska et al., 2012; Abdelatty et al., 2018). In several studies, the importance of diet and/or body adiposity during the pre- and periconceptual periods in humans and animal models has been clearly documented (Reynolds et al., 2013). For example, both underfeeding and overfeeding of sheep for 60 d before oocyte collection resulted in diminished oocyte quality and lead to decreased fertilization rates with in vitro fertilization (IVF), and subsequently poor embryonic development in vitro to the blastocyst stage (Table 1; Grazul-Bilska et al., 2012). Furthermore, overfed sheep had increased serum insulin, leptin, and progesterone concentrations, whereas underfed sheep had increased serum estradiol but decreased insulin-like growth factor-1, insulin, and leptin concentrations (Grazul-Bilska et al., 2012; Kaminski et al., 2015). Likewise, other studies reported decreased rates of fertilization with IVF and/or decreased rates of early embryonic development for ewes fed a low- (nutrient-restricted) or high- (ad libitum intake) energy diet during the periconceptual period (Papadopoulos et al., 2001; Lozano et al., 2003; Van Eetvelde et al., 2017; Abdelatty et al., 2018; D'Occhio et al., 2019). Conversely, others have shown that an altered plane of nutrition during the periconceptual period

**Table 1.** Effects of maternal under- and over-nutrition of ewes<sup>1</sup> on ADG and total numbers of follicles, oocytes collected, healthy oocytes, cleaved oocytes, morulas, and blastocysts after in vitro fertilization (IVF) and subsequent embryo culture.

Measurement	Maternal treatment <sup>2,3</sup>			SEM	P-value
	Control	Underfed	Overfed		
ADG, kg	-0.02 <sup>a</sup>	-0.24 <sup>b</sup>	0.20 <sup>c</sup>	0.01	0.0001
		Number/Ewe			
Total follicles	27.5	25.8	26.7	2.4	0.638
Total oocytes collected	26.1	23.3	25.9	2.5	0.651
Healthy oocytes	22.5	21.5	24.3	2.3	0.641
Oocytes used for IVF	12.5	13.6	14.7	1.2	0.490
Cleaved oocytes	10.5	6.6	7.5	1.1	0.057
Morulas	6.5 <sup>a</sup>	1.7 <sup>b</sup>	1.7 <sup>b</sup>	0.5	0.0001
Blastocysts	4.2 <sup>a</sup>	0.4 <sup>b</sup>	0.4 <sup>b</sup>	0.2	0.0001

<sup>1</sup>Table modified from Grazul-Bilska et al. (2012).

<sup>2</sup>Control ewes received 760 g/50 kg BW daily (100%; n = 13), underfed ewes received 456 g/50 kg BW daily (60% of control, dry matter basis; n = 17) of controls, and overfed ewes were fed ad libitum (≥200% of control, dry matter basis; n = 18) for 8 wk before oocyte collection.

<sup>3</sup>All values are expressed per ewe.

<sup>a,b</sup>Values are statistically different within a row.

had either positive or no effects on blastocyst formation and/or embryo health in sheep (Kakar et al., 2005), which is likely due to the short duration of nutritional treatments imposed in their studies. Interestingly, pre-mating nutrition altered mRNA expression in oocytes and follicular cells, which may account for reductions in reproductive performance of ewes fed restricted diets (Pisani et al., 2008). Thus, maternal nutrition immediately pre-mating seems to affect developing follicles and oocytes and in addition the processes of fertilization and early embryonic development.

In cows, the effects of diet fed before and during the periconceptual period on oocyte quality, as measured by rates of fertilization with IVF, blastocyst formation in vitro, and cell number per blastocyst, depend on body condition (i.e., adiposity) and diet composition (Adamiak et al., 2006). High maternal dietary intake improved early embryonic development for animals in low body condition but reduced early embryonic development for animals in good body condition (Pisani et al., 2008). Further, hyperinsulinemic cows in good body condition that were fed a high-energy diet produced fewer oocytes and had decreased blastocyst yields after IVF and in vitro culture (Adamiak et al., 2005, 2006). In comparison, lactating dairy cows that are fed a high-protein and high-energy diet are frequently in negative energy balance, which is characterized by low fertility that may be due to low-quality oocytes and embryos (Butler, 2003; Leroy et al., 2008). This long standing inverse relationship between conception rate and milk production is reflective of over a 20% decline in conception rates over time. In addition, in dairy cows, it has been suggested that altered endocrine and metabolic function, as well as genetic factors, may contribute to diminished oocyte and embryo quality (Leroy et al., 2008; Valckx et al., 2012).

### Early Pregnancy, Maternal Nutrition, and Developmental Programming

Early pregnancy is a critical period because of the major developmental events that take place (McLean, 2016; Crouse,

2020), which include embryonic development, physiological responses, organogenesis and formation of a functional placenta. Infertility, or the inability to conceive and maintain a pregnancy, is a major issue in humans and livestock (Reynolds et al., 2010a, b). Infertility primarily results from spontaneous abortion, which amounts to 30% to 70% of fertilized oocytes in humans and 20% to 30% in other mammals (Wilmot et al., 1986; Reynolds and Redmer, 2001; Dixon et al., 2007; Teklenburg et al., 2010). Most embryonic losses occur during the first third of pregnancy in all mammalian species studied, including humans and livestock (Wilmot et al., 1986). In beef heifers, first service conception rates to AI are ~90% (Bridges et al., 2013); however, only 48% remain viable by day 30 of gestation (Reese et al., 2020), and Thatcher et al. (1994) indicated that up to 80% of all embryonic loss in cattle occurs before day 40. Clearly, early pregnancy is a critical period in livestock production, and a better understanding of this critical period represents an opportunity for enhanced livestock production efficiency and, consequently, increased food security and agricultural sustainability for humans.

### Developmental events during the first 50 d of pregnancy

Multiple events must take place during the first 50 d of gestation for successful pregnancy establishment and maintenance, and these events have been previously outlined in reviews and text books (Bazer et al., 2011a, 2011b; Senger, 2012; Rizos et al., 2017; Crouse, 2020). The timeline shown in Figure 1 generally applies to cattle, but a similar timeline also generally applies to sheep (Reynolds et al., 2013). However, a detailed assessment and discussion of the early developmental events is beyond the scope of this review.

Briefly, fertilization of the ovum occurs in the oviductal ampulla, resulting in formation of the zygote. Multiple cell cleavage events take place to form the morula (16- to approximately 64-cell embryo) that enters the uterus on days 3 to 4 of gestation in cattle (McLaren, 1982; Senger, 2012; Rizos et al., 2017; Crouse, 2020). The embryo continues to grow, and

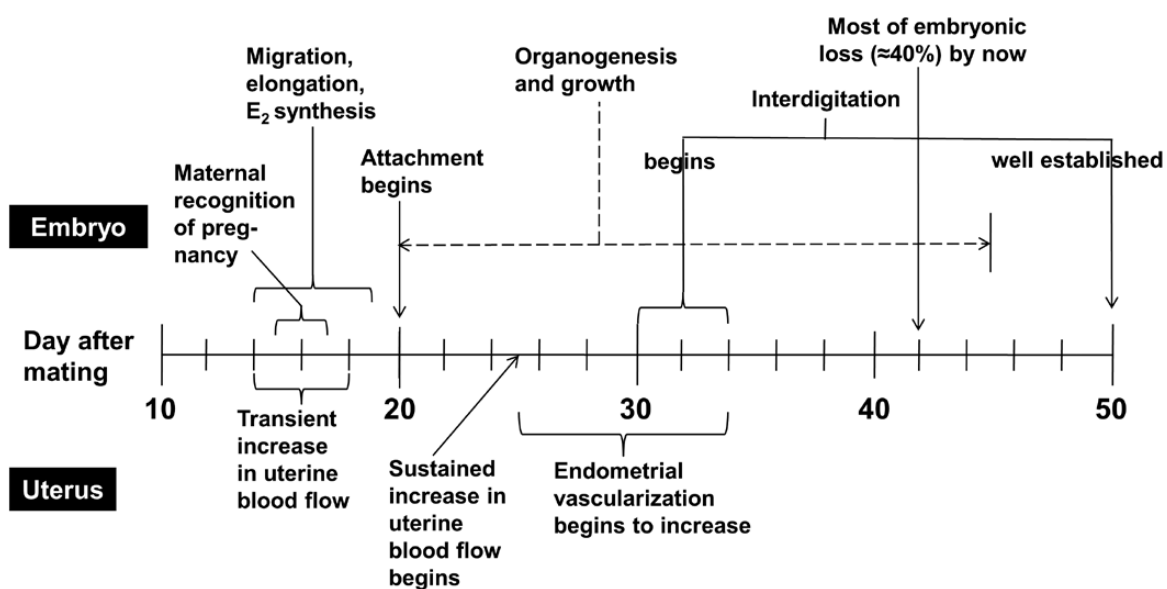


Figure 1. Timeline of placental and embryonic-fetal development during early pregnancy in cattle. Data are taken from Dey et al. (2004), Diskin and Morris (2008), Eley et al. (1983), Ford (1985), Ford et al. (1979; 1981), McLean et al. (2017b), Northey and French (1980), and Winters et al. (1942). For a similar timeline in sheep, see Reynolds et al. (2014).

by days 7 to 8 in cattle further cell divisions form the spherical blastocyst that consists of the inner cell mass (or embryo proper) and the trophoblast (McLaren, 1982; Senger, 2012; Crouse, 2020). The inner cell mass will give rise to the embryo/fetus, and the trophoblast (trophectoderm) will give rise to the placenta (Rowson and Moor, 1966; Bindon, 1971; Wintenberger-Torrés and Fléchon, 1974; Barcroft et al., 1998; Senger, 2012). The blastocyst will then break out of, or “hatch” from, the zona pellucida and subsequently transition from its spherical form by elongation into a filamentous conceptus containing the embryo and the extraembryonic membranes. Elongation of the conceptus, on days 14 to 19 (Figure 1), is important for maternal recognition of pregnancy and subsequent attachment of the developing placenta (chorioallantois) to the uterine luminal epithelium. During this time, the mononucleated trophoctoderm which is in direct contact with the uterine luminal epithelium, begins to release interferon- $\tau$  (IFN- $\tau$ ), which is the maternal recognition of pregnancy signal in ruminants and is secreted in amounts proportional to the size of the trophoctoderm. Successful release of IFN- $\tau$  inhibits upregulation of the uterine oxytocin receptor and silences expression of the genes involved in the pulsatile release of prostaglandin F $2\alpha$  (PGF $2\alpha$ ) that would terminate the pregnancy by causing regression of the corpus luteum and result in decreased production of progesterone to concentrations insufficient to maintain pregnancy (Bazer et al., 1997, 2015; Bazer, 2013). Furthermore, during this time, the placenta continues to develop from the extraembryonic membranes. Initiation of placental development is an obligatory step for the ability of the embryo to attach to and interact with the uterus. Attachment begins around day 20 and interdigitation between days 30 and 35, with both being well established by day 50 of gestation (Figure 1).

Throughout the first 50 d of gestation, the embryo is also growing rapidly. By approximately day 45 of gestation in cattle, organogenesis (development of the fetal organs) is completed for some organs; however, although differentiated, most organ systems like the gastrointestinal system (Noah et al., 2011) or lungs are not completely developed or fully functional. This indicates that during the first 50 d of gestation, the fetal organ systems are growing, developing, and differentiating (Winters et al., 1942; Crouse, 2020), and subsequently mature into functional organ systems throughout the remainder of gestation and into the neonatal period. Fetal organ differentiation follows the steps of: (1) morphogenesis and cell proliferation, (2) cell differentiation, and (3) functional maturation (Colony, 1983). During early pregnancy, these developmental events may not require measurable increases in whole animal energy, or other nutrient, demand to support energy needs of the fetus, as they do in late gestation; however, to complete the growth and differentiation of the embryo and placenta, there are most likely transitory increases in specific nutrient demands that allow for optimal embryonic and early fetal development (Caton et al., 2019), much like there is for folic acid during the periconceptual period in humans.

### Conceptus nutrient supply during the first 50 d of pregnancy

Upon entering the uterine lumen, ruminant embryos receive nutrients through histotrophic secretions, primarily from the uterine glandular epithelium (Crouse, 2016, 2020). Histotroph includes nutrient transport proteins, ions, mitogens, cytokines, lymphokines, enzymes, hormones, growth factors, proteases, protease inhibitors, amino acids, hexoses (such as glucose and fructose), vitamins, and other substances (Bazer et al., 2011a, b; Simintiras et al., 2019a, b). In ruminants, histotroph is essential

for the development of the conceptus and is secreted from glands within the uterine endometrium throughout pregnancy (Bazer, 1975; Gray et al., 2001; Martins et al., 2018; Simintiras et al., 2019a). The uterine endometrium of cattle contains multiple aglandular, caruncular areas that are highly vascular stromal areas covered by a simple luminal epithelium, as well as intercaruncular areas that contain the endometrial glands (Filant and Spencer, 2013).

In a cross section of the uterine wall, many hundreds of glands in the intercaruncular areas of the endometrium can be observed (Filant and Spencer, 2013). These glands begin to develop as invaginations of the luminal epithelium that progressively invade the stroma and result in an extensive network of epithelial glands (Filant and Spencer, 2013). If these glands do not develop, the conceptus will not receive sufficient histotroph for growth and elongation, resulting in insufficient secretion of IFN- $\tau$  to maintain pregnancy (Binelli et al., 2001; Rizo et al., 2012). A uterine gland knockout model (Bartol et al., 1988a, b) established that insufficient IFN- $\tau$  results in a failure to inhibit upregulation of the uterine oxytocin receptor, resulting in lysis of the corpus luteum by PGF $2\alpha$  and termination of pregnancy. Knockdown of uterine glandular development in sheep resulted in infertility, and although blastocysts were normal on day 9 after fertilization, conceptuses were severely growth-retarded by day 12 or 14 of gestation (Filant and Spencer, 2013). This lack of conceptus elongation is thought to result primarily from the absence of histotrophic secretions into the uterine lumen from the glandular epithelium (Gray et al., 2001, 2002), and thus suggests the importance of histotrophic nutrition to the growth and elongation of the conceptus and the subsequent importance of conceptus elongation to the maintenance of pregnancy. Furthermore, Martins et al. (2018) clearly demonstrated that perturbations in the uterine histotroph were detrimental to the establishment of pregnancy in cattle. Additional research demonstrated that the proteome profile of uterine histotroph is significantly altered by isocaloric maternal diets supplement with fat or protein in beef cattle (Harlow et al., 2018). Specifically, Harlow et al. (2018) reported that prebreeding supplement fat resulted in the greatest proteome responses with the extracellular exosome and cell to cell adhesions functional categories being highly enriched. They also reported that the categories of energy generation, protein stabilization, antioxidants, and protease inhibitors were enhanced.

### Uterine Luminal Fluid (Histotroph)

Early studies of uterine luminal fluid (histotroph) reported increased reducing sugars (i.e., monosaccharides) and free amino acids throughout the estrous cycle compared with maternal blood (Olds and Vandemark, 1957; Fahning et al., 1967). Although Ford et al. (1979) demonstrated increases in uterine blood flow during the estrous cycle in beef cows, Fahning et al. (1967) showed that the content of uterine fluid was not correlated to that of the maternal blood. Studies by multiple research groups have demonstrated that histotrophic secretions are regulated and subject to the hormonal control of the endometrial glands, as described briefly below. It should be noted, however, that although the content of histotroph appears independent of maternal blood, the nutrients secreted in histotroph originate from the maternal nutrient supply, which suggests metabolism by the uterus or metabolism by enzymes contained in histotroph.

As previously described, histotroph must be secreted from the uterine glands, and as such, specific nutrient transporters

of the solute carrier family (He et al., 2009) are present to transport histotroph into the uterine lumen. The uterine glands are stimulated to secrete histotroph by progesterone and IFN- $\tau$ . Comparisons of data for pregnant vs. cyclic ewes determined temporal, progesterone, and IFN- $\tau$  effects on hexose and amino acid transporters as well as concentrations of hexoses and amino acids in utero-placental tissues and fluids throughout the peri-implantation period (Gao et al., 2009abc), and as reviewed by Bazer et al. (2011b).

Characterization of the proteins, amino acids, and hexoses present in histotroph throughout early pregnancy in beef cows shows similarities to that of the ovine model and supports previous data from Fahning et al. (1967). These data have elucidated temporal changes in uterine secretions throughout the periconceptual period of gestation in cattle. For example, proteomic analysis of uterine fluid in cyclic dairy heifers on days 7 and 13 of the estrous cycle showed increases in copper amine oxidase, catalase, and superoxide dismutase, suggesting that a continual increase in the redox potential throughout early gestation until gas exchange can be established with formation of a functional placenta (Mullen et al., 2012). Forde et al. (2014) compared amino acid profiles of histotroph in pregnant vs. cyclic crossbred cows from days 7 to 19 of the estrous cycle (nonpregnant) or postinsemination (pregnant), and demonstrated temporal changes to amino acid abundance in the uterine secretions of both pregnant and cyclic cows as well as progesterone-induced changes in expression of amino acid transporters. Interestingly, circulating concentrations of arginine and methionine were decreased in the pregnant compared with the cyclic heifers from days 7 to 16. By day 19 of gestation, 11 out of 18 amino acids measured temporally increased (Forde et al., 2014), which further exemplifies the increased and transitory nutrient demands for the rapid growth of the placenta and fetus during early pregnancy (Negrin Pereira et al., 2017).

### Uterine nutrient transport

We developed a standing flank ovariohysterectomy procedure (McLean et al., 2017a) to investigate the temporal effects of gestation in Angus-cross beef heifers on the expression of nutrient transporters and retroviruses involved in the formation of the ruminant placenta on day 16, 22, 28, 34, 40, or 50 of pregnancy (Crouse et al., 2016b). From these data, we selected days 16, 34, and 50 of gestation for further investigation because these days exhibited the greatest transcript abundance of multiple target genes in utero-placental tissues. When evaluating these days of gestation further, they coincided with key developmental time frames. In the bovine, day 16 is the time of maternal recognition of pregnancy (Northey and French, 1980; Thatcher et al., 1994), which, as described earlier, involves rapid placental growth and elongation and secretion of anti-luteolytic molecules. By day 34 of gestation, embryonic organogenesis is well underway, with differentiation and further organization of the conceptus organs and tissues and development of the limbs (Winters et al., 1942). Furthermore, by days 45 to 50 of gestation, the conceptus has developed all of its organ systems and is deemed a fetus (Negrin Pereira et al., 2017; C. R. Dahlen, N. Negrin Pereira, P. P. Borowicz, J. S. Caton, M. S. Crouse, K. J. McLean, X. Sun, A. K. Ward, and L. P. Reynolds, unpublished data). Although not yet fully functional, all fetal organs are present by day 50 and will continue to mature into functional organ systems as gestation progresses.

Based on previous work (Arias et al., 2012, 2013; Lake et al., 2013), we imposed nutritional treatments on heifers immediately post-insemination such that they gained 0.51 kg/d

(CON) or maintained (average daily gain, ADG = -0.08 kg/d; restricted, RES) body weight through day 50 of gestation. Data from these studies were interpreted to imply that although a moderate maternal nutritional restriction was imposed upon beef heifers from breeding to day 50 of gestation, placental mRNA expression of specific hexose and amino acid transporters were regulated temporally, with only a small effect of maternal nutrition on their expression (Crouse et al., 2017; Greseth et al., 2017). Evaluations of transporter abundance using immunofluorescence and image analysis clearly demonstrated that moderate maternal nutrient restriction reduced neutral amino acid transporters in utero-placental tissues during the first 50 d of pregnancy (Table 2; Crouse et al., 2020b).

### Histotrophic nutrient supply

Data from the same study further demonstrated temporal changes in abundance of amino acids and hexoses in histotroph, allantoic, and amniotic fluids. In histotroph, concentrations of fructose and 7 (alanine, glutamate, histidine, leucine, lysine, methionine, proline, and valine) of 20 amino acids measured increased as gestation progressed (Crouse et al., 2019d). In allantoic fluid, concentrations of aspartate were less ( $P = 0.03$ ) and glucose, cystine, glutamine, glycine, histidine, and methionine tended ( $P = 0.11$ ) to be less in heifers that were nutrient restricted compared with controls. Temporal changes were also observed in allantoic fluid with concentrations of glucose, asparagine, leucine, isoleucine, phenylalanine, and tryptophan decreasing, and ornithine, asparagine, citrulline, and glycine increasing from days 34 to 50 of gestation in beef heifers. Moreover, in follow-up work, Menezes et al. (2020) reported that concentrations of glutamine, cystine, arginine, and aspartate in allantoic fluid were increased at day 84 of gestation in heifers on a moderate rate of gain (0.79 kg/d) compared with those on a low rate of gain (0.28 kg/d). In amniotic fluid (Crouse et al., 2019d), 14 of 20 measured amino acids decreased from days 34 to 50 of gestation in beef heifers; however, glucose and fructose were decreased in the restricted compared with control heifers. In heifers receiving the restricted diet compared with the controls, only serine, glycine, and threonine were less (Crouse et al., 2019d). Also, by day 50, glucose, fructose, and methionine were decreased in fetal fluids, and homocysteine was increased in serum of restricted heifers (Figure 2; Caton et al., 2019; Crouse et al., 2019d).

Simintiras et al. (2019b) investigated the metabolome of bovine uterine luminal flushes (histotroph) on days 12, 13, and 14 postinsemination in a normal or high progesterone group (progesterone-releasing intravaginal device inserted day 3 postestrus and remained until sample collection) to test temporal and hormonal effects on the uterine luminal fluid metabolome. An increase in concentrations of fructose and mannitol/sorbitol of the normal vs. high progesterone cows and on day 14 compared with day 12 of the estrous cycle was noted. Furthermore, the most enriched nutrients and pathways affected by a progesterone  $\times$  day interaction were phenylalanine, glutathione, creatine, polyamine, methionine, cysteine, S-adenosyl methionine, taurine, urea cycle and arginine, proline metabolism, amino sugars, lysine, tyrosine, pentoses, glycolysis, gluconeogenesis, and pyruvate, as well as aspartate (Simintiras et al., 2019b).

Taken together, all of these data highlight nutrients, metabolites, and metabolic processes that may be critical to the establishment and maintenance of pregnancy, including (1) hexoses, such as fructose and glucose, which supply energy to the developing conceptus and activate nutrient sensing pathways such as the mammalian target of rapamycin (Kim

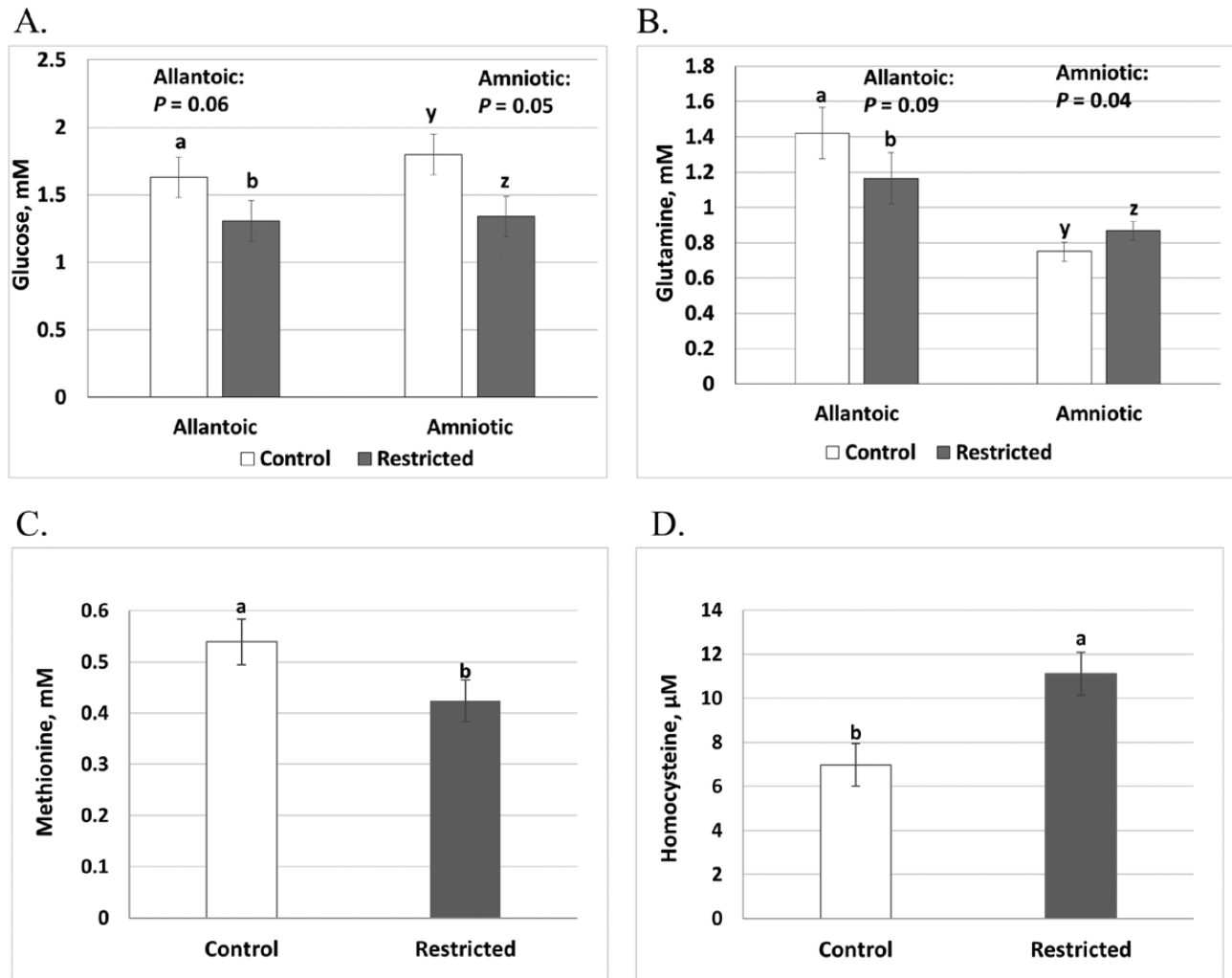


Figure 2. Comparison of (A) glucose concentrations in allantoic and amniotic fluid, (B) glutamine concentrations in allantoic and amniotic fluid, (C) methionine concentrations in allantoic fluid, and (D) homocysteine concentrations in maternal serum of heifers receiving control or restricted dietary treatment from the day of mating (day 0) until day 50 of gestation. Treatments provided for 0.5 kg of gain/hd daily vs. -0.08 kg of gain/hd daily between days 0 and 50 of gestation for control vs. restricted heifers, respectively. Figure modified from [Caton et al. \(2019\)](#).

[et al., 2012](#)) and play a critical role in producing nicotinamide adenine dinucleotide phosphate (NADPH) and nucleotides via the pentose phosphate pathway, thereby donating electrons to reduce oxygen radicals as well as synthesize nucleotides via the production of ribose-5 phosphate; (2) specific amino acids needed for rapid cellular growth and proliferation and potentially for metabolic substrates; (3) metabolism of arginine via nitric oxide synthase to produce nitric oxide (an oxygen radical) and reduce free radicals through glutathione peroxidase and NADPH, which has a key role in oxygen radical metabolism, stimulates cell proliferation and prevents cell death due to oxidative stress; (4) arginine metabolism to polyamines with S-adenosyl methionine donating carbon skeletons ([Clare et al., 2019](#)) to further increase cell proliferation that is needed for the successful elongation of the trophoblast to maintain pregnancy; and (5) methyl donors, such as methionine (metabolized to S-adenosyl methionine), which may be critical for early embryonic development not only for regulation of free radicals and polyamine synthesis but also regulating transcription via methylation of DNA and/or post-translational modification of histones ([Crouse et al., 2020a](#)).

In cattle, by day 50 of gestation, the placenta is still not fully functional ([Reynolds and Redmer, 1995](#)), and therefore the embryo must continue to receive its nutrients primarily from histotrophic secretions. Data from our lab ([Crouse et al., 2019d](#)) demonstrate the decrease in amino acids in allantoic fluid and increase in amino acids in the amniotic fluid of nutrient-restricted heifers coinciding with decreases in glucose and fructose, which may suggest several outcomes for offspring: (1) they may lack sufficient energy substrates for growth due to low reducing sugars and thus may oxidize amino acids for energy thereby reducing the amino acids available for protein synthesis, (2) conversely, there may be an increase in programmed efficiency of the offspring via reduced utilization of amino acids, or (3) there may be changes in placental and amniotic metabolism and transport of nutrients from histotroph to allantoic and subsequently to amniotic fluid.

Interestingly, there were no differences in fetal crown-rump length of these offspring at day 16, 34, or 50 of gestation due to nutritional treatment ([Negrin Pereira et al., 2017](#)). In the same study, hexose and amino acid transporter mRNA expression were affected by day of gestation but not by

maternal nutritional treatment (Crouse et al., 2017; Greseth et al., 2017). However, follow-up research (Crouse et al., 2020b) using immunohistochemistry and image analysis clearly demonstrated that moderate maternal nutrient restriction during the first 50 d of gestation reduced the abundance of neutral amino acid transporter proteins in utero-placental tissues (Table 2).

### Early placental vascular growth

Many of the same factors that negatively affect fertility and fetal growth and development also have similar effects on placental growth and development. Placental vascular development begins very early in pregnancy, and placental vascular growth determines, to a large degree, placental function (Reynolds and Redmer, 1995; Grazul-Bilska et al., 2010; Reynolds et al., 2010a, b; Grazul-Bilska et al., 2011).

We evaluated the pattern of placental vascular growth and development during early pregnancy after natural breeding in sheep and demonstrated that the major initial changes appear in the endometrium (the maternal portion of the placenta) very early in pregnancy (as early as day 16 after mating), well before the placenta is functional (Grazul-Bilska et al., 2010, 2011; Reynolds et al., 2013, 2014; Bairagi et al., 2016). In addition, changes in placental vascularization in sheep, as measured by cross sectional area, surface area, number, and size of capillaries were highly correlated with changes in expression of several angiogenic factors in maternal placenta (Grazul-Bilska et al., 2010, 2011; Reynolds et al., 2013, 2014; Bairagi et al., 2016). For several other species (e.g., humans, marmoset, and rats), intensive vascular development in the placenta was also observed during the first 3 to 4 wk of pregnancy and was associated with enhanced metabolic demand to support the dramatic fetal growth that was occurring (Reynolds et al., 2013, 2014; Bairagi et al., 2016).

We used the standing flank ovariohysterectomy procedure described earlier to evaluate the effects of maternal nutrient restriction during the first 50 d of pregnancy on fetoplacental development in beef heifers (McLean et al., 2017a). Applying this model, we found that as early as day 16 after mating moderate maternal nutrient restriction altered placental transcript abundance of endogenous retroviruses and IFN- $\tau$ , both of which are important in placentation and establishment of pregnancy (McLean et al., 2016a, 2018). In addition, heifers exposed to moderate nutrient restriction (ADG of  $-0.08$  vs.  $0.51$  kg/d for the first 50 d of pregnancy) had altered placental transcript abundance of angiogenic factors and associated alterations in placental vascular development (Figure 3; McLean et al., 2017b).

### Fetal gene transcript abundance

Using this same model, pregnant heifers receiving moderate nutrient restriction (ADG restricted heifers =  $-0.08$  kg/d vs. ADG control heifers =  $0.51$  kg/d during the first 50 d of pregnancy) also exhibited dramatically altered gene transcript abundance in fetal organs. Using RNAseq, we evaluated global transcript abundance in fetal liver, muscle from the hind limb, and brain (cerebrum) on day 50 after mating (Crouse et al., 2019b). We found that 201, 144, and 28 genes were differentially expressed in fetal liver, muscle, and brain, respectively, in nutrient-restricted compared with control heifers. When these genes were placed into functional categories (Table 3; Crouse et al., 2019b), we observed an 84%, 60%, and 97% upregulation of differentially expressed genes in the liver, muscle, and brain, respectively, due moderate nutrient restriction.

**Table 2.** Abundance of neutral amino acid transporters in fetal membranes (chorioallantois; FM), endometrium (luminal epithelium; ENDO), superficial endometrial glands (SG), deep endometrial glands (DG), and myometrium (MYO) as influenced by maternal nutrition on days 34 and 50 of gestation<sup>1</sup>

Transporter	Nutr. Trt <sup>2</sup>			Tissue					P-values <sup>3</sup>		
	CON	RES	SEM <sup>4</sup>	FM	ENDO	SG	DG	MYO	SEM <sup>5</sup>	Nutr.	Tissue
SLC1A1	3.93 <sup>a</sup>	3.08 <sup>b</sup>	0.19	3.93 <sup>c</sup>	3.73 <sup>c</sup>	3.61 <sup>c</sup>	4.04 <sup>c</sup>	2.24 <sup>d</sup>	0.28	<0.01	<0.01
SLC1A5	9.88	9.09	0.48	12.79 <sup>c</sup>	11.64 <sup>cd</sup>	10.61 <sup>d</sup>	8.50 <sup>e</sup>	3.90 <sup>f</sup>	0.73	0.23	<0.01
SLC7A5	16.22 <sup>a</sup>	10.98 <sup>b</sup>	0.99	15.66 <sup>c</sup>	13.70 <sup>c</sup>	17.13 <sup>c</sup>	14.77 <sup>c</sup>	6.75 <sup>d</sup>	1.50	<0.01	<0.01
SLC38A2	11.51 <sup>a</sup>	10.30 <sup>b</sup>	0.41	12.43 <sup>c</sup>	11.98 <sup>cd</sup>	12.64 <sup>c</sup>	10.57 <sup>d</sup>	6.92 <sup>e</sup>	0.62	0.03	<0.01
SLC38A7	4.46 <sup>a</sup>	3.80 <sup>b</sup>	0.33	5.48 <sup>c</sup>	4.52 <sup>cd</sup>	5.04 <sup>cd</sup>	4.39 <sup>d</sup>	1.22 <sup>e</sup>	0.34	0.03	<0.01

<sup>1</sup>Data are presented as relative fluorescence units (determined by quantitative image analysis) as an indicator of transporter abundance. Table modified from Crouse et al. (2020b).

<sup>2</sup>CON average daily gain =  $0.51$  kg/d (NASEM, 2016), and RES received 60% of CON and had an average daily gain =  $-0.08$  kg/d.

<sup>3</sup>Probability values for the effect of maternal nutrition and tissue on the fluorescence of neutral AA transporters.

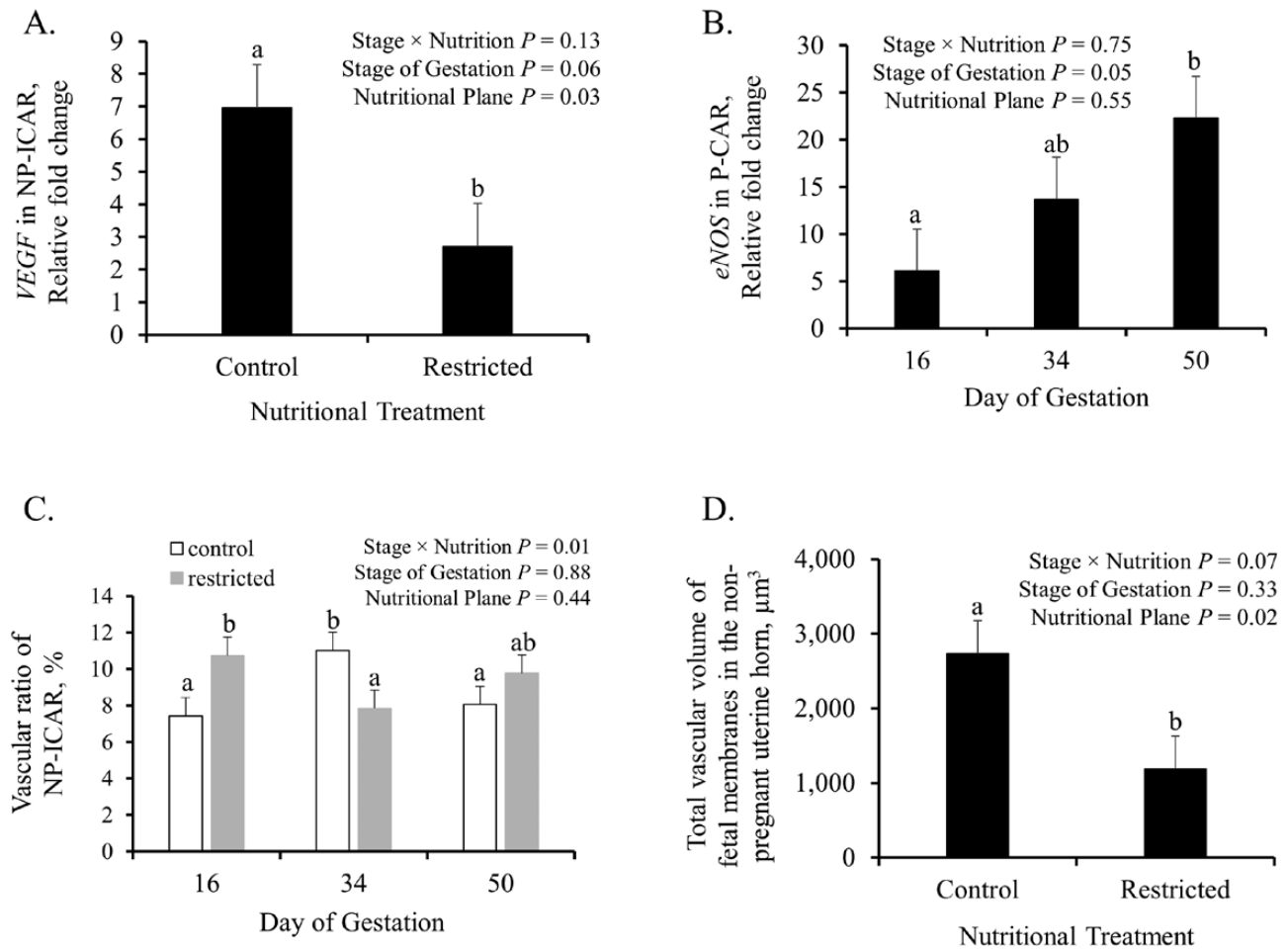
<sup>4</sup>Average SEM for the main effect of nutrition. CON = 13; RES = 16.

<sup>5</sup>Average SEM for the main effect of tissue. Day 34 CON n = 6, day 34 RES n = 9, day 50 CON n = 7, day 50 RES n = 7.

<sup>a,b</sup>Across nutrition treatment without common superscript differ ( $P \leq 0.05$ ).

<sup>c,d</sup>Across tissue type without common superscript differ ( $P \leq 0.05$ ).





**Figure 3.** The influence of nutritional treatment [CON average daily gain = 0.51 kg/d (NASEM, 2016), and RES received 60% of CON intake and had an average daily gain = -0.08 kg/d] initiated at breeding and stage of gestation (day 16, 34, or 50) on (A) mRNA expression of *vascular endothelial growth factor* (*VEGF*) in maternal intercaruncular endometrium of the uterine horn contralateral to the conceptus (NP-ICAR) during the first 50 d of pregnancy in beef heifers. Data presented as a  $2^{-\Delta\Delta\text{CT}}$  fold change normalized to  $\beta$ -actin and the average of non-bred, non-pregnant heifers. (B) mRNA expression of *endothelial nitric oxide synthase* (*eNOS*) in maternal caruncle of the uterine horn containing the conceptus (P-CAR). Data presented as a  $2^{-\Delta\Delta\text{CT}}$  fold change normalized to  $\beta$ -actin and the average of non-bred, non-pregnant heifers. (C) Vascular ratio in maternal intercaruncular endometrium contralateral to the conceptus (NP-ICAR) dependent on maternal dietary intake (control, restricted) and stage of gestation. Vascular ratio was calculated by dividing overall total vascular volume by total volume of tissue and expressing it as a percentage. (D) Effects of maternal dietary intake (control, restricted) on total vascular volume of fetal membranes in the uterine horn contralateral to the conceptus during the first 50 d of gestation. <sup>a,b</sup>Means without a common superscript differ ( $P < 0.05$ ). Figure modified from the data of McLean et al., (2017a, b).

Building on the work of Crouse et al. (2019b), Diniz et al. (2020) reported that the bovine fetal liver, muscle, and brain tissues at 50 d of gestation exhibited differences in transcriptional regulation between the control (0.51 kg ADG) and moderately nutrient restricted (-0.08 kg ADG) groups. They concluded that the “rewiring” of major regulators of gene abundance is likely an adaptive response to nutrient availability and probably impacts tissue development (Diniz et al., 2020). For example, nutrient restriction led to differential regulation of myogenic factors by the *ZBTB33* and *ZNF131* transcription factors that may negatively affect myogenesis. Their work (Diniz et al., 2020) provided unique insights into nutrient-sensing pathways, such as mTOR, PI3K/Akt, and insulin, across tissues, thereby gaining a systems-level insight into fetal programming in response to moderate nutrient restriction during the first 50 d of pregnancy in beef heifers.

### Current synthesis and potential practical ramifications

These observations suggest that very moderate nutrient restriction during early pregnancy, which could be expected to occur under

typical management systems for grazing ruminants, not only profoundly affects transcript abundance in the fetal organs but may “set up” the pregnancy for failure, or perhaps altered fetal growth and development and, ultimately, developmental programming of postnatal health and productivity. Although fetal and placental growth are minimal during the first 50 d of pregnancy, many of the critical events that take place, including fetal organogenesis and placentation, seem to be susceptible to even moderate changes to maternal nutrient supply. Thus, we are suggesting that even moderate nutritional stress may cause developmental programming that can impact offspring developmental outcomes. We further propose that these events likely involve an interaction between nutritional stress level and a combination of the genetic and epigenetic ability of that embryo to adapt to the nutritional challenge.

As alluded to, an important point is that despite the effects of maternal undernutrition on nutrient supply, transporter abundance, placental and fetal organ development, tissue vascularity, and gene transcript abundance in multiple tissues,

**Table 3.** Functional categories for differentially expressed genes involved in tissue metabolism, accretion, and function ( $P < 0.01$ ) of fetal liver, fetal muscle (hind limb), and fetal cerebrum presented as upregulation (Upreg.) or downregulation (Downreg.) in fetuses from restricted (RES) compared with control heifers (CON)<sup>1,2</sup>

Category	Total genes <sup>3</sup>	Upreg. <sup>4</sup>	Downreg. <sup>5</sup>	P-value <sup>6</sup>
<b>Liver<sup>7</sup></b>				
Metabolic pathways	43	32	11	0.017
Protein kinase	47	40	7	0.020
Nucleosome core	22	21	1	0.005
mRNA splicing	7	6	4	0.041
Complement/coagulation	6	6	0	0.041
<b>Fetal muscle<sup>8</sup></b>				
Skeletal muscle	74	45	29	<0.001
Embryogenesis	14	12	2	<0.001
Signaling cascades	18	7	11	0.003
<b>Cerebrum<sup>9</sup></b>				
Hippocampus and neurogenesis	32	31	1	<0.001
Metal binding	23	22	1	0.006
Cytoskeleton	5	5	0	0.003

<sup>1</sup>Table modified from Crouse et al. (2019b, tables 1 to 3).

<sup>2</sup>CON average daily gain = 0.51 kg/d (NASEM, 2016), and RES received 60% of CON and had an average daily gain = -0.08 kg/d.

<sup>3</sup>Total number of differentially expressed genes associated with a category.

<sup>4</sup>Number of differentially expressed genes that were upregulated in fetuses from RES vs. CON heifers.

<sup>5</sup>Number of differentially expressed genes that were downregulated in fetuses from RES vs. CON heifers.

<sup>6</sup>Probability value associated with a specific category. P-value as presented is for the entire pathway, not individual genes within a pathway.

<sup>7</sup>Functional annotations for each category of fetal liver metabolic pathways: amino acid, purine and pyrimidine, carbohydrate, reducing equivalent (NAD/FAD), steroid and lipid biosynthesis, and cytochrome and heme; protein kinase: serine/threonine protein kinase, ATP binding, and nucleotide binding; nucleosome core: histones and histone modifiers; mRNA splicing: spliceosome; and complement/coagulation: complement factors and coagulation factors.

<sup>8</sup>Functional annotations for each category of fetal muscle hind limb skeletal muscle: contraction, intermediate filament, microtubule, actin, myosin, troponin, calcium binding, and ATP binding; embryogenesis: myogenesis and homeobox; and signaling cascades: Wnt and MAPK.

<sup>9</sup>Functional annotations for each category of fetal cerebrum hippocampus and neurogenesis: hippo signaling pathway, collagen, netrin, SMAD, and developmental protein; metal binding: iron binding, zinc binding, copper binding, nickel binding, and calcium binding; and cytoskeleton: actin remodeling.

fetal size at day 50 of pregnancy was not affected by moderate maternal nutrient restriction during early pregnancy in beef heifers (Negrin Pereira et al., 2017). These data were confirmed by a more recent study in which we evaluated fetal weight at day 84 of pregnancy in beef heifers receiving a basal diet or the basal diet with an energy-based supplement (McCarthy et al., 2020). Thus, just as for placental vascular development, altered transcript abundance likely precedes any detectable effects on organ, or in this case fetal, size in cattle or other ruminants (Barnes, 2000; Bertolini et al., 2002; Redmer et al., 2005, 2009; McLean et al., 2017a, 2018; Reynolds and Vonnahme, 2017).

In addition, although there is little doubt that defects in placental development lead to poor fetal growth and development early in pregnancy, programming of development may be occurring before the placenta is functional. For example, we have observed changes in nutrient supply, uterine transporter abundance, and gene expression of placental and fetal organs at day 50, as well as reduced neutral amino acid concentrations in allantoic fluid (Menezes et al., 2020) and changes in intestinal and femur mass at day 84 (McCarthy et al., 2020) but no changes in fetal mass in response to moderate nutrient restriction at either time point. However, in a companion study investigating moderate maternal nutrient changes (0.25 vs. 0.75 kg targeted ADG from breeding to day 84 of pregnancy, with a common diet afterwards) in beef heifers, calf birth weights were decreased in the low compared with the moderate gain group at parturition (Baumgaertner et al., 2020). Interestingly, in a combined analysis of the study by Baumgaertner et al. (2020) and McCarthy et al. (2020) data sets (C. R. Dahlen, A. K. Ward, P. P. Borowicz, L. P. Reynolds, F. Baumgaertner, K. L. McCarthy, A. C. B. Menezes,

W. J. S. Diniz, A. K. Ward, and J. S. Caton unpublished data), fetal biparietal distance at day 84 was reduced for heifers on a low compared with those on a moderate rate of gain. Furthermore, we observed altered embryo-fetal growth in sheep subjected to assisted reproductive technologies (Grazul-Bilska et al., 2013, 2014, 2019; Reynolds et al., 2015a; Bairagi et al., 2018) and in artificially inseminated beef heifers (Baumgaertner et al., 2020; McCarthy et al., 2020). These differences in embryonic growth rates are likely due to altered fetal nutrient supply and fetal organ gene transcript abundance that we have observed very early in pregnancy due to moderate maternal nutritional restriction that results in small changes in heifer ADG that are within ranges observed in production (Crouse et al., 2017, 2019b,d, 2020c; Greseth et al., 2017).

## Conclusions and Future Directions

The available evidence indicates that changes in maternal periconceptual nutrition can result in developmental programming of the offspring. In fact, very moderate changes in maternal nutrition during the first 50 d of pregnancy that result in body weight gain differentials of approximately 0.5 kg/d can alter nutrient supply, transporter abundance, placental vascularity, and gene transcript abundance of offspring from beef heifers. We would therefore argue that maternal nutrition during the periconceptual period clearly matters to the developing offspring. With that concept in hand, we now must begin to understand the underlying mechanisms. For example, some of the remaining questions that deserve further investigation include:

- “What are the mechanisms that drive the processes of fetal and placental development and how are they modulated?”;
- “Do these early programming events persist later into pregnancy, and do they affect the offspring?”;
- “What management, therapeutic, or strategic supplementation strategies can we employ to overcome the negative consequences of early and persistent programming of offspring growth and development?”; and
- “Can we use programming of fetal and placental development and function to our advantage; that is, can we mitigate the negative and take advantage of the positive aspects of early programming events?”

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## Conflict of Interest Statement

We declare that the submitted work was carried out with no personal, professional, or financial relationships that could potentially be construed as a conflict of interest.

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