Maternal Nutrition and Fetal Programming

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Introduction

The maternal system can be influenced by many different extrinsic factors, including nutritional status, which can program nutrient partitioning and ultimately growth, development and function of the major fetal organ systems (Wallace, 1948; Wallace et al., 1999; Godfrey and Barker, 2000; Wu et al., 2006). The trajectory of prenatal growth is sensitive to direct and indirect effects of maternal environment, particularly during early stages of embryonic life (Robinson et al., 1995), the time when placental growth is exponential. Understanding the impacts of the maternal environment on placental growth and development is especially relevant as the majority of mammalian livestock spend 35-40% of their life within the uterus, being nourished solely by the placenta. Moreover, pre-term delivery and fetal growth restriction are associated with greater risk of neonatal mortality and morbidity in livestock and humans. Offspring born at an above average weight have an increased chance of survival compared with those born at a below average weight in all domestic livestock species, including the cow, ewe, and sow. Just as growth restricted human infants are at risk of immediate postnatal complications and diseases later in life (Barker et al., 1993; Godfrey and Barker, 2000), there is increasing evidence that production characteristics in our domestic livestock may also be impacted by maternal diet (Wu et al., 2006). Some of the complications reported in livestock include increased neonatal morbidities and mortalities (Hammer et al., 2011), intestinal and respiratory dysfunctions, slow postnatal growth, increased fat deposition, differing muscle fiber diameters and reduced meat quality (reviewed in Wu et al., 2006).

The objective of this proceedings paper is to highlight some of our laboratories investigations on how maternal environment can impact fetal and placental development, impacts on uterine and/or umbilical blood flow in cattle and sheep, and potential timing of intervention, or potential therapeutics, that may increase uteroplacental blood flow.

Placental vascular development

The placenta plays a major role in the regulation of fetal growth. In ruminants, the fetal placenta attaches to discrete sites on the uterine wall called caruncles. These caruncles are aglandular sites which appear as knobs along the uterine luminal surface of non-pregnant animals, and are arranged in two dorsal and two ventral rows throughout the length of the uterine horns (Ford, 1999). The placental membranes attach at these sites via chorionic villi in areas termed cotyledons. The caruncular-cotyledonary unit is called a placentome and is the primary functional area of physiological exchanges between mother and fetus. In the ewe, the growth of the cotyledonary mass is exponential during the first 70 to 80 days of pregnancy, thereafter slowing markedly until term (Stegeman, 1974). In the cow, the cotyledonary growth progressively increases throughout gestation (Reynolds et al., 1990; Vonnahme et al., 2007). Using the same vascularity determination techniques, capillary area density (CAD; a flow-related measure), capillary number density (CND, an angiogenesis-related measure), capillary surface density (CSD, a nutrient exchange-related measure), and capillary size were determine in the sheep and cow. In sheep caruncular tissue, CAD, CND, CSD, and capillary size increased 214, 37, 140, and 45% from d 50 to 140 in normal pregnancy (gestation length of sheep = ~147 days; Reynolds et al., 2005; Borowicz et al., 2007). In the ovine cotyledon, CAD, CND, CSD increased 437, 1,093, and 576%, and capillary size decreased 25% from d 50 to d 140 in normal pregnancy.

In cows, caruncular CAD and capillary size

decreased by 30 and 68%, whereas CND and CSD increased 151 and 32% from d 125 to 250 of gestation in control animals (gestation length in cattle ~280 d; Vonnahme et al., 2007). Furthermore, cotyledonary CAD, CND, CSD, and capillary size increased by 186, 80, 172, and 71% from d 125 to 250 of gestation, respectively. Thus, the pattern of placental angiogenesis (particularly in the maternal tissue) appears to differ between the cow and sheep.

Placental nutrient transport efficiency is directly related to uteroplacental blood flow (Reynolds and Redmer, 1995). All of the respiratory gases, nutrients, and wastes that are exchanged between the maternal and fetal systems are transported via the uteroplacenta (Reynolds and Redmer, 1995, 2001). Thus, it is not surprising that fetal growth restriction in a number of experimental paradigms is highly correlated with reduced uteroplacental growth and development (Reynolds and Redmer, 1995, 2001). Establishment of functional fetal and uteroplacental circulations is one of the earliest events during embryonic/placental development (Patten, 1964; Ramsey, 1982). It has been shown that the large increase in transplacental exchange, which supports the exponential increase in fetal growth during the last half of gestation, depends primarily on the dramatic growth of the uteroplacental vascular beds during the first half of pregnancy (Meschia, 1983; Reynolds and Redmer, 1995). Therefore, an understanding of factors that impact uteroplacental blood flow will directly impact placental function and thus fetal growth.

Nutritional impacts on placental function

Reports of changes in placental vascularity in response to realimentation of nutrient restricted ewes and cows are very limited. In cows nutrient restricted from d 30 to 125 of gestation, there was a decrease in total placentome weight on day 125 versus control cows. This suppression in total placentome weight was still observable even after realimentation until day 250 (Zhu et al., 2007; Vonnahme et al., 2007). Looking more closely at placentome weight in the cow, both the cotyledonary and caruncular portions were decreased in nutrient restricted versus control cows at the end of the nutrient restriction (day 125), however, only the weight of the cotyledonary tissue remained suppressed at d 250. In contrast, several sheep models of maternal nutrient restriction from early to mid-pregnancy followed by realimentation showed significant compensatory growth of the entire placentome (Foote et al., 1958; Robinson et al., 1995; Heasman et al., 1998; McMullen et al., 2005). The differences in the impacts of nutrient restriction and realimentation in the cow (Vonnahme et al., 2007) and the sheep models described above may result from inherent species differences in placental development between sheep and cattle, the duration or intensity of the restriction, or the duration or intensity of the realimentation.

While maternal nutrient delivery during pregnancy has been shown to program the growth and development of the fetus, both during pregnancy and later into adult life, it appears that maternal nutrition also programs the development of the placenta. In the cow, realimentation after ~90 days of nutrient restriction is the stimulus not only for altering placental vascularity and development but also placental function (Vonnahme et al., 2004a,b). The ability to impact the plasticity of the placenta by dietary, or other managerial means, has caused our laboratory to focus on how modulating placental function can impact fetal and postnatal growth and development.

Uterine and umbilical blood flows

Adequate uteroplacental blood flow is critical for normal fetal growth, and therefore, not surprisingly, experimental conditions designed to investigate fetal growth retardation and placental insufficiency, be it overnutrition, nutrient restriction, hyperthermia, or high altitude, commonly share reduced uterine and umbilical blood flows (for review see Reynolds et al., 2006). Therefore, modifying uterine blood flow and nutrient transfer capacity in the placenta allows for increased delivery of oxygen and nutrients to the exponentially growing fetus. 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. Discovery of novel

therapeutic agents that improve placental function would decrease the incidence of morbidity and mortality as well as suboptimal offspring growth performance in livestock species.

Therapeutic agents targeting placental blood flow increased fetal growth in compromised pregnancies (Reynolds et al., 2006). For example, supplementing arginine, the precursor for nitric oxide production (an important regulator of blood flow), increased birth weights in compromised pregnancies (Vosatka et al., 1998). Kwon et al. (2004) nutrient restricted ewes from day 28 to 135 of gestation and reported lowered amino acids and polyamines in maternal and fetal plasma as well as fetal allantoic and amniotic fluids at both mid and late gestation. There is an ever-increasing wealth of data that are demonstrating how realimentation, or other therapeutic agents, may be used to rescue at-risk pregnancies. In our laboratory, we have investigated the role that realimentation, protein supplementation, melatonin supplementation, and maternal activity has on uteroplacental blood flow and/or vascular reactivity of the placental arteries. In order to perform the former, we have employed the use of Doppler ultrasonography. Other methods of determining blood flow are very invasive and require increased numbers of animals to determine blood flow at different time points during pregnancy. While these are effective, they are also labor intensive and time consuming resulting in decreased animals monitored throughout a study. By continuously monitoring the same animal, which has not undergone surgical manipulation, we feel that we can effectively determine how different interventions may regulate uteroplacental blood flow. Our current animal models are outlined below.

Nutrient Restriction

In normal pregnancies, resistance of the uteroplacental arteries have been documented to decrease as gestation advances. Our laboratory has reported that when pregnant ewe lambs are nutrient restricted, lamb birth weight is reduced compared to control fed ewes (Swanson et al., 2008; Meyer et al., 2010). Moreover, we have demonstrated that when ewes are restricted, there is ~33% decrease in endothelial nitric oxide synthase mRNA expression on d 130 of gestation in the maternal portion of the placenta compared to control-fed animals (Lekatz et al., 2010a). We hypothesized that this reduction in birth weight was due to a greater placental vascular resistance in restricted ewes compared to control ewes. In order to evaluate the effects of maternal nutrition on the percentage change in pulsatility and resistance indices (PI and RI, respectively) pregnant ewes receiving either 100% of NRC recommendations, or 60% of the controls were fed to individually housed ewes once daily from d 40 to 108 of gestation. Umbilical cord hemodynamics were assessed by using a duplex B-mode (brightness mode) and D-mode (Doppler spectrum) program of the color Doppler ultrasound instrument (Aloka SSD-3500; Aloka America, Wallingford, CT) fitted with a 5.0 MHz finger transducer (Aloka UST-672). Ultrasonography was performed on d 40, 45, 52, 80, 94, and 108 of gestation. In B-mode a longitudinal section of the umbilical cord was visualized and the pulsatile umbilical artery was confirmed by switching to a duplex screen containing B-mode imaging and Doppler spectrum waveform plots. Measurements were obtained by placing the sample cursor over the vessel in B-mode while simultaneously recording pulsatile waves in D-mode. Pulsatility index (PI; PI = [peak systolic velocity (cm ⁄ s) – end diastolic velocity (cm ⁄ s)]) / (mean velocity (cm ⁄ s)), and resistance index (RI = peak systolic velocity (cm ⁄ s) – end diastolic velocity (cm ⁄ s)]) / (peak systolic velocity (cm ⁄ s)), were calculated using preset functions on the ultrasound instrument. Maternal diet altered the percentage change of both PI and RI with restricted ewes having increased ($P = 0.01$) PI and RI compared to control ewes. We are continuing to evaluate how maternal restriction may impact vascular function and nutrient delivery in pregnant ewes. Moreover, we are developing methodologies to reverse the negative effects of nutrient restriction.

In cattle, nutrient restriction, followed by realimentation, resulted in alterations in placental vascularity and function (Vonnahme et al., 2004 a,b; Vonnahme et al., 2007). Our

hypothesis was that, upon realimentation, the vascular resistance of the uterine artery would over-compensate for the previously nutrient restricted dam. In order to test this hypothesis, pregnant cows (n = 18) were randomly assigned to receive no restriction (Control), or either a short (55 d) or long (110 d) period of nutrient restriction (60% intake of control). Nutrient restriction began on d 30 of gestation. Uterine artery RI was measured every 14 days from d 30 of gestation and continuing until d 254 of gestation. While there was no treatment by day interaction in RI, there was a main effect of treatment. Cows restricted for the longer duration had an overall decrease in RI compared to the short-restricted and control cows, which did not differ (Camacho et al., 2011). Interestingly, the RI decreased upon realimentation in those cows which experienced the longer duration of restriction. The ability of the uteroplacenta to compensate upon realimentation is quite intriguing and we are continuing our studies to determine which portions of the placenta (i.e. maternal or fetal) may contribute to compensatory prenatal growth of the fetus.

Protein Supplementation

While the literature is now booming with increasing evidence of how nutrient restriction impairs several physiological parameters, few concentrate on enhancing postnatal growth in livestock species. In a recent series of papers in cattle, cows gestated on range (where crude protein of forage is < 6%) that were protein supplemented during late gestation had calves similar in birth weight, but had calves with increased weaning weight compared to protein unsupplemented cows (Stalker et al., 2006, Martin et al., 2007; Larson et al., 2009). It is valuable to note that the protein supplementation enhanced growth after birth. Furthermore, the pregnancy rates in heifer calves born from protein supplemented cows were enhanced compared to control cows (93 vs 80%; Martin et al., 2007). It was our hypothesis that the increased fertility and growth rate of the calves from supplemented dams may be due to enhanced uterine blood flow and/or placental nutrient transfer. Ongoing studies in our laboratory are investigating how protein supplementation during late gestation can impact uterine blood flow. Studies are currently underway to determine how protein supplementation in the beef cow can alter uterine blood flow. We hypothesize that uterine blood flow would be increased to enhance nutrient transfer to the fetus, and while birth weights may not be altered (as reported by Stalker et al., 2006; Martin et al., 2007; Larson et al., 2009), growth trajectory of the musculoskeletal and reproductive systems of the offspring may be enhanced.

In order to more fully understand the impacts of maternal protein on uteroplacental blood flow and placental vascular development, we are currently utilizing an ovine model where the diets are isocaloric, with differing levels of protein in the diet. Singleton fetuses from ewes consuming the high protein diet are heavier on d 130 of gestation compared to fetuses from ewes consuming the low protein diet, with no differences in placental weight apparent (Camacho et al., 2010). When uterine blood flow was obtained from a single time point (d 130 of gestation), ewes consuming the high protein diet had a decrease in uterine blood flow compared to the low group, with the control being intermediate (Camacho et al., 2010). Moreover, when investigating the ability of the fetal placental arteries to vasodilate to increasing concentrations of bradykinin, placental arteries from high protein ewes had a decreased responsiveness compared to control and low protein ewes (Lekatz et al., 2010). Understanding if additional calories (i.e. cow study), or a greater proportion of total calories coming from protein (i.e. sheep study), needs to be elucidated, and further work is underway in our laboratory.

Melatonin

Therapeutic supplements thought to target placental blood flow and nutrient delivery to the fetus have been shown to increase fetal growth in animal models of intrauterine growth restriction (Vosatka et al., 1998; Richter et al., 2009; Scatterfield et al., 2010); however, few studies have addressed uteroplacental hemodynamics in models of improved fetal growth. For instance, melatonin supplementation

was shown to negate the decreased birth weight in nutrient restricted rats (Richter et al., 2009), which was attributed to increased placental antioxidant enzyme expression in nutrient restricted rats supplemented with melatonin. Our hypothesis was that dietary melatonin treatment during a compromised pregnancy would improve fetal growth and placental nutrient transfer capacity by increasing uterine and umbilical blood flow. The uteroplacental hemodynamics and fetal growth were determined in ewes that received a dietary supplementation with or without melatonin (5 mg) in adequately fed (100% of NRC recommendations) or nutrient restricted (60% of control) ewes. Dietary treatments were initiated on d 50 of gestation and umbilical blood flow, as well as fetal growth (measured by abdominal and biparietal distances) were determined every 10 d from d 50 to d 110 of gestation. By d 110 of gestation, fetuses from restricted ewes had a 9% reduction ($P = 0.01$) in abdominal diameter compared to fetuses from adequately nourished ewes, whereas fetuses from melatonin supplemented ewes tended to have ($P = 0.08$) a 9% increase in biparietal diameter (Lemley et al., 2012).

We did observe a significant melatonin treatment by day interaction ($P < 0.001$) for umbilical artery blood flow which was increased in melatonin supplemented ewes from day 60 through 110 of gestation compared to control (no melatonin supplementation). Moreover, at day 110 of gestation melatonin supplemented ewes had a 20% increase in umbilical artery blood flow compared to control ewes. In addition, a significant nutritional plane by day interaction ($P < 0.0001$) was observed for umbilical artery blood flow, which was decreased in restricted ewes from day 80 through 110 of gestation compared to adequately fed ewes. Moreover, at day 110 of gestation restricted ewes had a 23% decrease in umbilical artery blood flow compared to adequately fed ewes (Lemley et al., 2012). While we are continuing our investigations into the impacts of melatonin supplementation in at-risk pregnancies, we feel that melatonin treatment may be useful in negating the consequences of intrauterine growth restriction that occur due to specific abnormalities in umbilical blood flow.

Summary and conclusions

We hope to improve approaches to management of livestock during pregnancy which may impact not only that dam's reproductive success, but her offspring's growth potential and performance later in life. Future applications of this research may be used to develop therapeutics for at-risk pregnancies in our domestic livestock. If these therapeutics can be used on-farm, producers would have the ability to increase animal health while also reducing costs of animal production. While each species is unique in its placental development and vascularity, comparative studies may ultimately assist researchers in understanding how the maternal environmental impacts placental, and thus fetal, development.

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