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

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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 (Vonnhahme 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; Vonnhahme, 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 size in 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 by each 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).
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 it is 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 of brain-to-liver weight ratios in smaller fetuses during late gestation means 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 pondered as 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 is insufficient to support the fetus’ growth and development such as reduced intestinal weight, 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 the fetus’ growth and development. Besides appropriate arginine synthesis in neonate piglets is crucial because of its deficiency in the sow’s 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 newborn 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, adecuida 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-kinases 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
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 intrapartum asphyxia 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).

![Fig. 1: Pre-and postnatal hypoxia consequences: metabolic pathways activation that impact on piglet thermoregulation, vitality and viability](image)

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., 2011).
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 (0.13-0.14 mMol/L) at (d 40) of gestation, porcine allantoic fluid presents higher arginine concentrations (4-5 mMol/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 conceptus 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<sup>a</sup>           | L-arginine               | 0.8% or 16 g/d per gilt    | Day 0-25<sup>g</sup>                      | Reduced uterine weight, total number of corpora lutea and conceptuses and total fetal weight<sup>h</sup> |
| Bazer et al. (2014)             | Gilts<sup>a</sup>           | L-arginine               | 0.8%                        | Day 0-25<sup>g</sup>                      | Higher total number of piglets born per litter, number of piglets born alive per litter and litter birth weight of all piglets born and born alive |
| Li et al. (2015)                | Gilts and sows<sup>a</sup>  | L-arginine HCl           | 1.3%                        | Day 1-30                                   | Increased total volume of amniotic fluid, total amounts of arginine in amniotic fluid, total amounts of fructose and most amino acids in amniotic fluid, placental growth |
| Li et al. (2011)                | 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<sup>l</sup> Reproductive performance did not differ<sup>l</sup> |
| Li et al. (2014)                | Gilts                       | L-arginine               | 0.4% or 0.8%               | Day 14-25                                 | No alteration of placental weight. Increased litter size of viable fetuses (by 3.7/L) and litter weight of viable fetuses (by 32%/L)<sup>f</sup> |
| Berard and Bee (2010)           | Gilts                       | Arginine                 | 0.87% or 26 g/d per gilt   | Day 14-28                                 | Increased litter size of born-alive piglets (by 1/L)                       |
| Ramaekers et al. (2006)         | 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)                 |
| Campbell (2009)                | Gilts and sows              | Arginine                 | 1% or 25 g/d per animal    | Day 14-28                                 | Decreased number of piglets born alive and increased stillbirth rate<sup>e</sup> |
| Dallanora et al. (2017)         | Gilts<sup>b</sup>           | Arginine                 | 1%                          | Day 25-80                                 |                                                                         |
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.

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