MANAGING THE PREGNANT FEMALE – FETAL PROGRAMMING

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Implications

- An environmental stimulus or insult during critical periods of development can program life-long production characteristics of an animal irrespective of their genetics.
- Several environmental factors have been shown to negatively impact placenta development and blood flow during pregnancy, all of which can hinder offspring health and vigor.
- Doppler ultrasonography can increase our understanding of blood flow and blood perfusion of the reproductive tract in association with fertility and developmental programming.
- Elucidating the consequences of specific supplements on the continual plasticity of placental functional capacity will allow us to determine important mediators of offspring growth and development.

Developmental Programming

Irrespective of an animal's genotype, an environmental stimulus or insult during a critical period of development can program the observed phenotype of an animal. This exposure to an environmental stimulus or insult may establish a permanent phenotype throughout the remainder of an animal's life, which can have adverse consequences for milk production, carcass yield, feed efficiency, and/or reproductive function. This process of permanently altering an animals' phenotype through environmental stimuli has been referred to as the developmental programming hypothesis. For example, two animals possessing the same genotype but raised in different environments are expected to have differing lifelong phenotypic characteristics which is further explained by developmental plasticity. Importantly, the magnitude of phenotypic change is vastly different between these two animals possessing the same genotype if their exposure to different environments occurred while they were embryos, fetuses, calves, weaned heifers, or mature cows. Furthermore, the changes to these animals' developmental trajectory and any lasting consequences is thought to be greatest in embryos and fetuses with decreasing developmental plasticity with increasing animal age. The study of developmental programming during the fetal period, an age of high developmental plasticity (Figure 1), is known as fetal programming.

Studies from different laboratories have show overwhelming support for the concept of fetal programming by reporting a strong association between birth weight and lifelong developmental consequences. For example, low birth weight offspring are at an increased risk of morbidity and mortality, slowed postnatal growth, poor body composition (increased fat and reduced muscle growth), metabolic disorders, cardiovascular pathologies, and dysfunction of several organs, such as the ovaries, testes, mammary gland, and gastrointestinal tract (Reynolds et al., 2013; Vonnahme et al., 2015). Livestock are specifically at risk due to poor nutritional environments during pregnancy such as breeding of young growing peripubertal dams that are competing for nutrients with the fetus. In addition, poor pasture conditions or environmental heat stress in relation to seasonal breeding can specifically decrease nutrient availability for both dam and fetus during critical periods of development. Although these initial fetal programming studies focused exclusively on offspring (fetal or birth) weight, we now understand that multiple measurements of offspring size at birth can predict their developmental trajectory. Therefore, phenotypic changes in cattle production as a result of fetal programming may be independent of calf weight at birth. This is evident when environmental insults occur during early pregnancy alone, such that birth weights are unaltered but evident phenotypic changes still impact calf production.

Insufficiencies during pregnancy, resulting in reduced fetal growth and development, are detrimental to all livestock species, where the newborns represent the next generation of meat and milk producing animals. Several animal models of fetal and placental growth restriction (e.g., maternal nutritional plane, maternal age, heat stress, hypoxic stress, and fetal number) have been developed to better unravel the relationship among uterine blood flow and offspring development (Thureen et al., 1992; Regnault et al., 2003; Kwon et al., 2004; Reynolds et al., 2005). Establishment of functional fetal and placental circulation is one of the earliest events during conceptus development (Patten, 1964; Ramsey, 1982) and the exponential increase in placental exchange is vital for maintaining the exponential growth and development of the fetus during the last half of gestation (Redmer et al., 2004). Therefore, understanding the impacts of maternal environment on placental function is especially relevant to these proceedings, as the majority of mammalian livestock raised for red meat production spend 30 – 40% of their life being nourished by the placenta. The percentage of total time in each phase of beef production from conception to harvest is depicted in Figure 1. In addition, the amount of developmental plasticity of offspring varies during their lifespan, with maximal influences

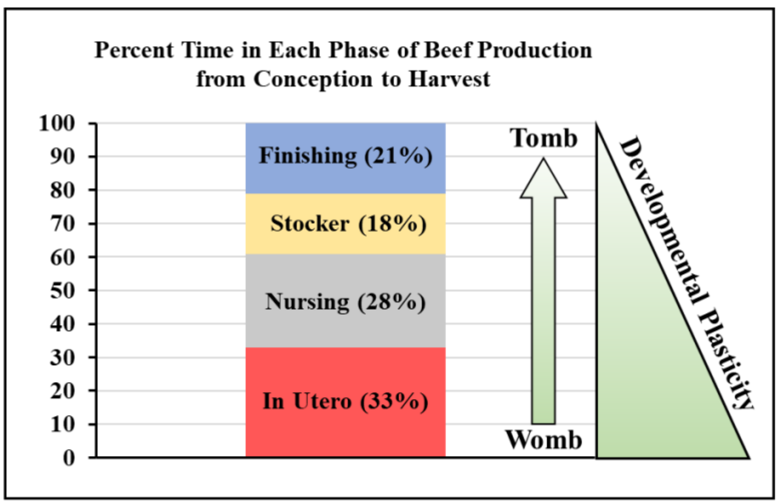

Figure 1. Percentage of total lifetime in each phase of beef production from conception to harvest (womb to tomb). Nearly a third of life is spent developing in utero when the fetus is most vulnerable to the environment because of increased developmental plasticity.

of developmental programming occurring during the embryonic and fetal stages of life (Figure 1)

Fetal Growth and Organ Development

The embryonic period in cattle is defined as the time from conception (single cell embryo, referred to as a zygote) to the completion of organogenesis. This embryonic period typically runs from day 1 to 42 of gestation with the largest percentage of pregnancy wastage occurring during this period of development. The fetal period is defined as the remainder of gestation from day 42 until day 280 when the completion of organ differentiation occurs (Figure 2; Lemley et al., 2015). The characterization of bovine fetal growth throughout gestation has allowed researchers to hypothesize phenotypic changes to offspring that experience specific periods of environmental insults that may perturb normal development in utero. For example, nutrient deprivation or heat stress during days 60 – 120 of pregnancy will undoubtedly have different impacts on fetal development compared to the same environmental insults from day 180 – 240 of pregnancy. This is where timing becomes a critical component of fetal programming outcomes.

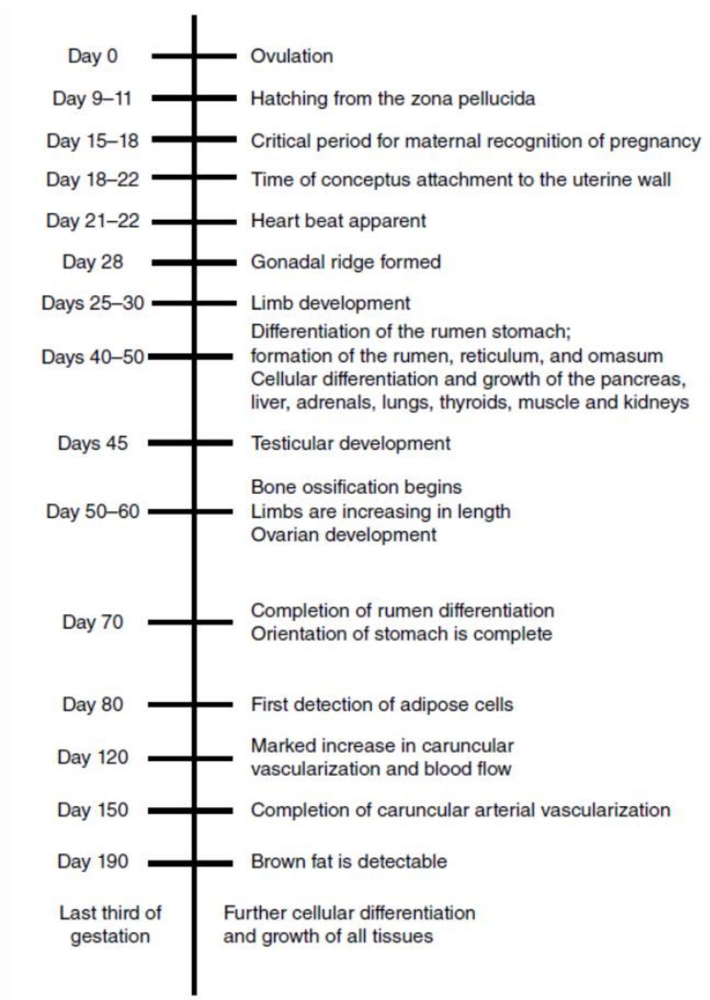

Figure 2. Timeline of bovine fetal development (Lemley et al., 2015).

Adaptations during Pregnancy and Placental Development

Offspring growth in utero is sensitive to direct and indirect effects of the maternal environment, particularly during the early stages of embryonic life (Robinson et al., 1995). During early pregnancy hormone secretions from the ovary and conceptus help establish a healthy pregnancy. During mid to late pregnancy the dam undergoes significant but reversible changes in physiology to help maintain the increase in metabolic demand. Maternal cardiovascular functional capacity changes dramatically during pregnancy, whereby systemic arterial blood pressure and resistance of the blood vessels decrease and cardiac output, heart rate, stoke volume, and blood volume increase (Magness, 1998). The increase in cardiac output is associated with a dramatic fall in blood vessel resistance, allowing researchers to characterize pregnancy as a state of systemic vasodilation resulting in profound increase in total systemic flows to all vascular beds. Therefore, adequate blood flow to the reproductive tract is critical for normal development of the offspring. Moreover, several ewe models of compromised pregnancies (overfed, underfed, heat stressed, multiple pregnancy, hypoxic stress) have shown consistent decreases in uterine and/or umbilical blood flow (Reynolds et al., 2006; Vonnahme and Lemley, 2012). In addition, the magnitude decrease in blood flow is reflective of the magnitude decrease in fetal weight. In all domestic livestock species, offspring born at average weight have an increased chance of survival than those born below average weight. Increasing evidence in livestock species have associated poor growth performance of offspring born to mothers with decreased blood flow to the uterus and placenta, which accounts for a substantial loss in livestock production (Greenwood et al., 1998; Wu et al., 2006). While the literature is booming with increasing evidence of how nutrient restriction or overfeeding impairs several physiological parameters, fewer concentrate on enhancing postnatal growth in livestock species.

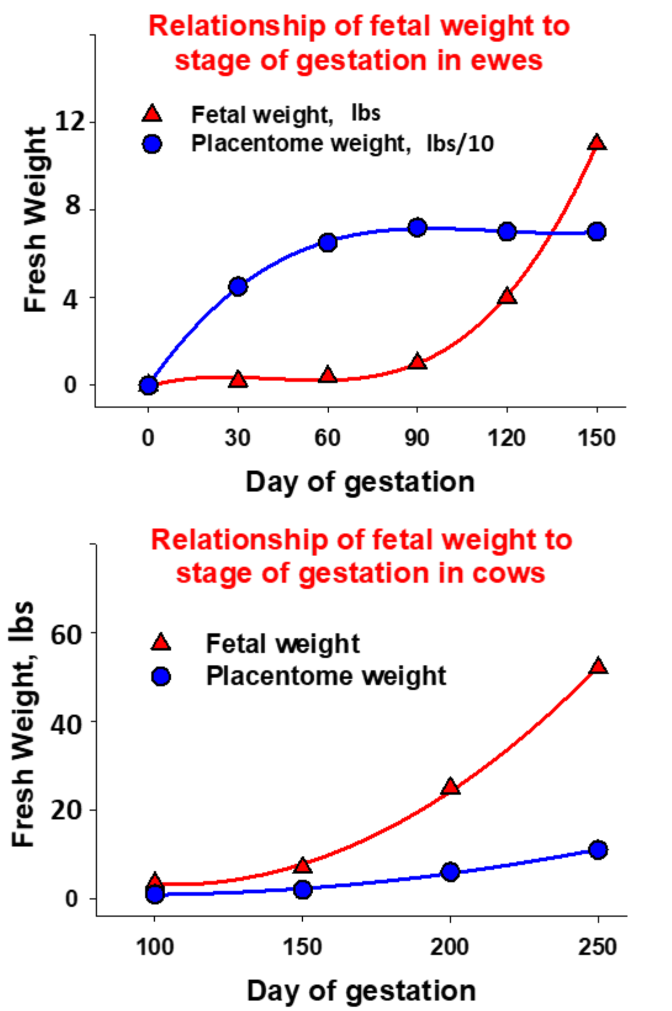

Figure 3. Comparison of fetal and placental growth in the ewe (top graph) versus the cow (bottom graph). Redrawn from Redmer et al. (2004) and Reynolds and Redmer, (1995).

Several animal models of fetal programming have been extensively studied in the ewe (Reynolds et al., 2005), and extrapolation to cattle should be minimal because of the drastic differences in placental development between sheep and cattle (Figure 3). In the ewe, the placenta reaches its maximum size during the first two thirds of gestation, while approximately 90% of fetal growth occurs during the last third of gestation (Redmer et al., 2004). In contrast, the bovine placenta continues to increase in size exponentially as gestation proceeds; however, the exponential rate in growth of the bovine fetus is much greater compared to the growth of the placenta (Figure 3; Reynolds and Redmer, 1995).

The placenta is involved in transporting nutrients and wastes between maternal and fetal circulation and altered placental function has been associated with abnormalities in fetal development. The efficiency of placental nutrient transport is directly related to placental blood flow (Reynolds and Redmer, 1995; 2001). Fowden et al. (2006) reviewed key factors affecting placental nutrient transfer capacity, which were size, nutrient transporter abundance, nutrient synthesis and metabolism, and hormone synthesis and metabolism. Large increases in blood flow to the reproductive tract are necessary to support both nutrient and waste exchange between the mother and offspring. This relationship is best depicted by placental efficiency calculations (Figure 4). Placental efficiency is calf birth weight divided by placental weight and explains the pounds of calf that can be grown per pound of placenta. Undoubtedly a strong positive relationship exists between calf birth weight and placental weight; however, focusing on the calves born above or below this trend line (Figure 4) shows that some calves are born from an efficient or inefficient placenta. One of the most important indicators of placental efficiency is uterine and umbilical blood flow. Using Doppler ultrasonography our research team has investigated alterations in blood flow to the reproductive tract during specific windows of development. Several environmental factors have been shown to negatively impact placenta development and blood flow during pregnancy, all of which can hinder offspring health and vigor. The regulators of placental nutrient transport and uteroplacental blood flow are still largely incomplete with the majority of research efforts focusing on rodent models, which are different from livestock species. Elucidating the consequences of specific hormonal supplements on the continual plasticity of placental function will allow us to determine important endogenous mediators of offspring growth and development.

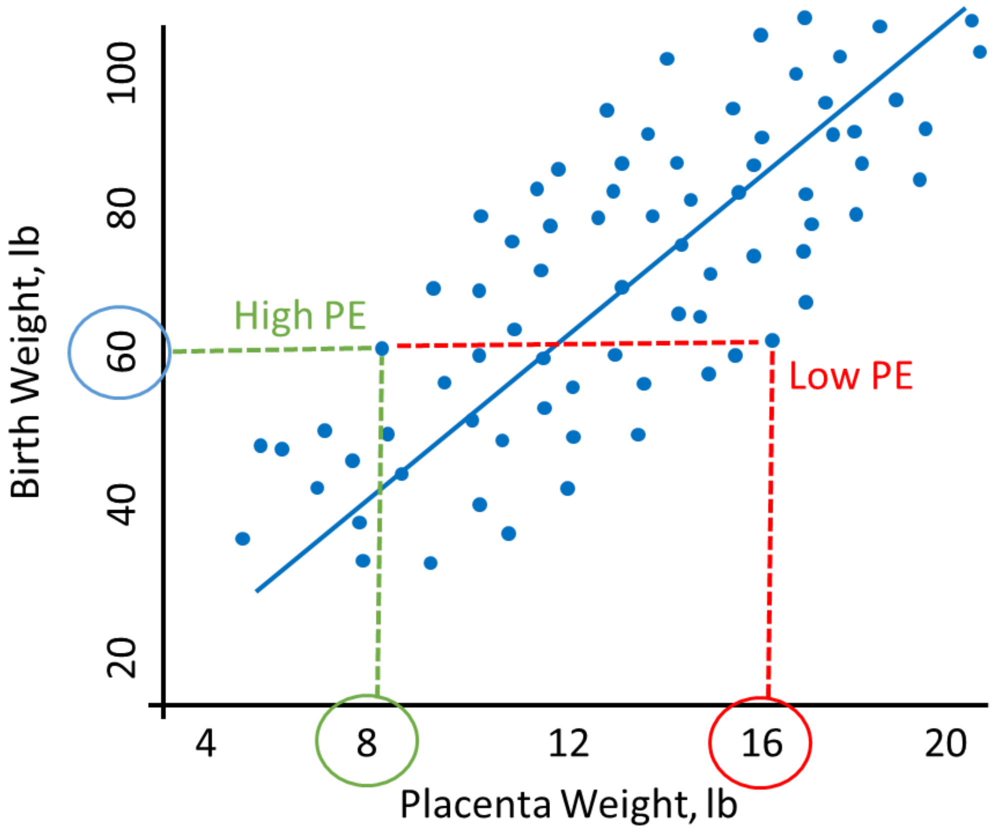

Figure 4. Positive association between calf birth weight (y-axis) versus placenta weight (x-axis). Placental efficiency is calculated as birth weight divided by placental weight (lbs of calf that can be grown per lb of placenta). The green lines depict a highly efficient placenta, while the red lines depict a poorly efficient placenta, while both calves weighed 60 lbs at birth.

Maternal Nutrient Restriction

Poor forage quality in grazing systems can negatively impact the nutritional intake of beef cattle. Pregnant beef cows grazing poor forage can alter fetal growth during increased periods of developmental plasticity. Thus, provisions from the environment can program these offspring to experience changes in mortality and morbidity rates, slowed postnatal growth, altered carcass weights, and meat quality characteristics (Robinson et al., 2013). The relationship between maternal nutritional plane during late gestation and calf mortality was examined as early as 1975, where maternal nutrient restriction for 100 days prepartum decreased calf birth weight by 7% and increased calf mortality rate by 10%, while an additional 20% of calves died between birth and weaning due to scours (Corah et al., 1975). The direct effects of nutritional plane on offspring production characteristics are dependent on the timing of insult and magnitude of nutrition deprivation in relation to fetal and placental development (Funston et al., 2010). In dealing with timing, it is also important to consider the separation of prenatal versus postnatal maternal factors that may influence these developmental programming responses. For example, changes in meat quality of offspring born to dams experiencing a late pregnancy maternal nutrient restriction may carry over into the early lactation period of this dam. Thus, preventing researchers from identifying the important time of maternal nutritional insult that led to the negative outcomes of the offspring. This is vital when considering the most economically feasible therapeutic interventions to mitigate negative developmental programming outcomes.

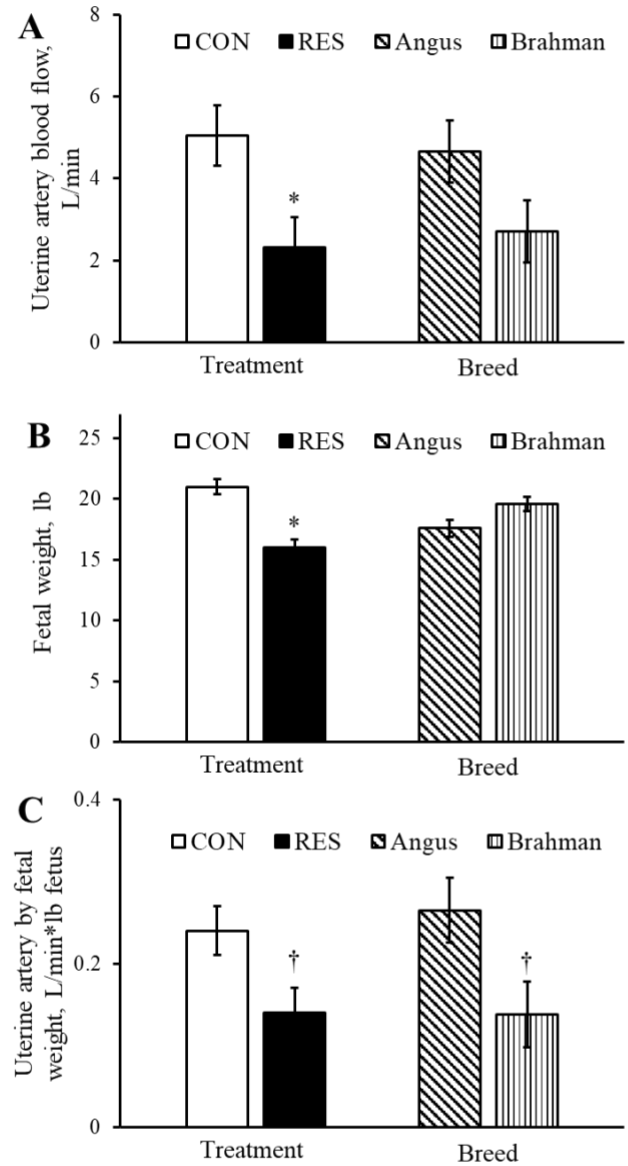

Figure 5. Uterine artery blood flow (A) at day 175 of pregnancy and fetal weight (B) at day 180 of pregnancy in nutrient restricted (RES) or control (CON) fed Angus and Brahman heifers. Nutritional treatments were applied from day 50 to 180 of pregnancy. Data redrawn from Lemley et al. (2018).

The adaptions of the placenta during maternal nutrient restriction are incomplete and less is known about specific differences amongst breeds of cattle. Normal physiology such as gestation length, fetal growth, placentome weight, and even uterine blood flow can differ substantially between breeds of cattle (Ferrell, 1991a; 1991b). Therefore, the magnitude of fetal programming is expected to be breed dependent and further research is needed to identify when and with what breeds should interventions be sought. In a recent study we examined the effect of early to mid-gestational nutrient restriction on uterine blood flow and fetal development in Brahman and Angus heifers (Lemley et al., 2018). In this study, heifers were restricted to 60% of net energy requirements for gestating cattle from day 50 to 180 of pregnancy. This early to mid-pregnancy nutrient restriction decreased uterine artery blood flow and fetal weight at day 180 of pregnancy irrespective of heifer breed (Figure 5A and 5B). Moreover, the efficiency of uterine artery blood flow relative to fetal weight was improved in nutrient restricted dams versus adequate fed (Figure 5C). A similar response was observed in Brahman heifers irrespective of nutrient restriction signifying a lesser amount of uterine blood flow needed to grow the same weight fetus from a Brahman dam as compared to an Angus (Figure 5C). A portion of these responses have been associated with increased placental efficiency in nutrient restricted dams and Brahman dams (Lemley et al., 2018). A subset of these Angus and Brahman heifers were allowed to calve and postnatal growth was followed though weaning (unpublished observations). Most postnatal measurements of growth were unaffected by maternal nutrient restriction from day 50 to 180 of pregnancy. However, heart girth was increased in calves born to nutrient restricted versus adequate fed dams, which may show in utero overcompensation of fetal growth when nutrient restricted dams are realimented to adequate nutrition during late pregnancy.

Apart from nutritional management during pregnancy, we have also examined heifer development practices and season on uterine artery blood flow during mid to late gestation. For example, beef producers opting for low-input forage-based replacement heifer management programs lead to lighter weights at breeding with some heifers reaching only 50-55% of expected mature body weight at breeding versus a traditionally recommended target weight of 60-65% of expected mature body weight. We concluded that heifers developed on low-input management schemes until confirmation of pregnancy (day 30 to 45 of gestation) showed no compromise in uterine blood flow or calf birth weights compared to conventionally developed heifers. Moreover, the volume of late gestation uterine artery blood flow relative to maternal body weight was significantly increased in low-input heifers versus conventionally developed, which may be a compensatory mechanism to safeguard fetal growth and development (Cain et al., 2017). In addition to low-input heifer development programs, we also examined the effect of calving season on uterine artery blood flow as differences in postpartum anestrus interval, conception rates, and weaning weights have been reported between fall and spring calving herds (King and Macleod, 1984; Gaertner et al., 1992). A portion of these responses could be programmed in utero via changes in nutrient and waste exchange between dam and fetus. For these initial studies we observed an increase in uterine artery blood flow in the last third of pregnancy, consistent with exponential growth of the fetus in spring calving versus fall calving heifers (Cain et al., 2017). Even though cattle are considered nonseasonal breeders, seasonal changes in photoperiod, thermal stress, and nutrient availability can influence numerous performance and reproductive traits. Changes in hormone concentrations, as a result of photoperiod, may be influencing blood distribution to the reproductive tract, specifically changes in melatonin have been shown to modulate cardiovascular function (Lemley and Vonnahme, 2017).

Maternal Melatonin Supplementation

The amplitude of melatonin secretion has been associated with improved oxidative status and altered hormone metabolism in rats and sheep, as well as altered cardiovascular function in several mammalian species (Wallace et al., 1988; Forcada et al., 2006; Juaniaux et al., 2006). Several studies have shown that melatonin partially regulates blood pressure and blood flow (Pandi-Perumal et al., 2008). Melatonin has both direct and indirect effects on the cardiovascular system and may cause either arterial vasodilation or vasoconstriction depending on the origin of the blood vessel under investigation. Taking into account the above physiological responses, which can be partially altered by peripheral concentrations of melatonin, our research team examined the effects of melatonin supplementation on uteroplacental development and functional capacity. Similar to other fetal programming models our initial studies focused on pregnant ewe lambs. Using this sheep model of intrauterine growth restriction, we supplemented dietary melatonin as a potential therapeutic during mid to late gestation (Lemley et al., 2012). In our sheep model, ewes were supplemented with 5 mg of melatonin or no melatonin and allocated to receive 100% (adequate) or 60% (restricted) of nutrient requirements from d 50 to 130 of gestation. Using Doppler ultrasonography, we observed an increase in umbilical artery blood flow at d 130 of gestation in ewes supplemented with dietary melatonin, while uterine artery blood flow was unaffected by maternal melatonin supplementation (Lemley et al., 2012). At d 130 of gestation, uterine artery blood flow was decreased in nutrient restricted ewes compared to adequate fed ewes. Although melatonin supplementation did not rescue fetal weight in restricted fed ewes, we

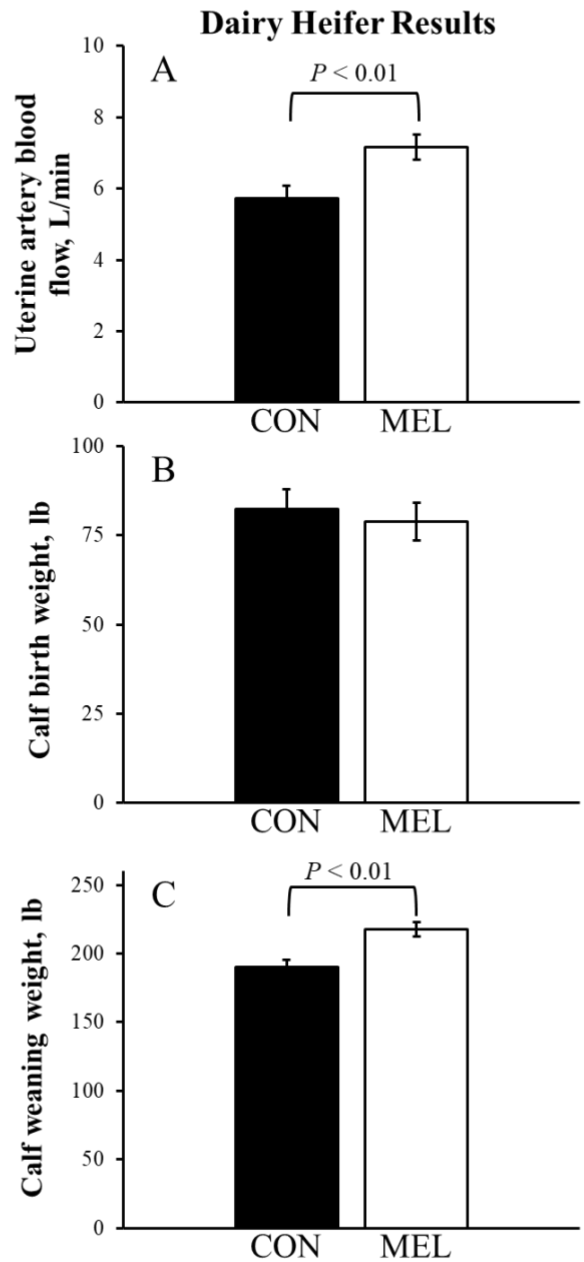

Figure 6. Uterine artery blood flow (A), calf birth weight (B), calf weaning weight at 9 weeks of age (C) from diary heifers treated with (MEL) or without (CON) dietary melatonin from days 190 to 262 of gestation. Data redrawn from Brockus et al. (2016a and 2016b).

did observe similarities between fetal size and measurements of uterine and umbilical blood flow during mid to late gestation.

Recently, we examined uterine artery blood flow in Holstein heifers supplemented with 20 mg of dietary melatonin from d 190 to 262 of gestation (Brockus et al., 2016a). Uterine artery blood flow was increased by 25% in the melatonin treated vs. control heifers (Figure 6). Surprisingly, calf birth weights were not different between treatments; however, calf body weight at 9 weeks of age was increased in calves born to melatonin supplemented dams vs. control dams (Brockus et al., 2016b). Therefore, similar to other pregnancy models, an increase in uteroplacental blood flow during mid to late pregnancy is associated with alterations in postnatal offspring growth and development. This is apparent in the dairy heifer study as calves were removed from dams, managed identically, and fed a similar milk replacer and starter diet prior to weaning at 8 weeks of age. Therefore, postnatal maternal factors were removed from this dairy project allowing us to propose direct fetal programming responses. Because of the observed differences in dairy calf body weights, we replicated a similar experiment in beef cows. In this follow up study, heifers and cows were assigned to 1 of 2 treatments: melatonin implants (MEL; n = 29) or no melatonin implant control (CON; n = 28) starting on day 180 of gestation and ending on day 270 (McCarty et al., 2018). As expected, uterine artery blood flow was increased in commercial beef heifers and cows supplemented with melatonin during the last third of pregnancy (Figure 7). Similar to the dairy heifer study, beef calf birth weights were not different; however, a 57 lb increase in weaning weights was observed in calves born to melatonin supplemented dams versus control (McCarty et al., 2018). Although similar results to the

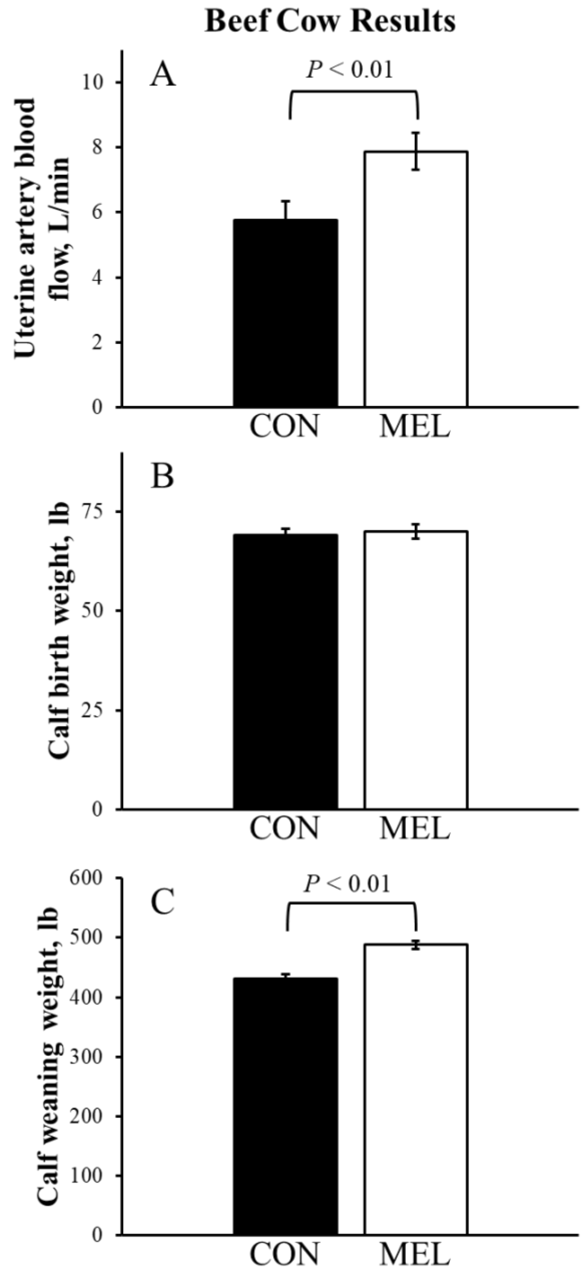

Figure 7. Uterine artery blood flow (A), calf birth weight (B), calf weaning weight at 28 weeks of age (C) from beef cows treated with (MEL) or without (CON) melatonin ear implants from days 180 to 270 of gestation. Data redrawn from McCarty et al. (2018).

dairy study, it is important to note that postnatal maternal factors (e.g. postpartum cow health, colostrum composition, and lactational performance) could be contributing to the increased weaning weight of calves born to melatonin supplemented dams.

Taken together, the results we have observed in both cattle studies following melatonin supplementation has allowed our research group to speculate on potential circadian alterations of the reproductive tract during pregnancy. For example, the rhythms generated from circulating concentrations of melatonin could mediate circadian rhythms in the placenta and developing fetus during pregnancy.

Circadian Disruption and the Placenta

Depending on latitude and season, mammals have adapted to a solar day of approximately 12 hours of light and 12 hours of dark. During the nighttime cattle experience an endogenous increase in circulating melatonin concentrations, which could be regulating blood distribution between maternal and fetal compartments. Based on our consistent observations of increased uterine and umbilical blood flow during melatonin supplementation in sheep and cattle (Lemley and Vonnahme, 2017), we hypothesized endogenous 24-hour rhythms of placental functional capacity. Specifically, nighttime may help shunt blood flow and therefore, nutrient and waste exchange between dam and fetus, while daytime exposure may decrease blood flow to the reproductive tract as endogenous concentrations of melatonin begin to decrease. This proposed pathway may be especially significant to fetal programming as identification of endogenous placental rhythms could directly inform the development of guidelines and recommendations for the proper administrative timing of blood flow therapeutics that could mitigate the consequences of multiple forms of developmental programming. An example of these 24-hour changes in uterine artery blood flow in late pregnant beef heifers from two separate projects, maternal nutrient restriction or melatonin supplementation, can be observed in Figure 8 and Figure 9, respectively (unpublished observations). Figure 8 illustrates total uterine artery blood flow in day 220 pregnant beef heifers following maternal nutrient restriction (RES; 60% of NRC recommendations) or being adequate fed (ADQ; 100% of NRC recommendations) beginning on day 160 of pregnancy. Doppler ultrasonography of blood flow occurred from

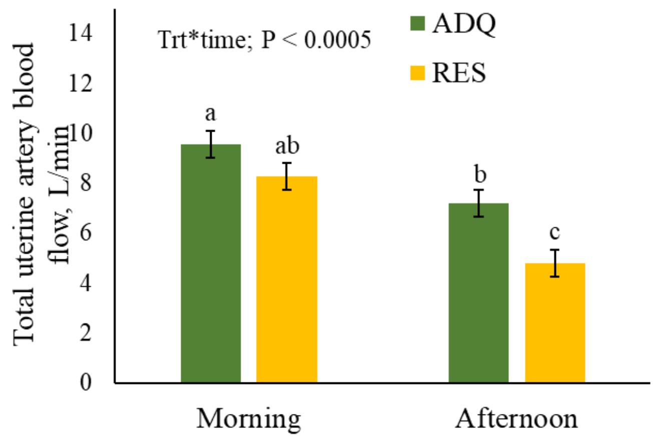

Figure 8. Total uterine artery blood flow in beef heifers at day 220 of gestation. Maternal nutrient restriction (RES; 60% of NRC) or adequate fed (ADQ; 100% of NRC) beginning on day 160 of pregnancy. Doppler ultrasonography occurred from 05:00 – 06:00 hours (morning) or 12:00 – 13:00 hours (afternoon).

05:00 – 06:00 hours (morning) or 12:00 – 13:00 hours (afternoon). Uterine artery blood flow decreased in both nutritional treatment groups from morning to afternoon hours. Moreover, maternal nutrient restriction caused a further decrease in uterine artery blood flow, which was only observable during the afternoon ultrasonography examinations (Figure 8). Figure 9 illustrates total uterine artery blood flow in day 240 pregnant heifers following dietary melatonin supplementation (MEL; 20 mg per day) or no dietary melatonin supplementation (CON) at 08:00 hours beginning on day 190 of gestation. Similar to the nutrient restriction model, total uterine artery blood flow was not different between treatment groups during the early morning ultrasonography examinations. In CON heifers, total uterine artery blood flow decreased from morning to afternoon, while total uterine artery blood flow increased from morning to afternoon in MEL treated heifers (Figure 9). We believe these results indicate a natural 24-hour rhythm in uterine artery blood flow, which can be influenced by melatonin supplementation. Therefore, from a livestock production standpoint, alterations in circadian rhythms during specific windows of gestation may lead to changes in offspring body composition; however, these fetal programming data are lacking. Irrespective, the potential of establishing and/or disrupting these circadian rhythms during specific time points of gestation may alter production characteristics of offspring, which warrants further investigation.

Conclusions

Insufficiencies during pregnancy, resulting in reduced fetal growth and development, are detrimental to beef cattle production. We have consistently observed positive associations with uterine and umbilical blood flow in sheep and cattle relative to fetal and postnatal offspring size. Doppler ultrasonography can increase our understanding of blood flow and blood perfusion during important reproductive events thereby allowing producers to apply specific strategies to improve reproductive efficiency of livestock. Early to mid-gestation nutrient restriction appears to increase placental efficiency in both Angus and Brahman heifers. However, late pregnancy nutrient restriction has been associated with decreased birth weight, increased mortality, and slowed postnatal growth of surviving offspring. Low-input heifer development programs resulting in 50% of mature body weight at breeding did not negatively impact uterine artery blood flow and calf birth weight. Spring calving heifers showed an increase in uterine blood flow compared to their fall calving counterparts, which may be related to environmental differences and even hormonal changes with decreasing daytime length. Furthermore, we have consistently identified an

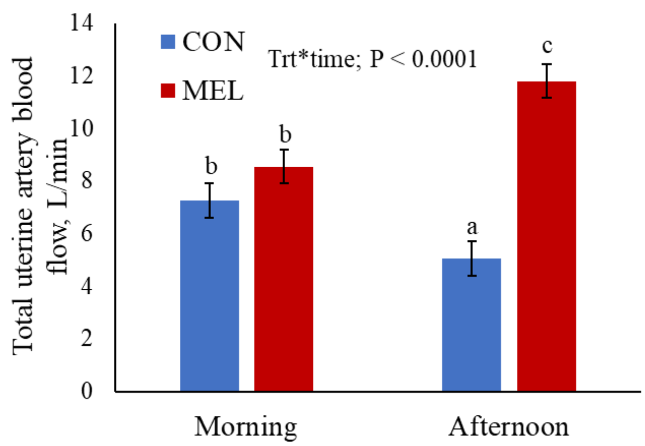

Figure 9. Total uterine artery blood flow in heifers at day 240 of gestation following dietary melatonin (MEL; 20 mg per day) or no melatonin supplementation (CON) at 08:00 hours beginning on day 190 of gestation. Doppler ultrasonography occurred from 05:00 – 06:00 hours (morning) or 12:00 – 13:00 hours (afternoon).

increase in umbilical and uterine blood flows in sheep and cattle during melatonin supplementation. The importance of this pathway in relation to the development and transmission of 24-hour rhythms to the offspring has not been elucidated in cattle. In addition, as melatonin is synthesized from tryptophan, several animal models of intrauterine growth restriction, such as nutrient restriction, could be decreasing endogenous melatonin concentrations and, in turn, decreasing fetal exposure to melatonin during significant time points of development. This deregulation could contribute to fetal programming responses outside of the common pathways studied to date.

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