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NUTRITION DURING GESTATION AND FETAL PROGRAMMING

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INTRODUCTION

Historically, considerable efforts have been made to understand how nutrition impacts health and productivity during the postnatal period. While maternal nutrition during pregnancy plays an essential role in proper fetal and placental development, less is known about how maternal nutrition impacts the health and productivity of the offspring. Indeed, the prenatal growth trajectory is sensitive to the direct and indirect effects of maternal dietary intake from the earliest stages of embryonic life when the nutrient requirements for conceptus growth are negligible (Robinson et al., 1977). Not only is neonatal health compromised, but the subsequent health may be "programmed" as offspring from undernourished dams have been shown to exhibit poor growth and productivity and also to develop significant diseases later in life (Barker et al., 1993; Godfrey and Barker, 2000).

Fetal, or developmental programming, defined as the concept that a maternal stimulus or insult at a critical period in fetal development has long term impacts on the offspring, was originally coined by Dr. David Barker, at Southampton University in England (Barker et al., 1993; Godfrey and Barker, 2000). Barker and his colleagues studied birth records in the United Kingdom and Europe, and related different maternal stresses to infant weight and physical characteristics at birth and to subsequent health status in later life. Of interest was that they determined that maternal undernutrition in the first half of gestation, followed by adequate nutrition from mid-gestation to term, resulted in infants of normal birth weight, which were proportionally longer and thinner than normal. This early fetal undernutrition resulted in an increased incidence of health problems experienced by these individuals as adults, including obesity, diabetes, and cardiovascular disease. In livestock production settings, undernutrition can often occur during gestation, particularly during the first two trimesters. This results from either low feed reserves and(or) management practices that result in cows losing weight during late fall and early winter (Sletmoen-Olsen et al., 2000a,b). However, current data indicate that health and growth of offspring born from undernourished mothers are diminished (Godfrey and Barker, 2000; Vonnahme et al., 2003). This theory of developmental programming has been experimentally challenged and verified using several animal models. While variations in the duration and severity of maternal undernutrition do not always result in a reduced birth weight, physiologic alterations such as glucose intolerance, skewed growth patterns and even alterations in carcass characteristics have been reported. Therefore, birth weight in and of itself may not be the best predictor for calf survival and productivity.

The objective of this paper is to review the literature on bovine fetal and placental development and how maternal nutrition impacts fetal, neonatal and postnatal health and performance of the offspring. While this work will concentrate on beef cattle, examples from other species will be added when appropriate.

FETAL AND PLACENTAL DEVELOPMENT

The bovine embryo enters the uterus 4 days after ovulation. The critical period of maternal recognition of pregnancy occurs between days 15-18 after ovulation, followed by the initial stages of early placentation. In the cow, the placenta attaches to discrete sites on the uterine wall called caruncles. These caruncles are aglandular proliferations of connective tissue which appear as knobs along the uterine luminal surface. These caruncles are arranged in two dorsal and two ventral rows throughout the length of the uterine horns. The placental membranes attach at these sites via chorionic villi in areas called cotyledons. By day 120 of gestation, the placental vasculature can be seen radiating out from the umbilicus to the individual cotyledons. The caruncular-cotyledonary unit is called a placentome and is the functional area of physiological exchanges between cow and calf. In association with the formation of the placentome, the caruncular area is progressively vascularized to meet the increasing demands of the conceptus. Approximately day 120 of gestation is a transitional period in caruncular vascularization, which sets the stage for subsequent increases in nutrient transfer required to support the rapidly growing fetus (Ford, 1995; Reynolds and Redmer, 1995). It is clear that the placenta plays a fundamental role in providing for the metabolic demands of the fetus; thus, although placental growth slows during the last half of gestation, placental function increases dramatically to support the exponential rate of fetal growth (Metcalfe et al., 1988; Ferrell, 1989; Reynolds and Redmer, 1995). For example, in sheep and cattle, uterine blood flow increases approximately three- to four-fold from mid- to late gestation (Rosenfeld et al., 1974; Reynolds et al., 1986; Reynolds and Redmer, 1995).

Establishment of a functional fetal/placental vascular system is one of the earliest requirements during conceptus development (Reynolds and Redmer, 1995). However, in order for the conceptus to effectively draw nutrients from the maternal system, the uterine vasculature must be properly developed. In cows, preferential vascularity of the caruncles begins around day 90 of gestation, with a marked increase in both blood flow and vascular density by day 120 of gestation (Ford, 1995). The establishment of the vascular architecture is essential if the maternal side is to support the exponentially growing fetus during the last trimester of gestation (Reynolds and Redmer, 2001). Any detrimental effects of maternal nutrition during this critical establishment of the maternal-fetal vascular systems would impact the ability of the fetus to acquire the proper amount of nutrients and oxygen. 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 (Eley et al., 1978; Prior and Laster, 1979), depends primarily on the dramatic growth of the uteroplacental vascular beds during the first half of pregnancy (Meschia, 1983; Reynolds and Redmer, 1995).

Fetal organogenesis is occurring simultaneously as placental development. In the beef cow fetus, as early as 21-22 days post-ovulation, the heart beat is apparent. Limb development occurs as early as day 25 of pregnancy followed by a sequential development of other organs, including the pancreas, liver, adrenals, lungs, thyroid, spleen, brain, thymus, and kidneys (Hubbert et al., 1972). By day 45, testicles of male calves are being developed, followed shortly thereafter by ovarian development occurring by day 50-60 of gestation. As the growth trajectories for these tissues vary, each tissue is susceptible to suboptimal conditions (i.e. maternal undernutrition) at different time periods.

NUTRITIONAL IMPACTS ON THE FETUS

Undernutrition of the pregnant cow during the initial stages of fetal development may appear to be unimportant because of the limited nutrient requirements of the fetus for growth and development during the first half of gestation. This is accentuated by the fact that 75% of the growth of the ruminant fetus, for example, occurs during the last two months of gestation (Robinson et al., 1977). However, it is during this early phase of fetal development that maximal placental growth, differentiation and vascularization occurs, as well as fetal organogenesis, all of which are critical events for normal conceptus development.

Recently, Vonnahme et al. (2007) reported that multiparous beef cows bred to the same bull and carrying female fetuses to either meet NRC requirements to gain weight (average = + 4.25% body weight) from d 30 to d 125 of gestation had fetuses which were heavier than cows fed below NRC to lose weight (average = - 6.8% body weight). Upon realimentation, fetuses in both groups were similar in weight near term. Previous studies in the sheep (Whorwood et al., 2001) and human (Ravelli et al., 1988; Barker et al., 1993; Godfrey et al., 1996) have demonstrated that an extended period of maternal nutrient restriction during the first half of gestation results in relatively normal birth weights, but leads to increases in the length and thinness of the neonate. The clinical significance of epidemiological data of the fetal programming lies in the associations between transient reductions in maternal nutrition during early gestation, and the risk of abnormalities in skeletal muscle function, mineralization of bone, liver cholesterol metabolism, insulin secretion, renal development and obesity (Godfrey and Barker, 2000; Rhind et al., 2001). Unfortunately, at present, little is known about the specific nutrient induced changes in fetal programming events resulting in the observed permanent alterations in adult structure, physiology and metabolism in the bovine.

Specifically, feeding pregnant rats a low-protein diet results in lifelong elevations in blood pressure in the offspring (Langley and Jackson, 1994). A documented response of the fetus to early chronic undernutrition is significantly increased blood pressure (Murotsuki et al., 1997). Increases in fetal blood pressure are known to result in alterations in lung vascular remodeling in association with the previously mentioned myocardial hypertrophy in the rat (Fabris and Pato, 2001). Fabris and Pato (2001) speculated that lung growth in late gestation is adversely affected by pulmonary hypertension. The pulmonary circulation develops concomitantly with distal lung air space growth during late gestation and early postnatal life (deMello et al., 1991). Wohrley et al., (1995) demonstrated that hypoxic conditions selectively induce the proliferation of smooth muscle cells associated with the pulmonary arteries in neonatal calves with pulmonary hypertension. The precise relationship between alveolar and vascular development during fetal and early postnatal life and the mechanisms that coordinate lung vascular growth and alveolarization are uncertain. However, the angiogenic factor, vascular endothelial growth factor (VEGF), produced from airway epithelial cells, play a major role in vascular growth development during fetal life (Zeng et al., 1998). These findings suggest that mechanisms may exist linking lung vascular development with alveolar growth, further suggesting that disruption of normal vascularization may contribute to altered alveolarization, and thus lung function. Bovine respiratory diseases make up the majority of illness and death loss in the feedlot segment. Historically, 15-45% of feedlot cattle have been affected with bovine respiratory disease (BRD), with 1-5% of total cattle placed on feed, dying of BRD (Kelly and Janzen, 1986). Respiratory disease alone accounts for 44.1% of deaths in beef feedlot cattle (Vogel and Parrott, 1994). It is possible that gestational nutrient restriction could increase susceptibility of cattle to respiratory disease during later life, i.e. in the feedlot.

Rats whose mothers had been fed a diet with a low ratio of protein to energy during pregnancy also showed permanently altered glucose production and utilization and associated insulin secretion (Desai et al., 1995). More specifically, Fowden and Hill (2001) have demonstrated in rodents that changes in the intra-uterine nutritional environment cause alterations in the structure

and function of the pancreatic islets. Altered pancreatic islets have life-long effects and predispose the animal to glucose intolerance and diabetes. Intra-uterine programming of the endocrine pancreas in ruminant species is less well established at present, however, recently in our laboratories at NDSU, we have demonstrated that ewe lambs from restricted dams have altered glucose metabolism (Effertz et al., 2007). While relative insulin resistance of the adult ruminant compared to other species make it difficult to establish whether fetal changes in islet development have long term consequences, Murphy et al. (2000) report that small changes in nutrient metabolism (determined via response to a glucose challenge) were sufficient to influence milk production in the dairy cow.

As with other tissues, maternal nutritional status is one of the extrinsic factors programming nutrient partitioning and ultimately growth and development of fetal skeletal muscle (Wallace, 1948; Wallace et al., 1999; Godfrey and Barker, 2000; Strickland et al., 2004; Rehfeldt at al., 2004). Growth restriction seems to be especially important when fetal muscle development (myogenesis) is adversely affected (Handel and Stickland, 1987a,b; Dwyer et al., 1993). Skeletal muscle has a lower priority in nutrient partitioning compared to the brain and heart in response to the challenges to the fetus during development, rendering it particularly vulnerable to nutrient deficiency (Bauman et al., 1982; Close and Pettigrew, 1990). The fetal period is crucial for skeletal muscle development, because no net increase in number of muscle fibers occurs after birth (Glore and Layman, 1983; Greenwood et al., 2000; Nissen et al., 2003). Recently, Greenwood et al. (2004) demonstrated that steers from cows which were nutritionally restricted during gestation had lower live and carcass weights compared to steers from adequately fed cows at 30 months of age. Interestingly, retail yield on the carcasses, based on indices of fatness, were greater in the steers from nutritionally restricted cows, indicating that while growth may be hindered in offspring from cows receiving low nutrition during pregnancy, ability to accumulate fat is not.

Most early work investigating the effects of maternal nutrition in the cow studied the latter part of pregnancy. Since most fetal growth occurs in the latter part of gestation, researchers hypothesized that the effects of variation in nutrient intake would have greater effects than in early pregnancy. Many studies report the effects of protein and energy deficiency on birth weight of the calf (see review by Holland and Odde, 1991). In a recent study, when cows are provided a protein supplement during the last third of pregnancy, birth weights were not different between the treated and control groups (Martin et al., 2007). However, heifers born from dams that were protein supplemented during the last third of pregnancy had an increased pregnancy rate compared to heifers from non-supplemented dams (Martin et al., 2007). The mechanism behind this increased reproductive capacity is still unknown.

Cow nutrition precalving has also been shown to affect calf survival. Corah et al. (1975) reported that pregnant cows fed 70% of their calculated energy requirements during the last 90 days of gestation produced calves with increased morbidity and mortality rates. Research conducted at Colorado State University (see review by Odde, 1988) investigated the relationship between precalving nutrition and disease susceptibility in the neonatal calf. First-calf heifers produce calves that have lower levels of serum immunoglobulins at 24 hours of age than calves born to three-year-old and older cows. This occurs even though colostral immunoglobulin levels are similar for these two age groups. The increased disease susceptibility observed in calves born to first-calf heifers is likely due to lower volumes of colostrum produced by first-calf heifers, although decreased calf vigor as a result of dystocia may also contribute. Calves born to thin (< 5 body condition score) two-year-old heifers are less vigorous and have reduced serum immunoglobulin levels at 24 hours of age.

Effects of maternal nutrition during pregnancy on the offspring may have confounded impacts on neonatal development, as the mammary gland, and colostrum yield are also impacted by maternal diet. In a recent study conducted at NDSU, lambs were immediately separated from

their dams, fed artificial colostrum to body weight, and levels of IgG were measured 24 hr later. Offspring from undernourished dams had increased IgG transfer compared to control fed dams (Hammer et al., 2007). This suggests that the fetal gastrointestinal system may be programmed in nutrient restricted animals to be more efficient in extracting nutrients, specifically large molecules like immunoglobulins immediately postnatal, although this has not been determined.

CONCLUSION

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. While the timing and exact nutrients are not yet clearly delineated, it appears that different physiological systems (i.e. reproductive axis, muscle development) may be impacted at different time points during pregnancy. Further research is necessary to fully explain how maternal nutrition impacts economical traits in the beef industry.

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