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Review article: Nutritional effects on fetal development during gestation in ruminants

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Abstract

Intrauterine growth retardation is a massive problem in animal production as it influences the body composition, carcass quality, and impairs health. This condition can lead to a reduction in neonatal survival, growth, feed efficiency utilisation, and future production by the animals. Pregnancy may negatively influence maternal nutritional status because of increased uteroplacental blood flow, nutrient mobilisation, and transfer of nutrients from the dam to the fetus. The critical factor for fetal survival and health is an adequate nutrient and oxygen supply to the dam during gestation. This ability is dependent on her nutritional supply, body size, body composition, and metabolism during pregnancy. The placenta is a unique organ of reproduction that helps in the exchange of nutrients, respiratory gases and excretory waste between the mother and offspring. Maternal nutrition restriction in embryonic, placenta and fetal stages of pregnancy can result in metabolic compromise, cardiovascular, renal and adipose tissue dysfunction. The major effects of nutritional challenges on fetoplacental growth and development appear to occur when the placenta is rapidly developing. Poor nutrition caused by inadequate, excess or imbalanced nutrient intake has been shown to adversely affect subsequent reproductive performance (delayed puberty, luteal inadequacy, reduced follicular reserve, reduced ovulation, and conception rates). Proteins, carbohydrates, fats, minerals and vitamins are key components in animal feeds that are required for a daily maintenance diet. Amino acids serve as building blocks for proteins and essential precursors for the synthesis of different physiological molecules–hormones, neurotransmitters, nitric oxide, creatine, glutathione, carnitine, and polyamines.

Keywords: Maternal, Nutrition, Fetus, Pregnancy, Placenta,

Introduction

The reproductive potential of mammals begins during the animal's fetal life. Fetal programming is used to describe a stimulus or insult caused during a critical period of fetal development that has long-lasting or permanent effects later in life including adulthood (Lucas, 1991). Fetal programming can be in response to hormonal, nutritional and/or metabolic challenges at any time during development. It can lead to altered cell proliferation, differentiation, and phenotype resulting in structural and/or functional modifications to the cells, tissues and organ systems (Sinclair *et al.,* 2016). The concept of fetal programming was originally proposed by Prof David Barker in 1990s (Barker *et al.,* 1993) and is referred to as the Barker hypothesis (Osmond *et al.,* 1993; Langley and Jackson, 1994; Barker and Clark, 1997). The concept that maternal nutrition at different stages of pregnancy can adversely influence the offspring's lifetime productivity, health and development has gained much interest and attention from epidemiological research in human populations. This has led to detailed experimental studies, in different animal models such as rodents and livestock (Greenwood *et al.,* 2010). Additionally, there is growing evidence that maternal nutrition can induce epigenetic modifications in the fetal genome (Sinclair

et al., 2016). Epigenetic changes could be described as the changes in the heritable gene expression without an alteration of the genetic code, such as DNA methylation and histone modification. The body system that has received the least attention has been the reproductive tract with limited studies investigating the effects of maternal nutrition on fertility-related parameters in the offspring. Therefore, there is a need to investigate the molecular mechanisms underlying the link between alterations to the intrauterine environment and the short and long-term effects on the reproductive health of the offspring. Intrauterine growth retardation (IUGR) is an impaired growth and development of the fetus during pregnancy. Consequently, IUGR is a massive problem in animal production as it influences the body composition, carcass quality, and impairs health. This will lead to a reduction in neonatal survival, growth, feed efficiency utilisation, and future production by the animals (Yates *et al.,* 2018). Maternal nutrient constraints during pregnancy reduce fetal growth in both humans and experimental animals (Wallace *et al.,*2004; Abu-Saad and Fraser, 2010; Mcnight *et al.,* 2011). Pregnancy may negatively influence maternal nutritional status because of increased uteroplacental blood flow, nutrient mobilisation, and transfer of nutrients from the dam to the fetus. Animal studies have revealed complex biological mechanisms responsible for IUGR (Wu *et al.,* 2006). These mechanisms are corroborated by clinical observations and include: (1) reduced placental growth and vascularity; (2) impaired placental function (including the capacity for transport of amino acids and glucose); (3) oxidative stress in the placenta and conceptus; (4) reduced concentrations of haemoglobins (because of iron deficiency) for oxygen transport; (5) impaired cell signalling for regulation of protein synthesis in the placenta and fetus; and (6) impaired immune response of maternal/fetal placenta (Wu *et al.,* 2004, Wu *et al.,* 2006). Maternal size and nutritional stressors are different maternal constraints that can affect the fetal growth and reproductive development during pregnancy (Redmer *et al.,* 2004; Rhind, 2004; Wu *et al.,* 2006; Gootwine *et al.,* 2007; enyon, 2008; Gardner *et al.,* 2009). Equally, the litter size can have a great influence on birth weight (Gardner *et al.,* 2007). For example, singleton offspring are heavier at birth and at weaning than multiple fetuses (Morris and enyon, 2004; Gootwine *et al.,* 2007; enyon, 2008).. Multiple fetuses have higher nutrient demand and are more greatly affected by maternal constraints than singletons, hence, IUGR is prevalent in animals with multiple fetuses (Gootwine *et al.,* 2007). Lighter dams carrying multiple fetuses (triplets and quartets) like pigs, rats and rabbits have smaller placentas, which effects the rate and capacity of maternal nutrient absorption and oxygen transfer to the fetuses (Gootwine *et al.,* 2007) resulting in a higher probability of IUGR. Maternal nutrient constraints are very common in animal production. Numerous factors affect nutrient requirements for livestock including breed, season, and physiological status. This can be caused by lack of feed availability, drought, poor pasture growth, overstocking of animals, breeding young dams, twin and triplet offspring, selection for increased milk production or breeding of livestock during poor pasture conditions (Wu *et al.,* 2006; Reynolds, 2010). The aim of this paper is to review the nutritional effects on fetal development during pregnancy in farm animals like sheep and cow. The review paper elucidated maternal influences on the fetus, effect of maternal nutrition during critical windows of pregnancy, effects of maternal nutrient restriction on the fertility of the female offspring, and effects of protein restriction during gestation.

Maternal influences on the fetus

The critical factor for fetal survival and health is an adequate nutrient and oxygen supply to the dam and this ability is dependent on her nutritional supply, body size, body composition, and metabolism. However, another important key factor is the composition of the diet in terms of protein, energy, fat, vitamin and mineral content (Robinson *et al.,*2006; Symonds *et al.,* 2006; Wu *et al.,* 2006; Symonds *et al.,* 2010). The placenta is a unique organ of reproduction that helps in the exchange of nutrients, respiratory gases and excretory waste between the mother and offspring (Redmer *et al.,* 2004). Thus, the developing fetus will be dependent on placental function, which is in turn dependent on maternal nutrition. The timing, duration and degree of nutritional insult may result in different effects on the growth and development of the fetus, neonatal survival and adulthood later in life (Vonnahme *et al.,* 2003; Vonnahme *et al.,* 2006; Gootwine *et al.,*2007; Quigley *et al.,* 2008). It is only extreme maternal deprivation that will severely compromise pregnancy and leads to termination of the fetus (Bloomfield *et al.,* 2003). Birth weight is an indicator of fetal and dam's nutrition/health during pregnancy (Gardner *et al.,*2007). That said, birth weight is not a conclusive measure of the quality of fetal growth (Harding and Johnson, 1995; Wu *et al.,*2004) as there can be a period of catch-up growth or sensitive critical windows for particular organs that are affected by undernutrition (Bloomfield *et al.,* 2006). Many studies have suggested that under or over-nutrition can specifically effect the total body weight as well as altering the ratios of the organ to fetal weights (Robinson *et al.,*1999; Vonnahme *et al.,* 2003; Bloomfield *et al.,* 2006; Quigley *et al.,* 2008).

Effect of maternal nutrition during critical windows of pregnancy

The average gestation length of sheep and cattle is ~147 and 285 days respectively; and typically studies have split pregnancy up into 3 trimesters: early pregnancy (up to 50 days [sheep] and 95 days [cows]), mid-pregnancy (50-95 days [sheep] or 96-190 days [cows]) and late pregnancy (after 96 days [sheep] or 191 [cows]. This takes into account that throughout the gestation period, the growth pattern of the placenta and fetus differ (Gootwine *et al.,* 2007; Kenyon, 2008). Pregnancy encompasses embryogenesis, fetal organogenesis, and placental development (Fig 1). The nutrient requirements in this window are relatively small, but the metabolic activity and growth rate of the fetus is high (Robinson *et al.,*1999). In mid-pregnancy, the placenta will have reached its maximal size and there will be the maximal number of germ cells in the developing ovary (Schneider, 1996). The late pregnancy is often referred to as the fetal phase as it is characterised by maximal fetal growth and is associated with the highest nutritional demand (Symonds *et al.,* 2006; Kenyon and Webby, 2007). There are long-term effects on the offspring following maternal nutritional restriction during all three critical periods (Fig. 1). For example, maternal nutrition restriction in embryonic, placenta and fetal stages of pregnancy can result in metabolic compromise, cardiovascular, renal and adipose tissue dysfunction (Fig. 1).

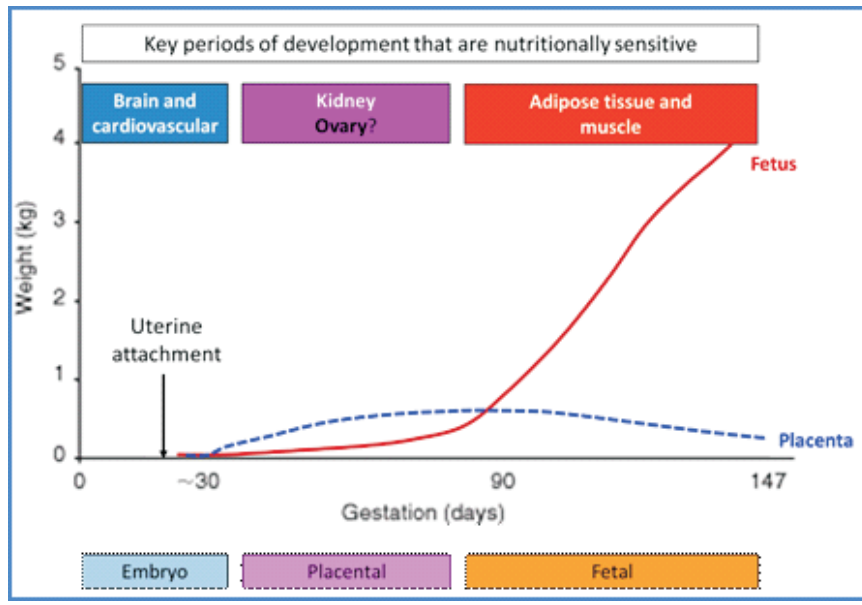

Fig. 1: Summary of long-term effects of maternal nutritional restriction during the critical developmental period on offspring
The key windows of placental and fetal organ development that are sensitive to nutrition during gestation in sheep are indicated. Adapted from (Symonds *et al.,* 2006; Symonds *et al.,* 2010).

During early pregnancy, the embryo's nutrient requirement is small but can be very specific in its temporal and qualitative requirements. This can result in subsequent altered fetal growth (Wu *et al.,* 2004; Bloomfield *et al.,* 2006). Indeed, any maternal nutrient manipulation during early pregnancy can lead to drastic changes in offspring live weight and body condition (Annett and Carson, 2006). For the first 3 weeks of pregnancy, nutrients for the embryo are derived from uterine secretions that can reflect any changes in the nutritional environment of the dam (Symonds *et al.,* 2006). Thereafter, nutrients are supplied via the placenta. Embryonic attachment occurs (~day 20), while placenta (maternal and fetal components) growth commences on ~day 30 (Symonds et al., 2010) with placentome number established by day 40 (Schneider, 1996). This is the time where the greatest proportion of cellular differentiation, organ formation and angiogenesis occur. Placentome number and size are nutritionally influenced (Heasman *et al.,* 1999). The nutrient supply will also affect the local placental production of growth factors (e.g. IGF2) that will influence placental and fetal growth. High protein content during the early trimester reduced body weight of the adult male offspring but protein restriction either early or mid-trimester did not affect body weight or carcass fatness in male or female adults (Micke *et al.,* 2011). The major effects of nutritional challenges (under- or overnutrition) on fetoplacental growth and development appear to occur when the placenta is rapidly developing, i.e. day 40–80 of pregnancy in sheep (Robinson *et al.,* 1999; Wu *et al.,* 2006). Placental growth appears to be more sensitive to maternal feed restriction during the early pregnancy and fetal growth during the mid-pregnancy (McCrabb *et al.,* 1992). It should be noted that there are studies where nutrient restriction during mid-pregnancy did not

result in functional placental insufficiency and restricted fetal growth. It is feasible that these contradicting reports may relate to differences in dam breed, age, parity, maturity, size, body condition and nutritional status or the postnatal life of animals (Anthony *et al.,* 1986; Vonnahme *et al.,* 2006; Greenwood and Cafe, 2007). There are few studies in cattle and the majority of those have varied dietary protein content (i.e. 70 vs 240% recommended) during both early and mid-trimesters (Micke *et al.,* 2010; Micke *et al.,* 2011). For example, nutrition restriction at 55% and 50% of energy and protein NRC recommendations during second trimester in heifers were unaffected with respect to birth weight, postnatal growth and carcass characteristics (Long *et al.,* 2010). Late pregnancy is the time when most of the increase in fetal size takes place (Robinson *et al.,* 1999; Symonds *et al.,* 2006; Kenyon *et al.,* 2007). Many important fetal growth factors (e.g. IGF2, insulin and thyroid hormones) are nutritionally regulated during this period (Bloomfield *et al.,* 2006). Insufficient maternal nutrition reduced the concentration of IGF1 and IGF2 in fetal circulation which decreased myogenic cell proliferation and formation of muscle fibres (Gonzalez et al., 2013).

Effects of maternal nutrient restriction on the fertility of the female offspring

Poor nutrition caused by inadequate, excess or imbalanced nutrient intake has been shown to adversely affect subsequent reproductive performance (e.g. delayed puberty, luteal inadequacy, reduced follicular reserve, reduced ovulation, and conception rates) (Smith and Somade, 1994; Ashworth *et al.,* 2009; Scaramuzzi et al., 2011; Mossa et al., 2013). For example, maternal undernutrition during late pregnancy in ewes reduced fetal growth (Rhind *et al.,* 1989) and the lambing rates in female offspring (Gunn *et al.,* 1995). The sexual differentiation of both female and male offspring is almost completed by mid-pregnancy (Rhind, 2004). In addition, restricted in the dietary protein altered total number of oocytes, delayed ovarian development in fetal sheep (Rae *et al.,* 2001), reduced ovulation rate in adult sheep (Rae et al., 2002), increased calving interval (Cushman *et al.,* 2014), decreased antral follicle number in adult cattle (Mossa *et al.,* 2013). More specifically delayed fetal ovarian development was observed on day 110 of gestation in restricted ewes (Rae *et al.,* 2001). This was associated with decreased Ki67 (proliferation marker) in germ cells on day 65 of gestation in the maternal nutritionally restricted fetuses (Lea *et al.,* 2006). In addition, pro-apoptotic, BAX expression in the primordial follicles was increased on day 110 gestation. This indicated increased loss of germ cells during the formation of follicles in nutrient-restricted animals (Lea *et al.,* 2006). Since the number of oocytes is defined by birth, the potential of the animal's lifetime reproductive performance could be reduced. Thus, a consequence of poor fetal ovarian development could be premature ovarian failure. It is hypothesised that is, in part, due to improper development of the stromal compartment leading to the poor follicular formation (Robinson *et al.,* 2006). These effects and the critical windows of maternal undernutrition on fetal ovarian development in sheep are summarises in Fig. 2. In general, there are fewer studies investigating the effects of maternal dietary restriction on the offspring's subsequent reproductive performance. Some studies that have been conducted have showed a reduced number of antral follicles and anti-Mullerian hormone (AMH) concentrations in the adult (Evans et al., 2012; Mossa et al., 2013). Importantly, female offspring with lower AMH concentration in their first year of age is a physiological indication of reduced or low follicular reserve (Evans *et al.,* 2012).

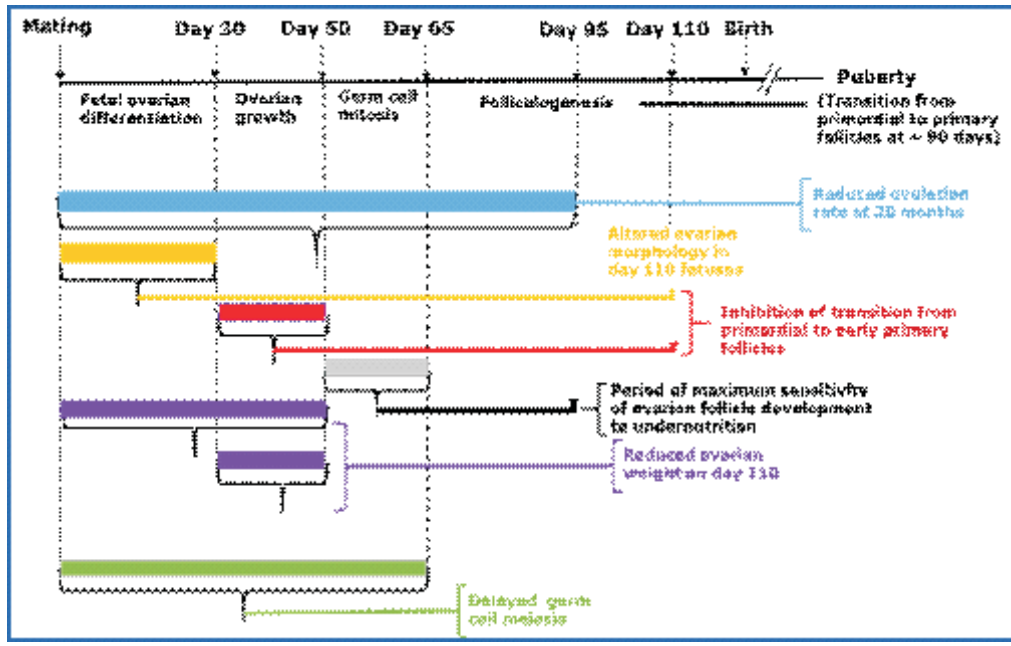

Fig. 2: Critical periods during gestation when maternal undernutrition has affected fetal ovarian development in sheep

Shaded areas refer to periods of contrasting maternal nutrition (0.5 vs 1.0 times maintenance) in discrete experiments. Adapted from Robinson *et al.,* 2006)

Effects of protein restriction during gestation

Proteins, carbohydrates, fats, minerals and vitamins are key components in animal feeds that are required for a daily maintenance diet. These are important for growth, production and reproduction (Rinehart, 2008). Protein is typically the most expensive nutrient in a diet and is regularly deficient in an animal's daily ration (Burroughs *et al.,* 1975; Jurgens, 2002). The primary aim of protein supplementation is to meet the amino acid requirement that is needed for de novo protein synthesis and tissue growth. Any protein supplement may contain true protein and/or non-protein nitrogen (e.g. urea) (Kellems and Church, 2002). However, the microbes in the sheep or cow's rumen will synthesise their amino acid requirements by converting non-protein nitrogen to ammonia to maintain microbial growth. Amino acids serve as building blocks for proteins and essential precursors for the synthesis of different physiological molecules–hormones, neurotransmitters, nitric oxide, creatine, glutathione, carnitine, and polyamines (Wu, 2009). For the provision of protein to the fetus, there must be a balance of adequate essential and non-essential amino acids. A pregnant dam must consume a high-quality protein meet the daily protein requirement as most grains are deficient in the essential amino acids: lysine, methionine, threonine, and tryptophan (Lyman *et al.,* 1956). Maternal protein supplementation during pregnancy can increase body condition score and body weight of the cow at calving (Sanson *et al.,* 1990; Bohnert *et al.,* 2002). More importantly, maternal protein supplementation affected the development of calf reproductive capabilities (Martin *et al.,* 2007). While protein malnourished rodents had a shorter lifespan in both males

and females (Ozanne and Hales, 2004; Langley-Evans and Sculley, 2006). However, in sheep with a 50% restriction of protein intake (17 vs. 8.7 g crude protein/MJ metabolizable energy) from day 0 to 65, there was no effect on maternal amniotic or fetal plasma amino acid concentration but urea was reduced indicating reduced protein turnover (Dunford *et al.,* 2014). In rodents, maternal protein malnutrition affected various body systems in the offspring including higher blood pressure (Langley and Jackson, 1994), reduced glucose tolerance (Langley *et al.,* 1994), lower birth weight (Simmons *et al.,* 2001) and metabolic syndrome (McMillen and Robinson, 2005). Maternal protein restriction can affect fetus metabolism, insulin resistance, and obesity. Protein restriction resulted in increased postnatal growth catch-up (Hales *et al.,* 1996; Zierath *et al.,* 1996; Balasa *et al.,* 2011). Maternal diet has affected placental factors in many species (Rutland *et al.,* 2007). This is important as placental weight and vascularity are indicators of placental function and related to fetal growth. The long-term effects of maternal protein restriction have not been fully elucidated in terms of the critical levels and time windows in relation to the germ cell development, postnatal growth and reproductive development of offspring even in their later life and generations to follow (Redmer *et al.,* 2004). Moreover, there is little or no literature investigating how the vascularisation to the fetal ovary might be influenced by maternal nutrition restriction.

Conclusion

Inadequate maternal nutrient supply leads to poor placental development, resulting in compromised fetal growth with long-term consequences for offspring reproduction, fertility, health and productivity. Factors that influence fetal and placental growth and development include maternal plane of nutrition, number of foetuses (twin and triplet), maternal parity and age, maternal and fetal genotype, and maternal stress. Placental circulation provides the developing conceptus with a uterine environment that is able to meet its metabolic demands and facilitates nutrient, respiratory gas, and metabolic waste exchange between the maternal and fetal systems throughout pregnancy. Fetal growth and development are influenced by vascular development and function of the placenta, ultimately influencing neonatal growth and survival. Placental growth and function (e.g. vascular contractility, blood flow, and nutrient delivery) are profoundly impacted by maternal nutrition. Maternal protein supplementation during pregnancy can increase body condition score and body weight.

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