Journal of Animal and Veterinary Advances 18 (7): 215-226, 2019
ISSN: 1680-5593

Dietary Amino Acid Supplementation and its Relationship with Placental and Fetal Growth in Pigs

[1, 2, 3]Agustina Romanelli, [1, 4] Susana N. Dieguez, [1, 2, 3]Alejandro L. Soraci
[1]Departamento de Fisiopatología, Facultad de Ciencias Veterinarias,
Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA-FCV),
Pinto 399, B7000 Tandil, Argentina
[2] Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET),
C1425FQB Buenos Aires, Argentina
[3]Centro de Investigación Veterinaria de Tandil (CIVETAN), UNCPBA-CONICET-CICPBA,
Facultad de Ciencias Veterinarias, Campus Universitario, B7000 Tandil,
Buenos Aires, Argentina
[4]Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CIC-PBA),
B1900 La Plata, Buenos Aires, Argentina

Abstract: It is widely accepted that adequate feeding strategies in gestating sows are important for fetal growth and survival. Recently, amino acid nutrition in pigs has been used effectively to improve pregnancy outcomes, especially, conditionally essential amino acids for gestating swine such as arginine and glutamine. Their angiogenic effect during pregnancy has provided an effective approach to solve reduced litter size and to improve sow's reproductive performance. In association with amino acid nutrition in sow diets, placental vascularization and uterine capacity are factors that contribute to mitigate Intrauterine Growth Restriction (IUGR), a common problem in both human medicine and animal production, including swine production. The purpose of this review is to highlight the effects of maternal amino acid supplementation on intrauterine environment and IUGR presentation and to outline recent scientific advances supporting its beneficial use as a nutritional tool in gestating sow diets.

Key words: Amino acid nutrition, hyper prolific sows, intrauterine environment, supplementation, gestation, intrauterine growth restriction

INTRODUCTION

In modern pig production, genetic selection for improved prolificacy has brought profits to the pork industry such as an increased ovulation rate that yields a higher number of piglets per sow per year (Vonnahme *et al*., 2002; Foxcroft, 2007; Panzardi *et al*., 2009; Santomá and Pontes, 2011; Lin *et al*., 2014; Yuan *et al*., 2015; Bin *et al*., 2018; Matheson *et al*., 2018), resulting in an increase of at least 1.8 piglets per litter in commercial sows. As a consequence, the improvement of prolificacy is accompanied by an increase in variability of the litter's birth weight with a higher proportion of lighter piglets (Quesnel *et al*., 2008). Undersized piglets correlate with higher pre and post weaning mortality (mostly due to poor colostrum intake), greater health problems (lighter piglets often exhibit underdeveloped defense mechanisms), lower growth rates (taking longer to reach slaughter weight) and higher management costs (handling litters with lower piglet's birth weight is laborious and brings about logistic issues throughout rearing) (Geisert and Schmitt, 2002; Van Rens *et al*., 2005; Rehfeldt and Kuhn, 2006; Foxcroft, 2007; Vonnahme, 2018; Amdi *et al*., 2013; Quesnel *et al*., 2014;Yuan *et al*., 2015).

It has been demonstrated that uterine blood flow positively correlates with litter sizein mammals, however, blood supply to each fetus decreases when as litter size increases, suggesting that there are certain limits within which uterine blood flow adapts to litter size (Reynolds *et al*., 2005). In this way, the acquisition of different amount of nutrients byeach fetus during gestation may partially explain within litter variation in birth weight variation as the correct supply of all metabolic demands necessary for fetal growth is influenced by uterine and umbilical blood flow (Reynolds and Redmer, 2001; Rootwelt *et al*., 2013). In this context, placentation is a key developmental event during pregnancy, since, it is associated with embryonic survival (Reynolds and Redmer, 2001).

Corresponding Author: Agustina Romanelli, Departamento de Fisiopatología, Facultad de Ciencias Veterinarias,
Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA-FCV),
Pinto 399, B7000 Tandil, Argentina, e-mail: aromanel@vet.unicen.edu.ar

Existing data indicate that pre-natal growth in placental mammals is sensitive to the effects of maternal nutrition at all stages of oocyte maturation until birth (Rehfeldt *et al*., 2004; Ferguson, 2005). Amino Acids (AA) are among the most important nutrients for fetal life. Some of them play crucial roles in regulation of fetoplacental development, intensifying placental angiogenesis, nutrient metabolism and embryogenesis which in turn regulate fetoplacental blood flow (Avagliano *et al*., 2012; Lin *et al*., 2014; Wu *et al*., 2014). Thus, these amino acids are encompassed within the modern concept of Functional Amino Acids (FAA) which are defined as those AA that regulate key metabolic pathways to improve health, survival, growth, development, lactation and reproduction of organisms (Wu, 2010). Supplementation of sow diets with functional amino acids (e.g., arginine, glutamate and glutamine)-in the proper ratio-may improve the survival of low birth-weight offspring by decreasing the incidence of piglets presenting Intra Uterine Growth Retardation (IUGR) (Foxcroft, 2007; Lin *et al*., 2014; Yuan *et al*., 2015). The purpose of this review is to highlight the effects of maternal amino acid supplementation on intrauterine environment and IUGR presentation and to outline recent scientific advances supporting its beneficial use as a nutritional tool in gestating sow diets.

MATERIALS AND METHODS

Intrauterine environment

Uterine capacity as limitation on litter size: Uterine capacity can be defined as the physiological and biochemical limitations imposed on conceptus growth and development by the uterus (Bazer *et al*., 1969a, b) and itis a genotypic characteristic of the animal. To date, it has been demonstrated that uterine capacity as a reproductive trait is lowly heritable and therefore it would hardly increase through genetic selection programs (Wilson *et al*., 1997).

An increase in ovulation rates in hyper prolific sows leads to a major number of conceptuses, exceeding uterine capacity. As gestation progresses, conceptus deaths occur between days 30 and 50 when uterine surface area is insufficient (Yuan *et al*., 2015). Due to the genetic selection for increased litter size, the low weight piglets at farrowing are the result of the increased uterine crowding and lower placental weight and vascularization among other aspects which reduce nutrient supply to the fetuses (Vallet *et al*., 2014).

According to Town *et al*. (2005), the increase ofbrain-to-liver weight ratios in smaller fetuses during late gestationmeans that uterine capacity impacts not only on fetal development but also on fetal survival. Likewise, several authors suggest that a great number of fetuses exceeding uterine capacity presents limiting number of muscle fibers which results in compromised fetal growth and development (Foxcroft *et al*., 2006) and negatively impacts on muscle mass and meat quality at slaughter (Foxcroft, 2007). These considerations support the idea that an imbalance between ovulation rate, embryonic survival and uterine capacity has repercussions on pre- and post-natal development and nutritional interventions need to be ponderedas an opportunity to correct intrauterine life (Foxcroft, 2007).

Intrauterine Growth Restriction (IUGR): Intrauterine Growth Restriction or retardation (IUGR) can be defined as the impaired growth and development of the mammalian embryo/fetus or its organs during pregnancy. According to Wang *et al*. (2003) and Sharma *et al*. (2016) IUGR may be caused by maternal, placental, fetal or genetic factors, or by a combination of them. It is associated with placental insufficiency and reduced fetal uptake of nutrients, especially, amino acids, from the placenta (Lin *et al*., 2014). It is a common problem in both human medicine and animal production, including swine production (Dong *et al*., 2014). By definition, IUGR is different from "Small for Gestational Age (SGA)" which is used in the medical literature almost interchangeably. SGA has been used for those infants whose birth weight is less than the 10th percentile for that particular gestational age and IUGR is a clinical term applied to neonates with clinical evidence of malnutrition (Sharma *et al*., 2016). Approximately 5-10% of human neonates and at least 15-20% of piglets from hyper prolific sows suffer from IUGR (Hu *et al*., 2015). IUGR not only causes mortality and morbidity during the perinatal period but also leads to permanent growth and development retardation of throughout the whole biological cycle (Zhang *et al*., 2015; Wang *et al*., 2005). IUGR piglets are born with immature digestive system, poor energy reserves and low vitality which lead to inappropriate colostrum intake. In turn, this situation would render neglected acquisition of immunoglobulins, reduced thermoregulatory capacity and impairment of gastrointestinal tract development. (Dong *et al*., 2014; Che *et al*., 2017). Consequently, IUGR would result in animals presenting malfunctioning immune systems, low efficiency of feed utilization, decreased growth rates and poor carcass quality (Wang *et al*., 2005).

The small intestine health is crucial for both nutrient absorption and antigen entry since IUGR neonates are more susceptible to infection. IUGR piglets have lower absolute immune organ weight and small intestine length, shorter microvilli, damaged and jagged villi and

decreased villus surface areas, presence of autophagosomes and swelled mitochondria in comparison with normal birth weight piglets. The lower number of epithelial goblet cells and lymphocytes suggests a weaker mucin barrier in the small intestine of these neonate piglets (Dong *et al*., 2014). In previous studies D'Inca *et al*. (2010a) also observed alterations in small intestinal development such as reduced intestinal weight, length, wall thickness, villi height and crypt depth, leading to a reduced intestinal absorptive area. On the other hand, the integrity of the small intestine in the fetus is important to synthesize citrulline and arginine from glutamine/glutamate and proline as transfer of arginine from the sow to the fetus is insufficient to support fetal requirements; besides appropriate arginine synthesis in neonate piglets is crucial because of its deficiency in the sows' milk (McPherson *et al*., 2004; Lin *et al*., 2014).

In gestating hyper prolific sows, fetuses respond to low placental/umbilical blood flow by adapting their circulation in order to preserve oxygen and nutrient supply to the brain, known as "brain sparing" (Cohen *et al*., 2015). As a result of this effect, higher brain-to-vital organs (such as liver, lungs or heart) weight ratios are observed in immature piglets. Furthermore, studies of brain sparing effects in IUGR revealed that the heart, liver and spleen were the most affected organs in stillborn pigs with low birth weight (Foxcroft, 2007). IUGR piglets can be characterized by morphological and behavioral criteria such as light weight, big oval head, a straight forehead, bulging eyes, isolation from the other piglets and lying on their side. Moreover, in multi fetal pregnancies, IUGR is diagnosed when neonates possess birth weights that are lower than the normal distribution of birth weights within litters (Royston *et al*.,1982; Wootton *et al*., 1983)

For ethical reasons, experiments involving human embryos/fetuses make animal models a crucial answer to various aspects of IUGR (Cooper, 1975). In comparison with other domestic mammals, pigs as a polytocous species, show the most severe naturally occurring IUGR due to placental insufficiency (Lin *et al*., 2014) and associated long-term outcomes are more accurately extrapolated to humans. In this context, it is important to keep in mind that advances in piglet's IUGR research could help in human medicine, since, the new born pig is biologically more similar to the human infant than other species commonly used for biomedical research (Wang *et al*., 2003, 2005). This is equally important in the swine industry for increasing animal production to provide high-quality animal proteins for human consumption (Wu *et al*., 2013). Understanding associations with IUGR effects measured in new born piglets contribute to define nutritional strategies in order to reduce their occurrence (Foxcroft, 2007).

Placental characteristics and development: The swine placenta, a transitional organ composed by maternal and fetal tissues is classified as epitheliochorial, diffuse, adecidua and pleated (Amoroso, 1952). Placental adaptations like the presence of areolas (accessory structures of the placenta specialized in the absorption of nutrients in the form of uterine secretions or histotrophe which first appear on d 30) and increased blood flow, arise in response to the nourishing needs during the development of the conceptus (Echeverri, 2004; Bertasoli *et al*., 2015).

The placenta is a highly vascularized organ through which nutrients, waste products, water, ions and respiratory gases are exchanged between the mother and the fetus (Avagliano *et al*., 2012; Sanchis *et al*., 2015; Yuan *et al*., 2015). It also plays a significant role in modulating the maternal immune response to prevent immunological rejection of the conceptus. Morphological characteristics of the placenta such as size, blood flow, vascularity and substrate transport capacity are important factors required for fetal growth (Zhang *et al*., 2015). Uteroplacental circulation and the umbilical vein are the way through which embryos and fetuses acquire nutrients (Yuan *et al*., 2015). It has been observed that blood flow within the placenta is lower in the cervix than in the uterine horns, coincident with fetal weight that increases from the cervix to the utero-tubal junction (Kim *et al*., 2013; Che *et al*., 2017). According to Yuan *et al*. (2015), those piglets located at the ovarian end of the horn are approximately 10% heavier than those located at the cervix. During the last half of gestation fetal weight increases exponentially (McPherson *et al*., 2004) where as placental growth slows down. Additionally, studies in mammalian species show that both uterine and umbilical blood flow increase exponentially during gestation to maximize fetal survival (Reynolds *et al*., 2005).

Placental efficiency (fetal weight/placental weight ratio) is a definition widely used to describe placental adaptations that occur in order to meet fetal growth demands during intrauterine development (Zhang *et al*., 2015). In other words, it stands for the grams of placenta required to support 1g of fetus and it is calculated as grams of fetus per gram of placenta (Vonnahme *et al*., 2001; Zhang *et al*., 2015). Placental efficiency appears to influence the number of fetuses that can survive in a given uterine space and also reflects the underlying mechanisms of fetal development which are significant for the onset of IUGR (Che *et al*., 2017).

Currently, evidence suggests that correct performance of female reproductive organs during gestation depends on an optimal vascular growth which allows an augmented blood flow enhancing nutrient transfer to the fetuses (Reynolds *et al*., 2005). There are two processes responsible for the vascular development of the placenta: vasculogenesis (i.e., formation of new blood vessels) and angiogenesis (i.e., formation of new branches from pre-existing vessels) which initiates with capillary proliferation and culminates in the formation of arterioles, capillaries and venules (Campos *et al*., 2012). Collectively, they allow a proper placental function and thus, a normal embryonic/fetal growth and development (Torry *et al*., 2004; Kassmeyer *et al*., 2009; Wu *et al*., 2012). It has also been reported in morphometric analysis, that vascular area depends on the gestational period and the haemotrophic diffusion distance decreases as the gestational period progresses. The number of blood vessels declines whereas the vascular area increases, in early gestation (d 30-40), intermediate gestation (d 60-70) and at term (d 114) while in advanced gestation (d 90) predominate numerous blood vessels of smaller area. These observations are consistent with an exponential growth of the placenta up to (d 60-70) when it reaches a plateau; conversely, maximum fetal growth occurs, at an exponential rate, from (d 60) until the end of gestation (Cristofolini *et al*., 2018).

In a hypoxic or mal-nourished environment the pig placenta increases villi branching and capillary growth which in turn, increases surface area for gas exchange. When placental (umbilical) blood flow is reduced during pregnancy, some piglets are likely to present IUGR (Yuan *et al*., 2015; Che *et al*., 2017). There by the relation between placental size and vascular development, uterine and umbilical blood flows and fetal weight reflect the important role of the mammalian placenta (Reynolds *et al*., 2005).

Vascular Endothelial Growth Factor (VEGF) and its receptors: There are angiogenic and non-angiogenic factors involved in placental vascular development. One of the most potent stimulators of placental angiogenesis is the Vascular Endothelial Growth Factor (VEGF), produced and secreted by the placenta of several species, including the pig (Vonnahme and Ford, 2004). Its expression is an indirect marker of placental vascularization (Dallanora *et al*., 2017). This factor increases during gestation and is also correlated to placental efficiency (Charnock-Jones *et al*., 2001; Vallet *et al*., 2014). VEGF plays an important role not only in physiological but also in pathological angiogenesis (Charnock-Jones *et al*., 2001) associated with tumor growth (Ferrara *et al*., 2003). VEGF belongs to the same family as the Placental Growth Factor (PLGF), Fibroblastic Growth Factor (FGF) and angiopoietins (ANGPT) (Ferrara *et al*., 2003).

Together with the literature reviewed above Ferrara *et al*. (2004) support that hypoxia represents the main inducer of VEGF gene transcription. VEGF shows a high specificity for endothelial cells of arteries, veins and lymphatic vessels and acts by binding to two specific tyrosine-kinasetrans membrane receptors, tyrosine kinase receptor 1 (Flt-1) and tyrosine kinase receptor 2 (Flk-1 or KDR), both expressed in endothelial and non-endothelial cells (Santos *et al*., 2014). Recent studies have emphasized that Flk-1 is the major mediator of the mitogenic, angiogenic and increased permeability effects (Ferrara *et al*., 2003; 2004), due to its greater capacity to translate the signal of VEGF. Evidence suggests there is an interaction between angiogenic factors and Nitric Oxide (NO) (an endogenous vasodilating factor produced from arginine)to coordinate placental angiogenesis and uteroplacental blood flow, increasing the nutrient supply to the fetuses and, consequently, promoting fetal growth (Che *et al*., 2013; Dallanora *et al*., 2017).

Neonatal piglet's survival: As it has been described above when investigating piglets survival, it is important to consider intrauterine environment including blood flow to the uterus, placental efficiency, adequate partitioning of nutrients from feed and uterine capacity (Baxter *et al*., 2008). An increase in uterine blood flow is often insufficient to compensate for the increased number of fetuses and nutrient delivery is not adequate for the fast growth of fetuses during late pregnancy (Beaulieu *et al*., 2010). Supporting this argument, correlations between body conformation measurements and placental insufficiency reflect an intimate relationship between a poor intrauterine environment and retarded piglet's growth (Baxter *et al*., 2008). Body weight at birth is the most commonly measured zoo technical parameter in newborn animals (Ashworth, 2013), although, it is not a sufficient indicator of survival in itself. Body shape, ponderal index, body mass index and post-partum vitality and viability, represent indicative characteristics of postnatal survival. Ponderal index and body mass index are measures of weight and length which reflect the dimensions of each piglet during gestation. These traits are used to identify human and animal IUGR (Baxter *et al*., 2008). Light-birth weight piglets are at greater risk of mortality and morbidity, especially, during the first three days after birth (Ashworth, 2013).

The umbilical cord is the linkage between mother and fetus and its morphology represents another important indicator of piglet vitality. Further more, measurements of

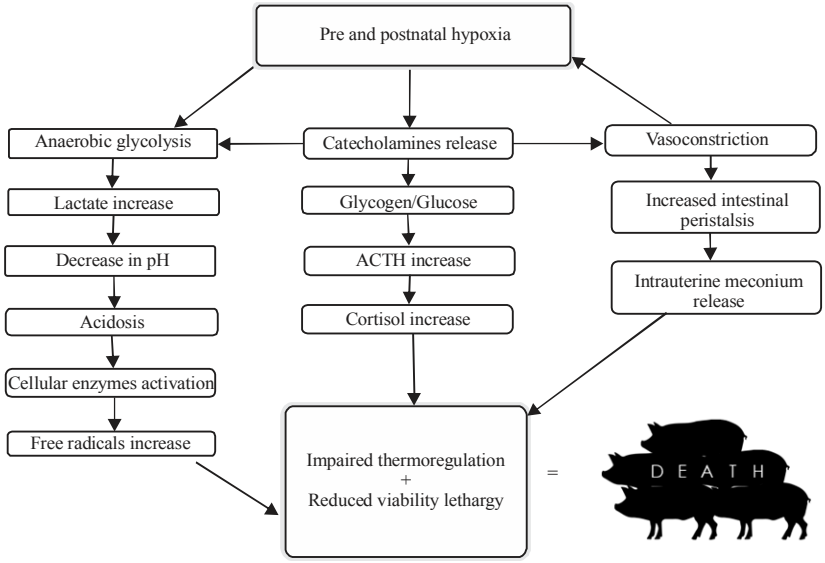

Fig. 1: Pre-and postnatal hypoxia consequences: metabolic pathways activation that impact on piglet thermoregulation, vitality and viability

blood gases provide useful information on oxygen delivery (Trujillo-Ortega *et al*., 2011). During birth, an increase in tensile stress level on the umbilical cord generates higher risk of intrapartumanoxia and perinatal mortality. Intrauterine hypoxia has shown to increase intestinal peristalsis and relaxation of the sphincters causing the expulsion of meconium into the amniotic fluid (Mota-Rojas *et al*., 2002). Augmented levels of plasma lactate in neonates indicates a high probability that piglets have suffered early tissue hypoxia (Trujillo- Ortega *et al*., 2011). Schematic diagram shows pre-and postnatal hypoxia consequences on piglets (Fig. 1).

As a result of physiological characteristics of the porcine placenta piglets are born without immune protection and are forced to obtain maternal antibodies through colostrum intake (Baxter *et al*., 2008). The access of the neonate to colostrum is limited by the sow and competition with litter mates. During the intense neonatal competition for teats, low weight piglets are prone to intake insufficient amount of colostrum to attain thermoregulation, passive immune protection and adequate gastrointestinal tract development (Le Dividich *et al*., 1997). In hyper prolific sows, an increased proportion of low weight piglets results in higher mortality rates. Animals presenting low vitality are slower to acquire colostrum, spend longer time near the udder with higher risk of maternal crushing and also possess poor thermoregulatory abilities leading to piglet lethargy and death due to hypothermia (Baxter *et al*., 2008; Andersen *et al*., 2011).

Some of the negative aspects of hyper prolific genetic lines described above could be overcome or improved by implementation of smart nutritional strategies. It is interesting to bear in mind that the composition of colostrum fatty acids largely depends on the lipid composition of maternal diet at late gestation. In addition, supplementation of fat-soluble vitamins (A and E) at this stage are accumulated in fat tissue and redistributed to colostrum (Mahan, 1994; Bland *et al*., 2001). Improvement of colostrum energy quality through the Sows diet is an important aspect to enhance piglet's survival but this subject is beyond the scope of the present review.

Nutritional strategies directed at gestating and lactating hyper prolific sows should consider increased protein and amino acid needs during these periods. In this way, nutrient requirements would not only contemplate mammary gland growth and colostrum production to support litter growth but also for achieving an optimum reproductive performance (Kim *et al*., 2013).

RESULTS AND DISCUSSION

Dietary amino acids supplementation; Benefits in placental and fetal growth: Adequate feeding strategies in gestating sows are important for fetal growth and survival and sow's reproductive performance. Recently, amino acid nutrition in pigs has been used effectively to improve pregnancy outcomes (Wu *et al*., 2004; Foxcroft, 2007; Mateo *et al*., 2007; Wu *et al*., 2010; Che *et al*.,

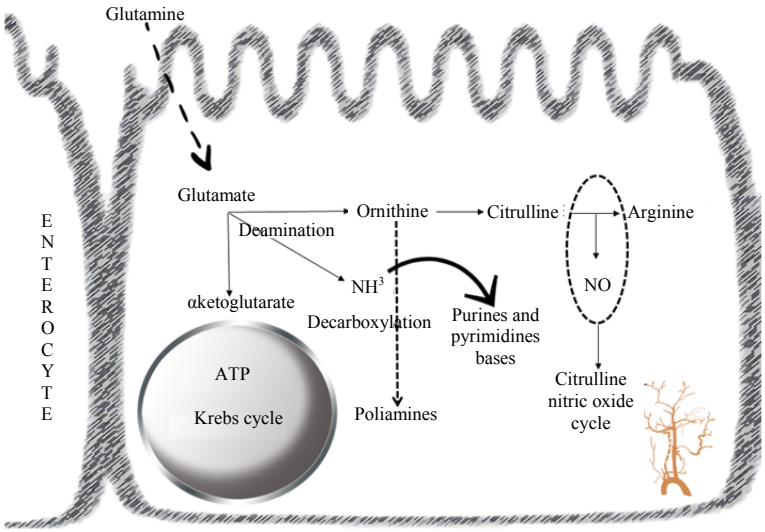

Fig. 2: Schematic description of metabolic pathways in enterocyte for arginine and glutamine

2013; Kim *et al*., 2013; Wu *et al*., 2013; Lin *et al*., 2014; Yuan *et al*., 2015; Bass *et al*., 2017; Dallanora *et al*., 2017; Bin *et al*., 2018; Nuntapaitoon *et al*., 2018).

The National Research Council classified Arginine (Arg) and Glutamine (Gln), among others, as conditionally essential amino acids for gestating swine (NRC., 2012). This means that they are normally synthesized in sufficient amounts by the body but must be provided in the diet to meet needs under specific physiological conditions such as pregnancy and lactation when rates of utilization are greater than rates of synthesis (Wu *et al*., 2013; Bazer *et al*., 2014; Lin *et al*., 2014). Functional amino acids such as arginine and glutamine intensify placental angiogenesis, nutrient metabolism and embryogenesis which result in higher fetoplacental blood flow and increased fetal growth performance and survival (Lin *et al*., 2014).

Arginine, the most abundant N carrier in the body protein is required for neonates and for placental synthesis of nitric oxide and polyamines (putrescine, spermidine and spermine) (Wu *et al*., 2004; 2010; 2013; Bazer *et al*., 2014; Li *et al*., 2014; Dallanora *et al*., 2017) which stimulate placental angiogenesis, vascular growth and provides an adequate uterine capacity for fetal growth and development (Fig. 2). NO is a major endothelium-derived vasodilating factor that regulates placental-conceptus blood flow for embryonic development and implantation and thus, the delivery of nutrients and oxygen from gestating sows to their fetuses. Polyamines, on the other hand, regulate DNA and protein synthesis in the porcine placenta (Wu *et al*., 2004; 2010; 2013; Che *et al*., 2013; Yuan *et al*., 2015). Further more, convincing data revealed that dietary arginine supplementation increases circulating concentrations of VEGF and Flk-1 transcriptional activity and consequently placental angiogenesis in fetoplacental tissues during late gestation (Che *et al*., 2013; Bass *et al*., 2017). Glutamine, a member of the arginine family of amino acids is a limiting factor for fetal growth during the last third of gestation (Wu *et al*., 2004) and is the most abundant free amino acid in porcine fetal umbilical venous plasma (Wu *et al*., 2011; Lin *et al*., 2012; 2014).

In pigs and other mammals, plasma concentrations of arginine derive from the diet and from endogenous sources (de novo synthesis and protein degradation). The maximum level of dietary arginine supplementation in pigs should be 2% on an as-fed basis (90% dry matter) in order to prevent a potential imbalance among basic amino acids, so that, the ratio of digestible arginine to digestible lysine in the diet is <3.0 (Wu *et al*., 2013). Compared with its maternal plasma level (0.13-0.14m mol/L) at (d 40) of gestation, porcine allantoic fluid presents higher arginine concentrations (4-5 m mol/L) when the fetal-placental growth is most rapid (Wu *et al*., 2004; Lin *et al*., 2014). In contrast, glutamine is the most abundant amino acid in amniotic fluid from (d 30-45) of pregnancy and it decreases dramatically in the allantoic fluid after achieving a peak value at d 45 of gestation (Lin *et al*., 2014).

The embryo is nourished by uterine secretions, whereas transport of amino acids and other nutrients between the fetus and the placenta is performed via the umbilical vein (Lin *et al*., 2014). It has been reported that the placental transfer of arginine from the sow to fetal pigs during late gestation is insufficient to meet fetus arginine requirements. In this context, fetuses require intestinal synthesis of citrulline and arginine from glutamine/glutamate and proline. All of the enzymes involved in their synthesis exist in the gut of fetal pigs

(Wu *et al*., 2013). This finding highlights the importance of the rapid growth of the fetal intestine during late gestation for arginine homeostasis and adequate growth of piglets (McPherson *et al*., 2004).

Interestingly, placental insufficiency generates intrauterine changes such as decreased essential amino acid transfer, insufficient caloric intake, altered hormone circulation and down-regulated metabolism. Reduction in blood flow, modifies the balance between anabolic vs. catabolic processes and leads to reductions in fetal development. Hence, improving the placental nutrient supply and consequently decreasing within-litter birth weight variation are two major factors to be considered when adopting nutritional strategies (Yuan *et al*., 2015). According to literature reviewed above, IUGR piglets compared with normal piglets, exhibit lower circulating concentrations of nutrients such as glucose, amino acids of the arginine family (arginine and glutamine) and branched chain amino acids (valine, leucine and isoleucine); these compounds are crucial for correct fetus growth and development. In contrast, they show increased concentrations of ammonia in umbilical vein plasma during late gestation (Yuan *et al*., 2015). Several animal studies indicate that maternal arginine deficiency causes IUGR, increases fetal resorption and death and increases perinatal mortality (Wu *et al*., 2004). Extending this context, the use of dietary amino acids in gestating sows, particularly gilts, may help to prevent IUGR. In fact, amino acids stimulate growth and development of the concept us due to their role as regulators of key metabolic pathways that are essential for maintenance, growth, reproduction and immunity (Wu *et al*., 2009).

Thus, supplementing arginine and glutamine but not total protein per se, to the swine diet during gestation enhances sow's reproductive performance, fetal growth and litter birth weight (Wu *et al*., 2013; Lin *et al*., 2014). However, the optimum timing and amount of amino acid as well as dietary intake of total nitrogen must be considered (Wu *et al*., 2013). Arginine supplementation increases the nitric oxide and polyamines synthesis, hence, it would stimulate not only placental angiogenesis and vasodilation but also transfer of nutrients and oxygen required for optimal conceptus growth (Dallanora *et al*., 2017).

In the present review we have highlighted emerging experimental research that supports the concept that arginine or glutamine supplementation have beneficial effects on embryonic/fetal survival or on preventing IUGR in pigs. Most studies done in countries such as China, United States, Sweden, New Zealand, the Netherlands, Thailand and Brazil have reported beneficial effects of dietary arginine supplementation to gestating swine on pregnancy outcomes (Ramaekers *et al*., 2006; Mateo *et al*., 2007; Berard and Bee, 2010; Wu *et al*., 2010; 2011; 2012; Li, 2011; Gao *et al*., 2012; Che *et al*., 2013; Li *et al*., 2014; 2015; Nuntapaitoon *et al*., 2018) whereas others have reported no effects or adverse effects (Li *et al*., 2010; Bazer *et al*., 2014; Bass *et al*., 2017; Dallanora *et al*., 2017). As described in Table 1, these studies present differences in the parity of gestation of the sows utilized, percentage of arginine or glutamine in the diet or gram/sow per day, moments of amino acid supplementation throughout gestation and amount of dietary intake per day/sow.

Table 1: Effects of maternal dietary amino acid supplementation during pregnancy on zootechnical parameters

References	Pigs	Amino acid	Dose	Period of supplementation during gestation	Effect
Li *et al.* (2010)	Gilts[a]	L-arginine per gilt	0.8% or 16 g/d	Day 0-25[b]	Reduced uterine weight, total number of corpora lutea and conceptuses and total fetal weight[c]
Bazer *et al.* (2014)	Gilts[a]	L-arginine	0.8%	Day 0-25[b]	Higher total number of piglets born per litter,
Li *et al.* (2015)	Gilts and sows[d]	L-arginine HCl	1.3%	Day 1-30	number of piglets born alive per litter and litter birth weight of all piglets born and born alive
Li *et al*. (2011)	Gilts	L-arginine	0.4% or 0.8%	Day 14-25	Increased total volume of amniotic fluid, total amounts of arginine in allantoic and amniotic fluids, total amounts of fructose and most amino acids in amniotic fluid, placental growth
Li *et al*. (2014)	Gilts	L-arginine	0.4% or 0.8%	Day 14-25	Increased number of viable fetuses per litter, total number of fetuses and number of live fetuses, rate of embryonic survival[e].Reproductive performance did not differ[f]
Berard and Bee (2010)	Gilts	Arginine	0.87% or 26 g/d per gilt	Day 14-28	No alteration of placental weight. Increased litter size of viable fetuses (by 3.7/L) and litter weight of viable fetuses (by 32%/L)[g]
Ramaekers *et al*. (2006)	Gilts and sows	Arginine	1% or 25 g/d per animal	Day 14-28	Increased litter size of born-alive piglets (by 1/L)
Campbell (2009)	Gilts and sows	Arginine	1% or 25 g/d per animal	Day 14-28	Increased litter weight of born-alive piglets (by 6.4%/L)
Dallanora *et al*. (2017)	Gilts[h]	Arginine	1%	Day 25-80	Decreased number of piglets born alive and increased stillbirth rate[i]

Table 1: Continue

References	Pigs	Amino acid	Dose	Period of supplementation during gestation	Effect
Gao *et al*. (2012)	Sows[j]	L-arginine HCl	1%	Day 22-114	Enhances placental growth. Increased total number of piglets (by 1.31 per litter), number of born-alive piglets (by 1.10/L), litter birth weight for all piglets (by 1.36 kg) and litter birth weight for born-alive piglets (by 1.70 kg). Increased placental weight (by 16.2%)[k]
Mateo *et al.* (2007)[l*]	Gilts	L-arginine HCl	1%	Day 30-114	Increased number of born alive piglets (by 22%)[*], born-alive piglets (by 2/L)[*] and litter birth weight (by 24%)[*]
Che *et al*. (2013)	Sows[h]	L-arginine HCl	1%	Day 30-114	Increased litter size by (1.4/L) and born-alive
Wu *et al*. (2010)	Gilts	L-arginine plus L-glutamine	0.4% 0.6%	Day 30-114	litter birth weight (by 15%). Reduced variation in birth weights of born-alive piglets (by 24%)
Nuntapaitoon *et al*. (2018)	Sows	L-arginine HCl	0.5 or 1.0%	Day 85-114	Increased proportion of live born piglets, birth weight, blood oxygen saturation and IgG concentration in the sow colostrum
Wu *et al*. (2011)	Sows	Glutamine	1%	Day 90-114	Increased average birth weight and litter birth weight of born-alive piglets. Reduced number of IUGR piglets, variation in birth weight and preweaning mortality of born-alive piglets (39, 33 and 46%, respectively) Increased milk production in lactating sows
Wu *et al*. (2012)	Sows[h]	L-arginine HCl or N-Carbamoyl glutamate	1% 0.1%	Day 90-114	Increased average of birth weight of all piglets born alive (16.2 and 14.3% higher in the arginine and N-carbamoylglutamate groups, respectively) Higher VEGF plasma concentration. Higher expression of VEGF in the allantochorion tissue
Bass *et al*. (2017)	Gilts and sows	L-arginine	1%	Day 93-110	Greater late pregnancy maternal birth weight gain. No effect on number of pigs born alive, piglet birth weight or lactation performance

[a]F1 crosses of Yorkshire x Landrace sows and Duroc x Hampshire boars, individually supplemented; [b]This period is coincident with conceptus implantation to the uterine wall that occurs by day 12-18 in the pig gestation (Vallet *et al*., 2011); [c]Considering that ovulation takes place about 44 h after the onset of estrus these results may be explained by the fact that the peri-ovulatory period is vulnerable to the increased production of Nitric Oxide (NO) due to arginine supplementation which leads to a reduced number of follicles that ovulate and therefore lower progesterone synthesis and corpora lutea regression; [d]Landrace; [e]In gilts with 15-18 corpora lutea on d 60 of gestation compared with the control group; [f]Between the 0.4 and 0.8% L-arginine groups; [g]Compared with the control group. These measures were made at day 75 of gestation; [h]Landrace x Large White; [i]When the litter size was <14, supplementation reduced the percentage of low-weight piglets at birth and increased the average birth weight. This could be the result of increased placental weight or increased placental efficiency; [J]Yorkshire x Landrace; [k]No effect was showed in the weaning-to-estrus interval of sows during gestation and [l]Birth weight or back fat thickness of gilts did not differ between treatment groups

CONCLUSION

Amino acid nutrition in hyper prolific sows and gilts is important to minimize the occurrence of fetal growth retardation in utero. IUGR results in physiological dysfunctions and in an increase of neonatal morbidity and mortality with potential retardation in the preweaning period. This retardation will prevail in every stage as there is no possibility of compensation throughout the animal´s life. At the same time, placental traits can impact on extrauterine challenges which makes the porcine placenta an organ to be taken into account in intensive pig farming. Concerning placental angiogenesis, VEGF increases during swine gestation and is correlated with the fetal-to-placental weight ratio. In spite of this, information on the effects of amino acid supplementation on VEGF expression is still not fully developed.

Due to the angiogenic effect of arginine, glutamine and glutamate supplementation in sows, it is possible to enhance placental weight as well as embryonic and fetal survival, growth and development. This has provided an effective approach to ameliorate reduced litters size and to improve sow's reproductive performance. Despite the existence of well-designed studies on amino acid nutrition in mammals including pigs and humans, many issues still remain to be considered before applying a nutritional strategy in gestation, including differences in breeds or crossbred gestating pigs; sow welfare and environmental factors (e.g., farrowing creates); direct effects produced by arginine or by its metabolites, nitric oxide and polyamines; level or dose of arginine supplementation; day for initiation of arginine or other amino acid supplementation; frequency of feeding in gestating sows and gilts (twice or once a day), the basal diet; management (practical vs. research facilities); number of parities; prolificacy, sow's body weight at the beginning of supplementation and interactions among nutrients or micro ingredients in maternal diets during gestation. The undesirable outcomes of several of the studies mentioned above should not be considered as a lack of a beneficial role of arginine in swine production but rather as a starting point for future research.

RECOMMENDATIONS

Future studies are necessary to fully understand the cellular and molecular mechanisms by which amino acids regulate metabolic pathways and embryonic/fetal growth and enhance placental-fetal blood flows and therefore, the transfer of nutrients and oxygen from mother to fetus, not only in swine production but also in human medicine.

ACKNOWLEDGEMENTS

This research was supported by Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)-CIVETAN (I and D PR3906), Argentina.

REFERENCES

Amdi, C., U. Krogh, C. Flummer, N. Oksbjerg, C.F. Hansen and P.K. Theil, 2013. Intrauterine growth restricted piglets defined by their head shape ingest insufficient amounts of colostrum. J. Anim. Sci., 91: 5605-5613.

Amoroso, E.C., 1952. Placentation. In: Marshall's Physiology of Reproduction, Parkes, A.S. (Ed.). Longmans Green, London, UK., pp: 127-311.

Andersen, I.L., E. Nævdal and K.E. Boe, 2011. Maternal investment, sibling competition and offspring survival with increasing litter size and parity in pigs (Sus scrofa). Behav. Ecol. Sociobiol., 65: 1159-1167.

Ashworth, C.J., 2013. Late pregnancy: The effects of intra-uterine life on production traits in offspring. Anim. Front., 3: 62-67.

Avagliano, L., C. Garo and A.M. Marconi, 2012. Placental amino acids transport in intrauterine growth restriction. J. Pregnancy, Vol. 2012, 10.1155/2012/972562

Bass, B.E., C.L. Bradley, Z.B. Johnson, C.E. Zier-Rush and R.D. Boyd *et al*., 2017. Influence of dietary L-arginine supplementation of sows during late pregnancy on piglet birth weight and sow and litter performance during lactation. J. Anim. Sci., 95: 248-256.

Baxter, E.M., S. Jarvis, R.B. D'eath, D.W. Ross and S.K. Robson *et al*., 2008. Investigating the behavioural and physiological indicators of neonatal survival in pigs. Theriogenology, 69: 773-783.

Bazee, F.W., O.W. Robison, A.J. Clawson and L.C. Ulberg, 1969a. Uterine capacity at two stages of gestation in gilts following embryo superinduction. J. Anim. Sci., 29: 30-34.

Bazer, F.W., A.J. Clawson, O.W. Robison and L.C. Ulberg, 1969b. Uterine capacity in gilts. Reproduction, 18: 121-124.

Bazer, F.W., G. Wu, G.A. Johnson and X. Wang, 2014. Environmental factors affecting pregnancy: Endocrine disrupters, nutrients and metabolic pathways. Mol. Cell. Endocrinol., 398: 53-68.

Beaulieu, A.D., J.L. Aalhus, N.H. Williams and J.F. Patience, 2010. Impact of piglet birth weight, birth order and litter size on subsequent growth performance, carcass quality, muscle composition and eating quality of pork. J. Anim. Sci., 88: 2767-2778.

Berard, J. and G. Bee, 2010. Effects of dietary L-arginine supplementation to gilts during early gestation on foetal survival, growth and myofiber formation. Animal, 4: 1680-1687.

Bertasoli, B.M., A.C. Santos, R.S. Paula, A.S. Barbosa, G.A.B. Silva and E.C. Jorge, 2015. Swine placenta and placentation. Braz. J. Biol. Sci., 2: 199-207.

Bin, P., M.A.K. Azad, G. Liu, D. Zhu, S.W. Kim and Y. Yin, 2018. Effects of different levels of methionine on sow health and plasma metabolomics during late gestation. Food Funct., 9: 4979-4988.

Bland, I.M., J.A. Rooke, A.G. Sinclair, V.C. Bland and S.A. Edwards, 2001. Effects of supplementing the maternal diet with vitamins and vaccinating the sow on immunoglobulin G concentrations in piglet plasma. Proc. Nutr. Soc., 60: 72A-72A.

Campos, P.H.R.F., B.A.N. Silva, J.L. Donzele, R.F.M. Oliveira and E.F. Knol, 2012. Effects of sow nutrition during gestation on within-litter birth weight variation: A review. Animal, 6: 797-806.

Charnock-Jones, D.S., D.E. Clark, D. Licence, K. Day, F.B.P. Wooding and S.K. Smith, 2001. Distribution of Vascular Endothelial Growth Factor (VEGF) and its binding sites at the maternal-fetal interface during gestation in pigs. Reproduction, 122: 753-760.

Che, L., P. Yang, Z. Fang, Y. Lin and D. Wu, 2013. Effects of dietary arginine supplementation on reproductive performance and immunity of sows. Czech J. Anim. Sci., 58: 167-175.

Che, L., Z. Yang, M. Xu, S. Xu and L. Che *et al*., 2017. Maternal nutrition modulates fetal development by inducing placental efficiency changes in gilts. BMC. Genomics, Vol. 18, No. 1. 10.1186/s12864-017-3601-1

Cohen, E., W. Baerts and F.V. Bel, 2015. Brain-sparing in intrauterine growth restriction: Considerations for the neonatologist. Neonatology, 108: 269-276.

Cooper, J.E., 1975. The use of the pig as an animal model to study problems associated with low birthweight. Lab. Anim., 9: 329-336.

Cristofolini, A., M. Fiorimanti, M. Campos, E. Sanchis, T. Diaz, E. Moschetti and C. Merkis, 2018. Morphometric study of the porcine placental vascularization. Reprod. Domest. Anim., 53: 217-225.

D'Inca, R., M. Kloareg, C.G.L. Guen and I.L. Huerou-Luron, 2010. Intrauterine growth restriction modifies the developmental pattern of intestinal structure, transcriptomic profile and bacterial colonization in neonatal pigs. J. Nutr., 140: 925-931.

Dallanora, D., J. Marcon, M.P. Walter, N. Biondo, M.L. Bernardi, I. Wentz and F.P. Bortolozzo, 2017. Effect of dietary amino acid supplementation during gestation on placental efficiency and litter birth weight in gestating gilts. Livestock Sci., 197: 30-35.

Dong, L., X. Zhong, H. Ahmad, W. Li, Y. Wang, L. Zhang and T. Wang, 2014. Intrauterine growth restriction impairs small intestinal mucosal immunity in neonatal piglets. J. Histochem. Cytochem., 62: 510-518.

D'Inca, R., C.G.L. Guen, L. Che, P.T. Sangild and I.L. Huerou-Luron, 2011. Intrauterine growth restriction delays feeding-induced gut adaptation in term newborn pigs. Neonatology, 99: 208-216.

Echeverri, H.M., 2004. Selection for placental efficiency in swine. Ph.D. Thesis, University of Missouri-Columbia, Columbia, Missouri.

Ferguson, J.D., 2005. Nutrition and reproduction in dairy herds. Vet. Clin. North Am. Food Anim. Pract., 21: 325-347.

Ferrara, N., 2004. Vascular endothelial growth factor: asic science and clinical progress. Endocr. Rev., 25: 581-611.

Ferrara, N., H.P. Gerber and J. LeCouter, 2003. The biology of VEGF and its receptors. Natl. Med., 9: 669-676.

Foxcroft, G.R., 2007. Pre-natal programming of variation in post-natal performance: How and when?. Adv. Pork Prod., 18: 167-189.

Foxcroft, G.R., W.T. Dixon, S. Novak, C.T. Putman, S.C. Town and M.D.A. Vinsky, 2006. The biological basis for prenatal programming of postnatal performance in pigs. J. Anim. Sci., 84: E105-E112.

Gao, K., Z. Jiang, Y. Lin, C. Zheng and G. Zhou *et al*., 2012. Dietary L-arginine supplementation enhances placental growth and reproductive performance in sows. Amino Acids, 42: 2207-2214.

Geisert, R.D. and R.A.M. Schmitt , 2002. Early embryonic survival in the pig: Can it be improved? J. Anim Sci., 80: E54-E65.

Hu, L., Y. Liu, C. Yan, X. Peng and Q. Xu *et al*., 2015. Postnatal nutritional restriction affects growth and immune function of piglets with intra-uterine growth restriction affects growth and immune function of piglets with intra-uterine growth restriction. Br. J. Nutr., 114: 53-62.

Kassmeyer, S., J. Plendl, P. Custodis and M. Bahramsoltani, 2009. New insights in vascular development: Vasculogenesis and endothelial progenitor cells. Anatomia Histologia Embryologia, 38: 1-11.

Kim, S.W., A.C. Weaver, Y.B. Shen and Y. Zhao, 2013. Improving efficiency of sow productivity: Nutrition and health. J. Anim. Sci. Biotechnol., Vol. 4, No. 1. 10.1186/2049-1891-4-26

Le Dividich, J., P. Herpin, E. Paul and F. Strullu, 1997. Effect of fat content of colostrum on voluntary colostrum intake and fat utilization in newborn pigs. J. Anim. Sci., 75: 707-713.

Li, J., H. Xia, W. Yao, T. Wang and J. Li *et al*., 2015. Effects of arginine supplementation during early gestation (day 1 to 30) on litter size and plasma metabolites in gilts and sows. J. Anim. Sci., 93: 5291-5303.

Li, X., 2011. Regulation of porcine conceptus survival and growth by L-arginine. Ph.D. Thesis, Texas A&M University, College Station, Texas, USA.

Li, X., F.W. Bazer, G.A. Johnson, R.C. Burghardt and J.W. Frank *et al*., 2014. Dietary supplementation with L-arginine between days 14 and 25 of gestation enhances embryonic development and survival in gilts. Amino Acids, 46: 375-384.

Li, X., F.W. Bazer, G.A. Johnson, R.C. Burqhardt, D.W. Erikson *et al*., 2010. Dietary supplementation with 0.8% L-arginine between days 0 and 25 of gestation reduces litter size in gilts. J. Nutr., 140: 1111-1116.

Lin, G., C. Liu, C. Feng, Z. Fan and Z. Dai *et al*., 2012. Metabolomic analysis reveals differences in umbilical vein plasma metabolites between normal and growth-restricted fetal pigs during late gestation. J. Nutr., 142: 990-998.

Lin, G., X. Wang, G. Wu, C. Feng, H. Zhou, D. Li and J. Wang, 2014. Improving amino acid nutrition to prevent intrauterine growth restriction in mammals. Amino Acids, 46: 1605-1623.

Mahan, D.C., 1994. Effects of dietary vitamin E on sow reproductive performance over a five-parity period. J. Anim. Sci., 72: 2870-2879.

Mateo, R.D., G. Wu, F.W. Bazer, J.C. Park, I. Shinzato and S.W. Kim, 2007. Dietary L-arginine supplementation enhances the reproductive performance of gilts. J. Nutr., 137: 652-656.

Matheson, S.M., G.A. Walling and S.A. Edwards, 2018. Genetic selection against intrauterine growth retardation in piglets: A problem at the piglet level with a solution at the sow level. Gen. Select. Evol., Vol. 50, No. 1. 10.1186/s12711-018-0417-7

McPherson, R.L., F. Ji, G. Wu, J.R. Jr. Blanton and S.W. Kim, 2004. Growth and compositional changes of fetal tissues in pigs. J. Anim. Sci., 82: 2534-2540.

Mota-Rojas, D., J. Martinez-Burnes, M.E. Trujillo-Ortega, M.L. Alonso-Spilsbury, R. Ramirez-Necoechea and A. Lopez, 2002. Effect of oxytocin treatment in sows on umbilical cord morphology, meconium staining and neonatal mortality of piglets. Am. J. Vet. Res., 63: 1571-1574.

NRC., 2012. Nutrient Requirements of Swine. 11th Edn., National Academies Press, Washington DC., USA., ISBN: 978-0-309-22423-9, Pages: 420.

Nuntapaitoon, M., R. Muns, P.K. Theil and P. Tummaruk, 2018. L-arginine supplementation in sow diet during late gestation decrease stillborn piglet, increase piglet birth weight and increase immunoglobulin G concentration in colostrum. Theriogenology, 121: 27-34.

Quesnel, H., L. Brossard, A. Valancogne and N. Quiniou, 2008. Influence of some sow characteristics on within-litter variation of piglet birth weight. Animal, 2: 1842-1849.

Quesnel, H., N. Quiniou, H. Roy, A. Lottin, S. Boulot and F. Gondret, 2014. Supplying dextrose before insemination and L-arginine during the last third of pregnancy in sow diets: Effects on within-litter variation of piglet birth weight. J. Anim. Sci., 92: 1445-1450.

Ramaekers, P., B. Kemp and T.V.D. Lende, 2006. Progenos in sowsTM increases number of piglets born. J. Anim. Sci., Vol. 84,

Rehfeldt, C. and G. Kuhn, 2006. Consequences of birth weight for postnatal growth performance and carcass quality in pigs as related to myogenesis. J. Anim. Sci., 84: E113-E123.

Rehfeldt, C., P.M. Nissen, G. Kuhn, M. Vestergaard, K. Ender and N. Oksbjerg, 2004. Effects of maternal nutrition and porcine growth hormone (pGH) treatment during gestation on endocrine and metabolic factors in sows, fetuses and pigs, skeletal muscle development, and postnatal growth. Domest. Anim. Endocrinol., 27: 267-285.

Reynolds, L.P. and D.A. Redmer, 2001. Angiogenesis in the placenta. Biol. Reprod., 64: 1033-1040.

Reynolds, L.P., P.P. Borowicz, K.A. Vonnahme, M.L. Johnson and A.T. Grazul-Bilska *et al*., 2005. Animal models of placental angiogenesis. Placenta, 26: 689-708.

Rootwelt, V., O., Reksen, W. Farstad and T. Framstad, 2013. Postpartum deaths: Piglet, placental and umbilical characteristics. J. Anim. Sci., 91: 2647-2656.

Royston, J.P., P.A. Flecknell and R. Wootton, 1982. New evidence that the intra-uterine growth-retarded piglet is a member of a discrete subpopulation. Neonatology, 42: 100-104.

Santos, T.C., M.F. Oliveira, P.C. Papa, V. Dantzer and M.A. Miglino, 2014. VEGF system expression by immunohistochemistry and real-time RT-PCR study on collared peccary placenta. Theriogenology, 82: 834-843.

Sharma, D., S. Shastri and P. Sharma, 2016. Intrauterine growth restriction: Antenatal and postnatal aspects. Clin. Med. Insights Pediatr., 10: 67-83.

Torry, D.S., M. Hinrichs and R.J. Torry, 2004. Determinants of placental vascularity. Am. J. Reprod. Immunol., 51: 257-268.

Town, S.C., J.L. Patterson, C.Z. Pereira, G. Gourley and G.R. Foxcroft, 2005. Embryonic and fetal development in a commercial dam-line genotype. Anim. Reprod. Sci., 85: 301-316.

Trujillo-Ortega, M.E., D. Mota-Rojas, O. Juarez, D. Villanueva-Garcia and P. Roldan-Santiago *et al*., 2011. Porcine neonates failing vitality score: Physio-metabolic profile and latency to first teat contact. Czech J. Anim. Sci., 56: 499-508.

Vallet, J.L., A.K. McNeel, J.R. Miles and B.A. Freking, 2014. Placental accommodations for transport and metabolism during intra-uterine crowding in pigs. J. Anim. Sci. Biotechnol., Vol. 5, No. 1. 10.1186/2049-1891-5-55

Van Rens, B.T.T.M., G. de Koning, R. Bergsma and T. van der Lende, 2005. Pre-weaning piglet mortality in relation to placental efficiency. J. Anim. Sci., 83: 144-151.

Vonnahme, K.A. and S.P. Ford, 2004. Differential expression of the vascular endothelial growth factor-receptor system in the gravid uterus of Yorkshire and Meishan pigs. Biol. Reprod., 71: 163-169.

Vonnahme, K.A., 2018. How the maternal environment impacts fetal and placental development: Implications for livestock production. Anim. Reprod. (AR), 9: 789-797.

Vonnahme, K.A., M.E. Wilson and S.P. Ford, 2001. Relationship between placental vascular endothelial growth factor expression and placental/endometrial vascularity in the pig. Biol. Reprod., 64: 1821-1825.

Vonnahme, K.A., M.E. Wilson, G.R. Foxcroft and S.P. Ford, 2002. Impacts on conceptus survival in a commercial swine herd. J. Anim Sci., 80: 553-559.

Wang, T., G.L. Chou, C.Y. Chen and R.J. Xu, 2003. The Piglet as a Model for Studying Intrauterine Growth Retardation. In: The Neonatal Pig: Gastrointestinal Physiology and Nutrition, Xu, R.J. and P. Crawnwell (Eds.). Nottingham University Press, UK., pp: 337-352.

Wang, T., Y. Huo, F. Shi, R. Xu and R.J. Hutz, 2005. Effects of intrauterine growth retardation on development of the gastrointestinal tract in neonatal pigs. Biol. Neonate, 88: 66-72.

Wilson, M.E., S.P. Ford and N.J. Biensen, 1997. A decreased placental size and increased vascular density results in increased prolificacy in the Meishan pig. M.Sc. Thesis, Iowa State University, Ames, Iowa.

Wootton, R., P.A. Flecknell, J.P. Royston and M. John, 1983. Intrauterine growth retardation detected in several species by non-normal birthweight distributions. Reproduction, 69: 659-663.

Wu, G., 2010. Functional amino acids in growth, reproduction and health. Adv. Nutr.: Int. Rev. J., 1: 31-37.

Wu, G., F.W. Bazer, G.A. Johnson, D.A. Knabe and R.C. Burghardt *et al*., 2011. Triennial Growth Symposium: important roles for L-glutamine in swine nutrition and production. J. Anim. Sci., 89: 2017-2030.

Wu, G., F.W. Bazer, M.C. Satterfield, X. Li and X. Wang *et al*., 2013. Impacts of arginine nutrition on embryonic and fetal development in mammals. Amino Acids, 45: 241-256.

Wu, G., F.W. Bazer, R.C. Burghardt, G.A. Johnson and S.W. Kim *et al*., 2010. Impacts of amino acid nutrition on pregnancy outcome in pigs: Mechanisms and implications for swine production. J. Anim. Sci., 88: E195-204.

Wu, G., F.W. Bazer, T.A. Cudd, C.J. Meininger and T.E. Spencer, 2004. Maternal nutrition and fetal development. J. Nutr., 134: 2169-2172.

Wu, G., F.W. Bazer, T.A. Davis, S.W. Kim and P. Li *et al*., 2009. Arginine metabolism and nutrition in growth, health and disease. Amino Acids, 37: 153-168.

Wu, G., F.W. Bazer, Z. Dai, D. Li, J. Wang and Z. Wu, 2014. Amino acid nutrition in animals: Protein synthesis and beyond. Annu. Rev. Anim. Biosci., 2: 387-417.

Wu, X., Y.L.Yin, Y.Q. Liu, X.D. Liu and Z.Q. Liu *et al*., 2012. Deng Z. Effect of dietary arginine and N-carbamoylglutamate supplementation reproduction and gene expression of eNOS, VEGFA and PlGF1 in on in late pregnancy of sows placenta. Anim. Reprod. Sci., 132: 187-192.

Yuan, T.L., Y.H. Zhu, M. Shi, T.T. Li and N. Li *et al*., 2015. Within-litter variation in birth weight: Impact of nutritional status in the sow. J. Zhejiang Univ. Sci. B, 16: 417-435.

Zhang, S., T.R. Regnault, P.L. Barker, K.J. Botting and I.C. McMillen *et al*., 2015. Placental adaptations in growth restriction. Nutrients, 7: 360-389.