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How the maternal environment impacts fetal and placental development: implications for livestock production

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Abstract

Fetal survival is dependent upon proper placental growth and vascularity early in pregnancy. The ability for the fetus to reach its genetic growth potential is dependent upon the continual plasticity of placental function throughout gestation. Inadequate maternal environment has been documented to alter fetal organogenesis and growth, thus leading to improper postnatal growth and performance in many livestock species. The timing and duration of maternal nutritional restriction appears to influence the capillary vascularity, angiogenic profile, and vascular function of the placenta in cattle and sheep. In environments where fetal growth and/or fetal organogenesis are compromised, potential therapeutics may augment placental nutrient transport capacity and improve offspring performance. Supplementation of specific nutrients, including protein, as well as hormone supplements, such as indolamines, during times of nutrient restriction may assist placental function. The use of Doppler ultrasonography has allowed for repeated measurements of uterine and umbilical blood flows including assessment of uteroplacental hemodynamics in cattle, sheep, and swine. Moreover, these variables can be monitored in conjugation with placental capacity and fetal growth at specific time points of gestation. Elucidating the consequences of inadequate maternal intake on the continual plasticity of placental function will allow us to determine the proper timing and duration for intervention.

Keywords: developmental programming, fetus, placenta.

Introduction

Livestock producers are interested in utilizing nutrients in the most efficient way to optimize growth of their animals. While growth is often thought to take place after birth, the majority of mammalian livestock (i.e. swine, sheep, and cattle) spend 35-40% of their life within the uterus, being nourished solely by the placenta. Therefore it is especially relevant to understand the impacts of the maternal environment on placental growth and development as this directly impacts fetal growth. 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. Moreover, it is recognized that the maternal system can be influenced by many different extrinsic factors, including nutritional status and level of activity, which ultimately 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). Pre-term delivery and fetal growth restriction are associated with greater risk of neonatal mortality and morbidity in livestock. 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. Complications of low birth weight 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 continual desire to enhance management methods to produce healthy livestock has led to increased research in the area of developmental programming of our livestock species. By understanding how the maternal system can, or cannot, adapt to differing stressors during normal pregnancies, we can develop interventions or therapeutics to augment placental development and enhance uterine blood flow and nutrient delivery in order to produce optimally developed offspring.

Growth and vascularization of the placenta

Establishment of functional fetal and uteroplacental circulations is one of the earliest events during 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.

In swine, the diffuse placenta has chorionic villi attachment distributed over the entire surface of the chorion. The presence of primary and secondary rugae increases the relative surface area of attachment between the endometrium and the fetal membranes

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(Dantzer, 1984). Within the large white breeds of domestic pigs, placental area of attachment continues to increase as gestation advances (Knight *et al*., 1977; Vonnahme *et al*., 2001) and vascular development of placenta, as measured by the density of larger blood vessels (i.e. arterioles), increases ~200% from mid to late gestation (Vonnahme *et al*., 2001). 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). However, in the cow, the cotyledonary growth progressively increases throughout gestation (Reynolds *et al*., 1990; Vonnahme *et al*., 2007). From mid to late gestation in sheep, the capillaries in the caruncle increase in area and number, albeit quite modestly compared to the cotyledon (Reynolds *et al*., 2005, Borowicz *et al*., 2007). Moreover, while the average size of a caruncular capillary increases ~45% from mid to late gestation, the capillary size in the cotyledon decreases ~25% (Reynolds *et al*., 2005; Borowicz *et al*., 2007). The pattern of vascularization of the bovine placentome from mid to late gestation differs from the sheep. In the caruncle, capillary area and size decrease from day 125 to 250 of gestation, whereas capillary number is enhanced (Vonnahme *et al*., 2007; Funston *et al*., 2010). Capillary area, size, and number all increase in the cotyledon from mid to late gestation. Thus, not only does the growth trajectory of placenta differ between sheep and cattle, but also the pattern of placental angiogenesis.

Uteroplacental dysfunction is a common link amongst various experimental approaches to studying intrauterine growth restriction

Regardless of the experimental approach employed to study intrauterine growth restriction, uteroplacental blood flow is reduced (Reynolds *et al*., 2005). In approaches where the pregnant female is undernourished, nutrient availability in maternal plasma is reduced and therefore uptake by the gravid uterus is limited. The other approaches include: exposing the pregnant female to a hyperthermic environment, overnourishing an adolescent pregnant female, reducing the amount of maternal tissue available for placental interaction, or embolizing blood vessels of the placenta. All of these approaches allow for sufficient maternal nutrition, but somehow reduce the functionality of the placenta. Without a properly functioning placenta, the fetus is already in an impaired environment. Regnault *et al*. (2003) induced intrauterine growth restriction by putting sheep at day 39 of pregnancy into hyperthermic conditions for almost 90 days to induce intrauterine growth restriction. In this particular model, placentas from intrauterine growth restricted females were approximately 50% smaller than placentas collected from controls. Not only were fetal weights different between the two treatments, but in the intrauterine growth restricted animal's umbilical vein and fetal artery oxygen carrying capacity was lower compared to controls even though in maternal circulation the oxygen carrying capacity was greater in the hyperthermic treatment. In trying to determine possible mechanisms for the altered placental development, it was determined that one of major angiogenic factors, vascular endothelial growth factor (VEGF), and its receptor, VEGF receptor-1, had increased expression in placental tissue in the intrauterine growth restricted group compared to the control. Another known placental angiogenic factor, placental growth factor, had decreased expression and protein abundance in the intrauterine growth restricted placentas compared to control (Regnault *et al*., 2003). Similar results were found by Redmer *et al*. (2005) in which they utilized the overfed pregnant adolescent model in which abnormal nutrient partitioning occurs and placental growth and function is dramatically impaired. It was found in this study that at the sites of intimate interaction between the maternal and placental tissue from the intrauterine growth restricted group had a reduced expression of VEGF, angiopoietins 1 and 2, and nitric oxide synthase 3.

Reports of changes in placental vascularity in response to realimentation of nutrient restricted ewes and cows are very limited, and appear to be largely lacking in swine. McMullen *et al*. (2005) have demonstrated that a short duration (i.e. 7 days) of fasting during mid-pregnancy in the ewe decreased VEGF mRNA level and placental weights on day 90. While differences in VEGF mRNA were not evaluated at term, placental weights were similar at lambing in nutrient restricted and control ewes. In beef cows nutrient restricted from days 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 (Vonnahme *et al*., 2007; Zhu *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 day 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. Collectively, stressful maternal environments lead to alterations in placental vascular development, which surely will alter nutrient transport and fetal development.

Fetal and postnatal development

Fetal organogenesis is occurring simultaneously with placental development. As the growth trajectories for these tissues vary, each tissue is susceptible to suboptimal conditions (i.e. maternal undernutrition) at different periods. Depending upon the objective of the livestock producer, the organ systems of greatest value may be those that contribute to carcass traits (i.e. muscle and fat development) as well as reproductive performance of replacement females.

As skeletal muscle has a lower priority in nutrient partitioning compared to the brain and heart in response to challenges to the fetus during development, it is particularly vulnerable to nutrient deficiency (Bauman *et al*., 1982; Close and Pettigrew, 1990). Moreover, as there is no net increase in the number of muscle fibers after birth, the fetal period is critical for skeletal muscle development (Glore and Layman, 1983; Greenwood *et al*., 2000; Nissen *et al*., 2003). Maternal nutrient restriction can significantly reduce the number of both muscle fibers and nuclei in the offspring (Bedi *et al*., 1982; Wilson *et al*., 1988; Ward and Strickland, 1991). For example, sows fed high-energy diets during the first 50 days of gestation have progeny with fewer fast glycolytic fibers present in semitendinosus muscle compared to progeny from sows fed low-energy diets (Bee, 2004). In addition, pigs from sows fed a high-energy diet grew slower during lactation, had lower feed to gain ratios, and a higher percentage of adipose tissue than pigs from sows fed a low-energy diet (Bee, 2004). Guinea pigs, provided a diet at 60% of ad libitum intake during gestation, gave birth to pups with a decrease in total muscle fiber development, mostly due to a decrease in secondary muscle fibers (Dwyer and Stickland, 1994). Protein supplementation negated this change in muscle development and the number of secondary muscle fibers was similar to controls (Dwyer and Stickland, 1994) providing evidence that protein supplementation of the dam may enhance weight gain by increased muscle fiber number, which is determined prior to birth. However, Bayol *et al*. (2004) reported that mice from dams fed restricted diets has similar muscle fiber number and mRNA for myostatin or MyoD (a myogenic regulatory transcription factor) compared to controls. Therefore, muscle fiber type development may be impacted by nutritional state, depending upon the energy needs of the muscle and species. Nutrient restriction from early to mid gestation results in a reduction of fetal skeletal muscle fibers, which may be related to a down-regulation of mammalian target of rapamycin (mTOR) signaling (Zhu *et al*., 2006). The mTOR pathway is believed to mediate nutrient signals such as amino acid sufficiency (Fumagalli and Thomas, 2000; Gringras *et al*., 2001) and provides a link between nutritional levels and skeletal muscle development (Erbay *et al*., 2003).

Protein supplementation during late gestation enhances steer calf performance as heavier weaning and carcass weights have been reported (Larson *et al*., 2009). Steers from supplemented dams have increased intramuscular fat and a greater overall percentage of body fat (Larson *et al*., 2009). If cows are nutrient restricted, steers had reduced live and carcass weights compared to steers from adequately fed cows at 30 months of age (Greenwood *et al*., 2004). Interestingly, retail yield of the carcasses, based on indices of fatness, were greater in the steers from nutritionally restricted cows (Greenwood *et al*., 2004), indicating while muscle growth may be hindered in offspring from cows receiving low nutrition during pregnancy, ability to accumulate fat is not.

Tissues needed for offspring reproductive performance would also be low on the priority list for the developing fetus if nutrients are limiting. However, there is evidence in the literature that reproductive performance of the female offspring can be influenced by the nutrient uptake from her dam. Heifers born from multiparous cows given a protein supplement during the last third of pregnancy had an increased pregnancy rate compared to heifers from non-supplemented dams (Martin *et al*., 2007). Fewer heifers from non-supplemented dams attained puberty before the first breeding season compared with heifers from supplemented cows in a subsequent study (Funston *et al*., 2008). Additionally, in rats where dams were protein restricted during pregnancy, female pups had a delay to vaginal opening (i.e. puberty) and time to first estrus compared to control dams (Guzman *et al*., 2006).

Our laboratory has also shown that maternal diet can impact the fetal reproductive tissues. Fetal ovaries from ewes experiencing a 40% nutrient restriction had a decreased cellular proliferation rate in primordial follicles compared to ovaries from fetuses of adequately fed ewes (Grazul-Bilska *et al*., 2009). This decreased proliferation in primordial follicles may impact future follicular activity, fertility, and

reproductive longevity of the female offspring. Unfortunately, these data do not provide information if the reproductive success of these offspring will be altered.

Uterine and umbilical blood flows

As mentioned above, 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, 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.

Nutrient restriction

At NDSU, we have been utilizing a primiparous ewe carrying a singleton fetus that is nutrient restricted 40% compared to controls from day 50 of gestation (Table 1). We have individually fed these ewes, and in studies where lambs were born, they were immediately separated from their dam to prevent confounding our postnatal assessments, as we have reported colostrum and milking performance of the dam to be altered due to gestational treatment (Swanson *et al*., 2008; Meyer *et al*., 2010).

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 eNOS mRNA expression on day 130 of gestation in the maternal portion of the placenta compared to control-fed animals (Lekatz *et al*., 2010). 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 nutrient restriction on the percentage change in pulsatility and resistance indices, 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). 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. Restricted ewes had increased ($P < 0.01$) PI and RI in the umbilical artery compared to control ewes. 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; Satterfield *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; National Research Council, 1985) or nutrient restricted (60% of control) ewes. Dietary treatments were initiated on day 50 of gestation and umbilical blood flow, as well as fetal growth (measured by abdominal and biparietal distances) were determined every 10 days from day 50 to day 110 of gestation. By day 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). When ewes were restricted, decreased umbilical blood flow was observed 30 days after the nutrient restriction was initiated, while melatonin supplementation increased umbilical blood flow just 10 days after supplementation. On day 90 of gestation, restricted ewes receiving melatonin had similar umbilical blood flows compared to adequately fed ewes not receiving melatonin (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.

Table 1. A summary of how maternal nutrient restriction from mid to late gestation impacts maternal, fetal, placental, and offspring parameters.

	Response in RES Compared to CON
Measured during gestation	
Plasma levels day 130 of gestation[1]	
Maternal Glucose	Decreased 12%
Fetal Glucose	Decreased 16%
Maternal NEFA	Increased 54%
Fetal NEFA	Increased 6% ***NS**
Maternal BUN	Decreased 10%
Fetus BUN	Decreased 12%
Placental weight[1,2]	Similar
Fetal weight[1,2]	Decreased 15-20%
Umbilical blood flow (day 50-110)[2]	Decreased ~20%
Umbilical vascular resistance[3]	Increased 15 to 25%
Measured at term[4]	
Birth weight	Decreased 13%
Crown rump length	Decreased 4%
Abdominal girth	Decreased 5%
Placental weight	Similar
Organ characteristics[2]	
Heart weight	Decreased 8%
RV binucleated cell area	Increased 36%
LV binucleated cell area	Increased 25%
Ovarian follicle proliferation[5]	Decreased 40%
Measured in offspring	
Plasma IgG 24 h old[6]	Increased 33%
Organ weights at 21 days[7]	
Brain	Similar
Heart	Decreased 16%
Total gastrointestinal	Decreased 11%
Liver	Decreased 16%
Visceral adiposity	Decreased 23%
Adrenal	Decreased 11%
Offspring from 3 to 6 months[4,8]	
Live weight, 6 months	Similar
Glucose tolerance, 3 and 5 months	Decreased 40%
Carcass weight[9]	Similar
Internal fat mass[9]	Decreased 23% ***NS**

RES = 60% nutrient restriction from day 50 to day 130 or to term; *NS = not statistically different at $P < 0.05$. References for data taken from: [1]Lekatz *et al*., 2010; [2]Lemley *et al*., 2012; [3]Lekatz *et al*., 2009; [4]Neville *et al*., 2010; [5]Grazul-Bilska *et al*., 2009; [6]Hammer *et al*., 2011; [7]Camacho *et al*., 2012; [8]Vonnahme *et al*., 2010; [9]Unpublished observations.

Maternal activity

As gestational housing of swine in the United States appears to be shifting from housing in individual stalls to group housing, there is limited information on how fetal development is being altered. While the impact of group housing on litter size is inconclusive, Lammers *et al*. (2007) hypothesized the increase in litter size and decrease in stillborn fetuses from sows in their study that were housed in groups during gestation could be attributed to the increased mobility of the females. Exercise during gestation has been studied in several animal species including the rat (Garris *et al*., 1985; Houghton *et al*., 2000), and sheep (Lotgering *et al*., 1983a, b; Chandler *et al*., 1985) with the duration and intensity of exercise impacting both umbilical and uterine blood flows (Lotgering *et al*., 1983b; see review by McMurray *et al*., 1993), as well as birth weight

(Garris *et al*., 1985). Our laboratory hypothesized that umbilical blood flow to the fetus would increase in female swine that were given the ability to increase their activity during gestation. For two parities, pregnant female swine were individually housed, and beginning on day 40 of gestation (gestation length = 114 days), a subset of females were selected to increase their activity levels. Whereas control females remained in their gestation stall for the duration of pregnancy, females selected for exercise were individually walked for 30 min, 3 times a week, at the pace of each individual. All animals received the same diet and were housed in the same room. Beginning on day 39, and approximately every 14 days until 90 days of gestation, umbilical blood flows were determined from two independent fetuses per litter by Doppler ultrasonography. On days 70 and 84 of gestation, umbilical blood flows were increased ~25% in females that were allowed to exercise compared to control females (Harris, 2010). Gestation length, obstetrical interventions, length of parturition, average birth weight, and placental weight did not differ ($P > 0.15$). Upon harvest at 6 months of age, it was determined that while hot carcass weight was not different between groups, pigs from the exercised gilts had increased carcass quality as measured by muscle color (Minolta L*), muscle pH at 45 min, and water content of the muscle (Vonnahme *et al*., 2011), indicating that carcass quality may be improved in pigs from active females. Studies are underway to determine if maternal activity alters nutrient transport across the placenta and if this impacts the muscular development of the fetus.

Summary and conclusions

The goal of our laboratory is to improve approaches to management of livestock during pregnancy which enhances 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, or alter management methods 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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