animal

Effects of sow nutrition during gestation on within-litter birth weight variation: a review

P. H. R. F. Campos[1,2], B. A. N. Silva[1†], J. L. Donzele[2], R. F. M. Oliveira[2] and E. F. Knol[1]

[1]*Institute for Pig Genetics BV, Schoenaker 6, 6640 AA Beuningen, The Netherlands;* [2]*Animal Science Department/Departamento de Zootecnia, Universidade Federal de Viçosa, 36571-000 Viçosa, MG, Brazil*

The increasing demand for efficiency in pork production requires great specialization of all sectors involved in this activity. In this context, the development of strategies that could reduce undesirable traits related with negative effects on piglet survival and postnatal growth and development are essential for the pig industry. Currently, special attention is given to variation in birth weight, as some evidences suggest an increased within-litter birth weight variation in modern sows. This variation has been shown to be associated with preweaning mortality, variable weights at weaning and deteriorated growth performance, which results in economic losses and lower efficiency. Therefore, understanding the factors that can influence the events that occur during gestation and that have an impact on the fetal growth and development are important to achieve better efficiency and also to develop strategies that can be used to achieve increased within-litter uniformity of piglet birth weight. This study concludes that even at a given placental size, fetal growth may vary because of differences in placental vascularization and efficiency. Feeding extra feed or energy during late gestation only marginally improves birth weight, and positive effects are not consistent between different studies. The detrimental effects of protein restriction on fetal growth during early gestation may be due to altered placental and endometrial angiogenesis and growth, which leads to a reduction in placental-fetal blood flow, nutrient supply from mother to the fetuses and ultimately to fetal growth retardation. The number of studies that attempted to influence within-litter birth weight variation by means of sow nutrition during gestation is limited. Therefore, more research concerning sow nutrition during gestation associated with the provision of balanced diets to meet requirements of the sows and fetuses are still required. This knowledge may subsequently provide starting points for the design of nutritional strategies that can influence within-litter birth variation.

Keywords: gestation, sow nutrition, within-litter variation, amino acids

Implications

Nutrition of gestating sows plays an important role in the within-litter variation. This is especially important for highly prolific sows in modern commercial environments. Because of its importance in the pork industry, the aim of the study was to review current knowledge about the physiological background of within-litter birth weight variation, and to explore possible nutritional opportunities to increase within-litter uniformity of piglet birth weight.

Introduction

Advances in pig production have brought many benefits for producers, such as higher number of piglets/sow per year, higher farrowing rates per year, decreased age at slaughter,

increased feed efficiency and higher lean gain (Ball *et al.*, 2008). Nevertheless, negative characteristics, such as within-litter birth weight variation have developed, resulting in economic losses and lower profits to the producer.

The within-litter birth weight variation is economically important because of its positive correlation with preweaning mortality (Wolf *et al.*, 2008). In litters with high level of variation in birth weight, the smallest piglets are not able to compete with the heavier litter-mates for the best teats; therefore, these animals consume a lower amount of colostrum and have lower milk intake, which leads to poor acquisition of passive immunity and low nutritional status (Quiniou *et al.*, 2002). Consequently, small piglets are physiologically deprived of energy stores. Therefore, they are more susceptible to hypothermia and have a lower capacity to maintain body temperature after birth (Herpin *et al.*, 2002; Wolf *et al.*, 2008).

---

† E-mail: Bruno.Nunes.Silva@ipg.nl

In addition, litters with more birth weight variation have more variable weights at weaning. This results in increased labor and complicated management requirements (Roberts and Deen, 1995). Further, reductions in the weight gains from birth have unfavorable effects on the subsequent growth. The low birth weight piglets are also older at slaughter compared with heavier birth weight litter-mates (Gondret et al., 2005).

Because of the importance of the within-litter birth weight variation in the pork industry, the aim of this study was to review current knowledge about the physiological background of within-litter variation in piglet birth weight to explore possible opportunities to reduce within-litter variation, and to develop nutritional strategies that can be used to achieve increased within-litter uniformity of piglet birth weight.

Causes of within-litter birth weight variation

Genetic selection and litter size

The genetic selection for improved prolificacy has increased litter size. Quesnel et al. (2008) showed that the genetic improvement over the past 10 years resulted in an increase of 1.8 piglets per litter in commercial sows. These findings are in agreement with other authors who reported a successful genetic selection for litter size (Merks, 2000; Foxcroft, 2008).

Once the number of fully formed fetuses that can be maintained by the uterus until farrowing is limited, the correlation between increased number of fetuses and individual fetal growth is negative (Wolf et al., 2008). Thus, various authors observed an increased within-litter variation in piglet birth weight and a decrease in average birth weight of the litter, because of the genetic selection for litter size (Lund et al., 2002; Tribout et al., 2003; Foxcroft, 2008; Quesnel et al., 2008). A higher number of fetuses exceeding the uterine capacity have been related to piglets with limited number of muscle fibers, which results in a compromised fetal growth and development (Foxcroft et al., 2006).

Quiniou et al. (2002) found a reduced average individual birth weight from 1.59 to 1.26 kg and an increased within-litter variation of individual birth weight from 0.26 to 0.30 kg when the smallest litters (≤11 piglets) were compared with larger litters (≥16 piglets), respectively, and an increased proportion of smaller piglets in larger litters (Table 1). Very little chance of survival until weaning was observed in piglets weighing less than 1 kg at birth, and when they survived their growth performance during the nursing and postweaning period was lower than those of heavier piglets at birth (Quiniou et al., 2002). These findings suggest that increased litter size induces an increased proportion of light piglets, a concomitant decrease in litter uniformity and average piglet birth weight, having negative effects on the piglets' viability and performance.

It is quite clear that the increased prolificacy of the modern sows leads to negative impacts on the fetal growth and development, as large litters are associated with reduced rates of fetal oxygen and nutrient uptakes, and also with reduced utero-placental blood flow per fetus (Reynolds and Redmer, 2001). Thus, these events may limit the uterine capacity, which can decrease fetal growth, increase fetal death and compromise the offspring's performance.

Differences between breeds

The ability of the uterus to meet the nutritional demands to maintain fetuses until farrowing, known as uterine capacity, is characteristic of the genotype and of the animal (Pere and Etienne, 2000). Thus, differences among breeds are related with differences in the maternal ability to farrow higher number of piglets, with good survival rates, litter uniformity and adequate birth weight. One example, which illustrates these differences in the uterine capacity and maternal ability between breeds, is the Chinese Meishan breed compared with the commercial sow breeds.

The Chinese Meishan breed is known for its prolificacy and higher litter size than the commercial European breeds (Christenson, 1993). There are some evidences suggesting that the Meishan breed have slower fetal growth rates, which could be involved in improved homogeneity and a higher uterine capacity (Ford, 1997). Wilson et al. (1998) found a lower growth rate of the Meishan fetus when compared with the Yorkshire fetus. This fact was associated with some form of growth inhibition in the Meishan uterus that slows the rate of fetal growth and also sets an absolute limit on individual fetal size, possibly by restricting placental growth. Ford et al. (2002) suggested that the improved uterine capacity observed in the Meishan sows seemed to have resulted from an increased placental efficiency or an increased uterine size.

According to Ford (1997), another factor that related with the higher uterine capacity of the Meishan sows is the ability

Table 1 *Effect of litter size on piglets' characteristics at birth*

Litter size (class)	≤11	12 to 13	14 to 15	≥16	r.s.d.
Number of sows	324	262	230	149	
Individual birth weight (kg)					
Mean	1.59[c]	1.48[d]	1.37[e]	1.26[f]	0.22
Within-litter variation	0.26[c]	0.27[cd]	0.28[d]	0.30[e]	0.09
Small piglets (%)[1]	7[c]	9[c]	14[d]	23[e]	13

r.s.d. = residual standard deviation.
Source: Quiniou et al. (2002).
[1]Mean proportion of piglets that weighted less than 1 kg at birth.
[c,d,e,f]$P < 0.001$.

of the fetus to increase the placental vascularization to support the increasing fetal growth during the last third of gestation. Biensen *et al.* (1998) evaluated the effects of uterine and fetal genotype on the placental size and vascularity, and observed that the Meishan × Yorkshire crossbred fetuses were lighter when gestated in the Meishan rather than in the Yorkshire uterus on days 90 and 110 of gestation. These authors reported, using image analysis, an increase in placental and endometrial vascular density for purebred Meishan bred conceptus compared with purebred Yorkshire bred. These data suggest that expression of angiogenic factors are influenced by breed differences leading to differences in placental and adjacent endometrial vascular density, and thus placental efficiency.

These findings suggest an important line of research to develop effective genetic improvement programs for uterine capacity.

Angiogenesis and placental development during follicular growth

The placenta is the organ through which respiratory gases, nutrients and wastes are exchanged between the maternal and fetal systems. Thus, the fetal growth and development is dependent of the maternal capacity to provide all the metabolic demands required for the fetuses. The efficiency of this process is influenced by the placental blood flow rates, which are dependent on placental vascularization and vasodilatation (Reynolds *et al.*, 1992; Ford, 1995; Reynolds and Redmer, 2001).

Angiogenesis. The formation of new vascular beds determines the placental vascularization. This process, known as angiogenesis, is a critical process for normal tissue growth and development, and numerous factors have been implicated in this process. However, Reynolds and Redmer (2001), evaluating the placental angiogenesis, reported that the vascular endothelial growth factor, fibroblast growth factor and the angiopoietin protein families, and also their respective receptors, are the major factors regulating the angiogenesis.

This process begins with the capillary proliferation and culminates in the formation of a new microcirculatory bed, composed of arterioles, capillaries and venules. Angiogenic factors interact with the local vasodilator nitric oxide to coordinate placental angiogenesis and blood flow (Reynolds and Redmer, 2001).

Vasodilatation. Some factors are known to enhance the blood flow rates by increasing the diameter of the placental circulatory channels and the placental vascularity. One of these factors is the endogenous relaxant nitric oxide, which is involved in the vasodilatation of the maternal systemic circulation, regulation of uterine and fetus-placental blood flow, and also the vascular endothelial growth factors that are specific stimulators of vascular permeability (Reynolds and Redmer, 2001).

The establishment of fetal and placental circulation is one of the earliest events during the embryonic and placental development (Wu *et al.*, 2004). This event is crucial to support the metabolic demands of the fetus, mainly during the later half of gestation when an exponential increase in fetal growth occurs (Reynolds and Redmer, 2001).

Therefore, any events that have negative impact on the placental growth and development or on the maternal ability to transfer the nutrients to the fetus are associated with fetal growth retardation.

Blood flow distribution. One of the factors that influence the fetal growth and development is the utero-placental blood flow. The placental circulation has a critical role in the transplacental exchange rates and in the delivery of nutrients for fetal growth (Reynolds and Redmer, 2001).

Pere and Etienne (2000) observed that uterine blood flow increased with litter size; however, the uterine blood flow per fetus decreased when the litter size increased, suggesting that uterine blood flow adapts to litter size, but within limits. Similarly, Reynolds *et al.* (1985) reported that uterine blood flow was positively correlated with the number of fetuses; however, the blood flow per fetus was negatively correlated with the number of fetuses in the uterine horn.

Because of the increased prolificacy of modern sows, the fetal growth and development has been limited by decreased uterine blood flow per fetus. According to the studies cited previously, there is a negative relationship between litter size and uterine blood flow per fetus. In addition, providing different amounts of nutrients to the fetus during gestation might explain partially the within-litter birth weight variation, as the correct supply of all metabolic demands necessary for fetal growth is influenced by the uterine and umbilical blood flow (Reynolds *et al.*, 1985).

Maternal nutrition during gestation

In addition to the higher prolificacy, higher nutritional requirements for supporting the metabolic needs of both the sow and its fetuses are required (Kim *et al.*, 2005). However, according to McPherson *et al.* (2004), the nutritional requirements of the animals may not be reached by providing a constant amount of dietary protein during gestation, as the demand for nutrients of both the mother and its fetuses increases throughout gestation. In addition, the nutritional recommendations for pregnant sows are based on the requirements of much less prolific and productive sows of the past than the modern sows (Ball *et al.*, 2008). As such there is a suboptimal nutritional feeding management during gestation. Thus, an incorrect maternal nutrition with respect to increased requirements to support the increased number of fetuses in the uterus may be associated with fetal growth retardation, and, consequently, negative effects on the piglet performance, such as decreased within-litter uniformity and decreased piglet birth weight. Kim *et al.* (2009) reported higher weight variations among fetuses mainly after 45 days of gestation, which could be associated with the limitation of sows to provide sufficient nutrient support through blood for maximal growth of all fetuses (Wu *et al.*, 2006).

As the fetal growth and development play a crucial role in the within-litter uniformity and piglet birth weight, and thereby in survival and postnatal growth, several studies have been conducted to evaluate different feeding strategies during gestation and consequences on fetal growth and development.

Sow nutrition as an opportunity to improve within-litter uniformity

Nutrition during the preovulatory period
Evidence for effects of preovulatory nutrition on within-litter diversity. Within-cohort variation in oocyte development and maturation during the preovulatory period may determine crucial events that influence the uniformity in embryonic development, such as within-litter variation in early embryonic development and growth, within-litter variation in placental development and growth, and thus consequently the within-litter variation in birth weight.

Many studies have shown a relationship between dietary composition during the preovulatory period and subsequent embryo survival and development (Kirkwood *et al.*, 1990; Baidoo *et al.*, 1992; Zak *et al.*, 1997a and 1997b; Quesnel *et al.*, 1998). Although effects of the preovulatory dietary composition on follicle and oocyte development, as well as carryover effects on embryonic survival and development have been established, there is at present no evidence for effects of preovulatory nutrition on variation in development within a preovulatory cohort of ovulating follicles or the oocytes shed at ovulation. However, there is limited evidence for effects of preovulatory nutrition on within-litter embryo diversity.

A significantly lower within-litter variation in birth weight was reported by Van den Brand *et al.* (2006), when first parity Yorkshire × Dutch Landrace sows received a dextrose supplementation diet during the weaning to estrus interval (WEI). The sows received, from weaning until the end of estrus, 150 g dextrose/day in addition to 3.5 kg/day of a sow ration containing 9.4 MJ NE/kg, 156 g/kg CP and 6.8 g/kg digestible lysine. Dextrose was used instead of starch, as an earlier experiment (Van Den Brand *et al.*, 1998) has shown that dextrose had a more pronounced effect on plasma glucose and insulin concentrations. Dextrose supplementation did not affect WEI, pregnancy rate, farrowing rate and subsequent litter size or birth weight (Table 2).

Nutritional effects mediated by insulin and IGF-I. The effect of preovulatory nutrition on follicles and oocytes is often associated with the effect of nutrition on circulating metabolic hormone concentrations, such as growth hormone and leptin concentrations, but especially insulin and IGF-I concentrations. Blood concentrations of insulin and IGF-I are considered to be important for mediating the effect of nutrition on the ovaries. In mammals, insulin stimulates *in vitro* the uptake and utilization of nutrients, granulosa cell proliferation and differentiation, either alone or in synergy with gonadotropins (Prunier and Quesnel, 2000b).

Table 2 *Effects of dextrose supplementation during the weaning-to-estrus interval on average piglet birth weight and within-litter variation in piglet weight*

Variable	Dextrose ($n = 91$)	No dextrose ($n = 85$)
Live born piglets	12.91	12.71
Piglet weight (g)	1608	1591
CV birth weight (%)	17.5[*]	21.2
Litters with piglets < 1000 g (%)	40.7	45.9
Piglets < 1000 g (%)	5.1	8.1
% Female piglets	52.3	52.7
Preweaning mortality (%)	6.9	7.4

CV = coefficient of variation.
Source: Van den Brand *et al.* (2006).
[*]Significantly different from the 21.2% CV in the 'No dextrose' group ($P = 0.03$).

Furthermore, numerous *in vivo* experiments have provided evidence for a stimulating role of both insulin and IGF-I in folliculogenesis. For instance, increasing plasma insulin during the late luteal phase or the early follicular phase, increased ovulation rate irrespective of changes in plasma LH, may be related to the ability of insulin to decrease atresia in small- and medium-sized follicles (Prunier and Quesnel, 2000b). On the basis of another literature review, Prunier and Quesnel (2000a) concluded that insulin has a positive influence on the nutrient supply, growth and development of follicular cells; however, that direct evidence is still missing to demonstrate that a decrease in insulin secretion due to feed restriction is responsible, even in part, for a decrease in follicle development and ovulation in pigs.

In contrast, increased insulin and IGF-I levels before or at weaning are positively associated with LH pulsatility after weaning. Higher levels of LH stimulate the development of larger follicles, because small follicles only have FSH receptors and not LH receptors; thus, small follicles will be less stimulated and become atretic (Van Den Brand *et al.*, 2009). Therefore, the follicle population becomes more uniform, and a more uniform follicle population seems to result in more uniform oocyte quality (Van Den Brand *et al.*, 2009). In this context, as cited previously, Van Den Brand *et al.* (2006) observed higher piglet birth weight uniformity in sows that received a dextrose supplementation diet during the WEI. Similarly, although not significant, Van Den Brand *et al.* (2009) reported a numerically lower within-litter birth weight variation in sows supplemented dextrose plus lactose during a prolonged period before and during follicular phase (1 week before parturition till the moment of insemination). These findings are possibly related with the fact that dextrose and lactose supplementation possibly increases plasma levels of insulin and IGF-I (Van Den Brand *et al.*, 2009).

Nutrition in relation to placental and fetal development and growth
Impact of different dietary energy levels during gestation. The effects of a low dietary energy intake during gestation on

reproductive traits were evaluated by Buitrago *et al.* (1974). In this study, the authors found that individual piglet weight and total litter weight at birth decreased significantly when offspring of sows fed 2.2 Mcal DE/day from breeding to farrowing were compared with offspring of sows fed 8.0 Mcal DE/day. Still in agreement, a direct relationship between maternal nutrition and fetal weight was shown by Noblet *et al.* (1985), where a decrease in 28% the feed intake after day 80 of gestation resulted in a reduction in fetal growth in gilts. However, some studies reported that the dams have the ability to mobilize maternal nutrient reserves to support placental and fetal development when these animals are subjected to a restricted energy diet (Anderson, 1975; Pluske *et al.*, 1995; Bee, 2004). Thus, several authors also reported no effects of low energy supply in the fetal performance (Liao and Veum, 1994; Jindal *et al.*, 1996). Bee (2004) found that different energy intake levels (6.6 and 10.7 MJ DE/kg) during early gestation in multiparous sows did not affect the average birth weight, weaning weight, number of piglets born alive or number of piglets at weaning, when considering all progenies.

Lawlor *et al.* (2007) found no influence in birth weight, weaning weight and within-litter weight variation when five different dietary digestible energy levels were provided during different gestation phases: (1) 30 MJ DE/day throughout gestation; (2) as for one but with 60 MJ DE/day from days 25 to 50 of gestation; (3) as for one but with 60 MJ DE/day from days 50 to 80 of gestation; (4) as for one but with 60 MJ DE/day from days 25 to 80 of gestation; (5) as for one but with 45 MJ DE/day from days 80 to 112 of gestation. Kongsted (2005), in a literature review, suggested that pregnancy rate and litter size can be influenced by energy intake. However, the latter authors concluded that the results of the literature were inconsistent and do not provide a clear idea of the relation between energy supply and reproductive performance.

Impact of different dietary protein levels during gestation. Almost everything that occurs in the cell involves one or more proteins. Proteins have different functions and biological activities. Some of these functions include structural roles, nutrition, enzymatic catalyses, molecular transport, organism defense and other functions (Lehninger *et al.*, 1993). Therefore, dietary protein intakes during gestation play a critical role in the maternal and fetal growth and development.

Wu *et al.* (1998), evaluating gilts receiving a protein-restricted diet containing 0.5% CP, observed that the maternal dietary protein deficiency decreased concentrations of basic amino acids (arginine, lysine and ornithine) and several neutral amino acids (alanine, glutamine, glycine, branched-chain amino acids, proline, serine, taurine and threonine) in the placenta and endometrium by 16% to 30%, compared with the gilts of the control group that received diets containing 13% CP. However, according to these authors, the protein reduction decreased the activities of nitric oxide synthase, citrulline synthesis from arginine and ornithine decarboxylase activity in placenta and endometrium by 30% to 51%, 34% to

42% and 44% to 47%, respectively, suggesting that these events may decrease the maternal ability to transfer nutrients and oxygen to the fetus, resulting in negative impacts on within-litter birth weight uniformity.

In agreement with these findings, other studies reported negative effects (i.e. intrauterine growth retardation, decreased piglet vitality and birth weight) of restricted-protein diets during gestation on the sow progeny (Atinmo *et al.*, 1974; Pond *et al.*, 1992; Schoknecht *et al.*, 1994; Wu *et al.*, 2006). Similarly, Redmer *et al.* (2004), evaluating the effect of nutrient intake during pregnancy, stated that maternal nutrition can have a profound effect on fetal growth and development by changing placental growth and vascular development. In addition, the authors suggest that placental expression of angiogenic factors and their receptors are disturbed by level of nutrition, and that nutrient restriction of the adult dam during pregnancy suppresses placental cell proliferation and vascularity.

Analyzing the relationship between sow nutrition during gestation and the offspring performance, the low birth weight of the piglets from immature gilts when compared with those from adult sows may illustrate the negative effects of inadequate maternal nutrition on fetal growth, as these immature gilts compete with their own fetus for nutrients (Redmer *et al.*, 2004; Wu *et al.*, 2004).

Impact of different feed intake levels during gestation. There are some evidences about the provision of nutrients below the maternal requirements during gestation; therefore, several studies have been conducted to evaluate the effects of an increased amount of feed during gestation.

In the study of Mahan (1998), the authors observed that the sows that received a greater quantity of feed, equivalent to 130 g additional feed per day, farrowed more total and live piglets compared with the control group that was given a feed intake similar to the National Research Council (NRC, 1988) recommendations. Similarly, Cromwell *et al.* (1989) concluded that additional feed in late gestation (+1.36 kg of feed/day from day 90 of gestation to farrowing) improves the reproductive performance. The results showed a greater total litter weight at birth (15.06 *v.* 14.36 kg), an increased weaning weight (5.37 *v.* 5.20 kg) and increased individual birth weight (1.48 *v.* 1.44 kg) in sows fed extra amounts of feed when compared with a control group. Likewise, these extra-fed sows also farrowed more piglets per litter (i.e. + 0.35) and more live piglets per litter (i.e. + 0.34) than the control group. In addition, a higher fiber diet during the estrus cycle, preceding mating, increased embryo survival and reduced the fetal intrauterine growth retardation at day 27 of pregnancy (Ferguson *et al.*, 2006). Nevertheless, several studies have shown no effect of feeding levels during gestation on the sow's reproductive performance. According to Dwyer *et al.* (1994) litter size, pig mortality and birth weights were not significantly affected by different quantities of feed during specific periods of gestation (2.5 kg/day throughout 21 to 90 days of gestation; 5.0 kg/day throughout 25 to 50 days; 5.0 kg/day throughout 50 to 80 days;

5.0 kg/day throughout 25 to 80 days). However, the authors concluded that the increased maternal nutrition during early to middle gestation can lead to an increased production of secondary myofibers in the fetus. These findings, suggesting a positive correlation between maternal nutrition during early to mid gestation in sows and fetal muscular fiber growth and distribution, are in agreement with the findings of Gatford *et al.* (2003) and Bee (2004).

By evaluating different nutritional strategies during gestation, Nissen *et al.* (2003) found no beneficial effects on average piglet birth weight, litter size at birth and at weaning, when sows were fed '*ad libitum*' during different gestation phases (25 to 50 and 25 to 70 days of gestation) compared with a control group (restricted diet), demonstrating no beneficial effect in fetal growth and development. In agreement, no differences were observed on within-litter birth and weaning weight variation, total number born and piglets born alive, when sows received 50% more of the same feed compared with the control group (2.5 to 3.0 kg/day, 2.9 Mcal ME/kg) during 45 to 85 days of gestation (Cerisuelo *et al.*, 2008). Rehfeldt and Kuhn (2006) stated no effect of maternal overnutrition on birth weight of the progeny. Similarly, Miller *et al.* (2000), Pond *et al.* (1981) and Sterling and Cline (1986) did not find effect of increased feed intake in sow reproductive performance.

In contrast, Lawlor *et al.* (2007), evaluating different diets during specific gestation phases, related an expressive increase in the number of piglets born dead per litter, when sows were overfed from 50 to 80 days of gestation. In addition, Redmer *et al.* (2004) showed a reduced expression of angiogenic growth factors leading to a lower placental growth and reduced uterine and umbilical blood flow in young ewes receiving a higher amount of nutrients from days 4 to 80 of gestation.

Musser *et al.* (2006), evaluating the effects of maternal feed intake during gestation on the fetal muscle development and carcass characteristics, observed that higher amounts of feed fed to sows (3.63 kg/day of gestation diet) from 30 to 50 days of gestation resulted in fewer total pigs born (-1.21 and -0.87). The sows tended to have lower number of pigs born alive (-1.00 and -0.89) when compared with sows fed with the control diet (1.81 kg/day of gestation diet) or the added maize diet (1.81 kg/day of gestation diet plus 1.81 kg/day of additional ground maize). A possible explanation for the lower reproductive performance might be that the maternal nutritional status influences the circulating progesterone, which can modify endometrial development and secretory activity, and affects the composition of allantoic fluids that provide nutrients to the fetus (Ashworth, 1991). This suggests a detrimental effect of high feed intake on embryo survival, as an inverse relationship between level of nutrition and circulating progesterone concentrations has been demonstrated in pigs (Dyck *et al.*, 1980; Prime *et al.*, 1988). Interestingly, when hyper-prolific Large White gilts received different amount of nutrients (2.00 *v.* 4.00 kg/day of gestation diet) during early gestation, 7 days after insemination, the high level of feeding had no effects on embryo survival, size and

variability (Quesnel *et al.*, 2010). However, in this later study, the progesterone concentration was not measured, and thus not allowing the establishment of a relation between circulating progesterone and embryo development.

Influence of amino acids on within-litter uniformity
There is strong evidence that the members of the arginine family of amino acids (AFAAs; arginine, glutamine, glutamate, proline, aspartate, asparagine, ornithine and citrulline, of which the last two are not substrates for protein synthesis) have an important role in placental vascularization and development, especially during the first half of pregnancy (Wu *et al.*, 2007). The AFAAs have an important role in placental angiogenesis and placental, embryonic and fetal development. AFAAs are interconvertible via complex interorgan metabolism in most mammals, including pigs (Wu *et al.*, 2007). Wu *et al.* (1996b) have shown an unusual abundance of arginine and ornithine in porcine allantoic fluid from 35 to 40 days of pregnancy, that is, the period of rapid placental growth. Glutamine was the most abundant amino acid in the amniotic fluid during the early fetal stage of pregnancy (days 30 to 45) and was also abundant in the allantoic fluid. These authors concluded that the allantoic fluid may serve as a nutrient-rich reservoir for arginine, ornithine and glutamine, at least during this stage of pregnancy. Besides being the building blocks of proteins and polypeptides, some amino acids, called functional amino acids (e.g. arginine, cysteine, glutamine, leucine, proline and tryptophan), are important regulators of key metabolic pathways that are crucial for maintenance, growth, reproduction and immunity (Wu, 2009). According to Wu *et al.* (2010), nitric oxide, polyamines, arginine and other functional amino acids (e.g. glutamine, leucine and proline) may regulate embryonic and fetal muscle growth and development via cell signaling through the mammalian target of rapamycin. In addition, the same authors concluded that arginine supplementation increases litter size and litter birth weight, and its combination with glutamine, leucine and proline can reduce variation in birth weights of piglets.

Arginine supplementation. Arginine is one of the most versatile amino acids in animal cells, serving as a precursor for the synthesis of proteins, nitric oxide and polyamines.

Nitric oxide is an endogenous relaxant factor; it is produced from arginine via nitric oxide synthase and is involved in the vasodilatation of the maternal systemic circulation, regulation of uterine and feto-placental blood flow (Wu and Morris, 1998; Wu *et al.*, 2006). Evidences suggest an interaction between angiogenic factors and nitric oxide to coordinate placental angiogenesis and blood flow, which are crucial events for the placental vascularization and, consequently, fetal growth (Reynolds and Redmer, 2001). Sladek *et al.* (1997) reported an increased uterine blood flow when stimulators of endogenous nitric oxide were infused into the uterine circulation in sheep and a reduced plasma volume and newborn weights caused by chronic administration of nitric oxide inhibitors to pregnant rats.

Table 3 *Reproduction performance of supplemented and non-supplemented gilts with 1% L-arginine-HCl*

| Parameters | Treatment | | |
	Control	Arginine	s.e.m.
Total piglets born alive per litter (*n*)	9.37	11.40*	0.56
Litter birth weight of all piglets born alive (kg)	13.19	16.38*	0.74
Piglets born dead per litter (*n*)	1.86	0.66*	0.147
Birth weight variation of all piglets born alive (kg)	0.240	0.253	0.017

s.e.m. = standard error of mean.
Source: Mateo *et al.* (2007).
*Different from the control group, $P < 0.05$.

Polyamines are related with protein synthesis regulation and cell function and differentiation. The inhibition of placental polyamine synthesis is related to decreased placental size and lower fetal growth (Wu *et al.*, 2004). Polyamines are organic compounds that are derived from ornithine by the arginase pathway, resulting in the synthesis of putrescine, spermidine and spermine (Lehninger *et al.*, 1993; Wang *et al.*, 2003). However, the polyamine synthesis in the porcine placenta is dependent on the conversion of arginine into ornithine and proline via the arginase pathway in other maternal tissues, as arginase activity is not detected in the maternal placenta (Wu *et al.*, 2006).

The relevance of arginine in fetal growth and development have been recognized, because of the participation of nitric oxide and polyamines in critical events during gestation – angiogenesis, placental vascularization and embryogenesis (Flynn *et al.*, 2002; Wu *et al.*, 2006).

Mateo *et al.* (2007) found an increased number of piglets born alive (22%) and live litter birth weights (24%) without any reduction in the average birth weight of piglets in gilts supplemented with 1% of L-arginine-HCL from days 30 to 114 of gestation compared with a control group that received a control diet (1.7% L-arginine – isonitrogenous diet). In addition, the piglet mortality decreased (65%), the plasma concentration of arginine and its metabolites (ornithine and proline) increased and the birth weight variation of all piglets born alive increased but was not significant (Table 3). According to the authors, the arginine supplementation may have increased the nitric oxide and polyamine synthesis, and thus the increasing placental angiogenesis and growth, enhanced the utero-placental blood flow, the nutrient transfer from mother to fetus and, consequently, fetal survival and development.

A higher number of live piglets were observed in sows supplemented with 25 g L-arginine per day from 14 to 28 days of gestation, without any effect in the average birth weight (Ramaekers *et al.*, 2006).

Glutamine supplementation. Glutamine is an important amino acid for a variety of metabolic processes in the whole organism, participating in the synthesis of amino sugars and nucleotides that are necessary for cell proliferation and differentiation, and playing crucial roles in fetal and placental nutrition. Among all amino acids transferred from the mother and placenta to the fetus, the concentration of glutamine is the highest, suggesting an active synthesis and release into the fetal circulation by the placenta (Self *et al.*, 2004).

The glutamine delivered to the fetus originates from glutamine from the maternal circulation and from the glutamine synthesis in the placenta. In this process, glutamine is synthesized from glutamate by glutamine synthetase in the placenta (DeMarco *et al.*, 1997). The placental supply of glutamate is derived from the branched-chain amino acid metabolism (Self *et al.*, 2004) and from the fetal circulation (Battaglia, 2000).

An increased placental glutamine synthesis and glutamine concentration in allantoic fluid in the second third of gestation in sows was observed in the study of Self *et al.* (2004), which evaluated the glutamine synthesis in the developing porcine placenta. These findings suggest a higher provision of glutamine because of the most rapid placental and fetal growth in the second third of gestation. In addition, the remained glutamine, which is not metabolized to glutamate in the fetal liver and transported to the placenta, is taken up by the fetal carcass for growth (Figure 1; Neu, 2001). In addition, glutamine is a substrate for arginine fetal synthesis, having an important role in regulating the arginine levels in the fetus, because of insufficient uterine uptake of arginine, required to support the fetal growth during the last third of pregnancy (Wu *et al.*, 1999; Self *et al.*, 2004). Petters *et al.* (1990), evaluating the effects of glutamine on the development of pig embryos, found a greater development of embryos in the presence of glutamine when compared with a control group (absence of glutamine).

Some evidences suggest a dependency of the rapidly growing fetus and premature infant to an adequate supply of glutamine and its metabolites for normal physiologic functions and growth (Neu, 2001). In addition, some studies demonstrated the possibility that glutamine supplementation might prove beneficial to neonatal piglets' performance (Dwyer *et al.*, 1994; Wu *et al.*, 1996a).

In agreement with our previous discussion of the important roles of arginine and glutamine on fetal nutrition and growth, Wu *et al.* (2010) found that supplementing a basal gestation diet with a mixture of 8 g of L-arginine and 12 g of L-glutamine from 30 to 114 days of gestation reduced the variation in birth weights among either all piglets born (−27%) or live-born piglets (−24%) and decreased the proportion of small piglets (−23% for all piglets born and −22% for live-born piglet).
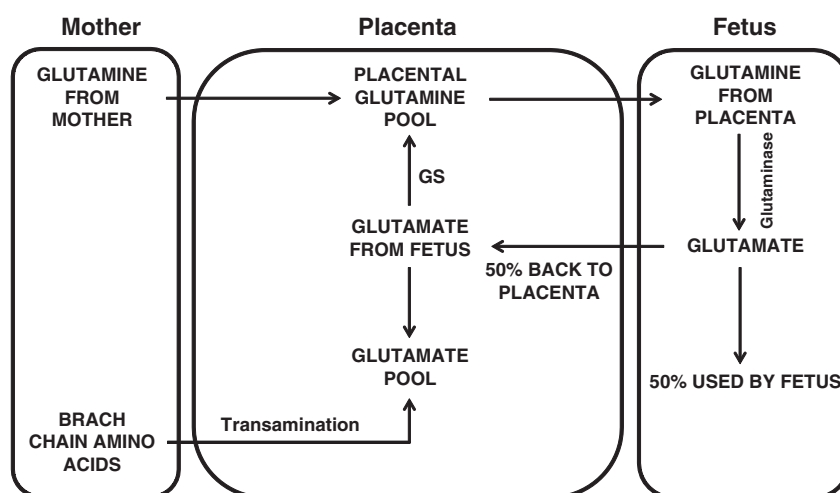
Figure 1 Flux of glutamine and glutamate between the mother, placenta and the fetus. *Source*: Neu (2001).

Despite many studies assessing the effect of glutamine supplementation in neonatal piglets, little is known about the effects of glutamine in placental growth and development. As the events related with the placental growth have impact on the fetal development, more research is necessary to evaluate the possible effects of glutamine supplementation during gestation in order to enhance the fetal development and maternal reproductive performance.

Concluding remarks

Within-litter birth weight variation is unfavorably correlated to piglet survival and postnatal growth. This is especially important for highly prolific sows in modern commercial environments. As the litter size increases, the amount of nutrients available per fetus decreases because of an increased fetal competition, which has been related with a suboptimal fetal development and consequently lower birth weight and higher within-litter variation.

A suboptimal maternal nutrition during gestation, unable to provide a correct amount of nutrients for supporting the metabolic needs of the sows and its fetuses, has been regarded as one of the causes of this higher within-litter variability in modern genotypes.

According to our review, there is a positive relationship between birth weight and energy intake of sows throughout gestation. In gilts, the relationship between birth weight and energy intake reaches a plateau, whereas in multiparous sows, birth weights still increase at very high levels of energy intake. Feeding extra feed or energy during late gestation only marginally improves birth weight, and positive effects are not consistent between different studies. It can also be hypothesized that the detrimental effects of protein restriction on fetal growth during early gestation may be due to altered placental and endometrial angiogenesis and growth, which leads to reduction in placental-fetal blood flow and nutrient supply from mother to the fetuses. Furthermore, the current practice to provide a constant amount of dietary protein during gestation is not in accordance with the nutritional requirements of the animals, as the demand for nutrients of both mother and its fetuses increases throughout gestation, which results in a increased fetal competition for nutrients and may be associated with fetal growth retardation, and, consequently, negative effects on the piglet performance.

The number of studies that attempted to influence within-litter variation in birth weight by means of sow nutrition during gestation is limited. In most studies that investigate the effects of sow nutrition on litter weight and piglet viability, within-litter birth weight variation is probably known, but is not mentioned in the results. However, much potential information on this relationship is available in those datasets that contain information on the sow diet during gestation and where individual birth weights are registered, and thus within-litter birth weight variation can be calculated. This knowledge may subsequently provide starting points for the design of nutritional strategies that can influence within-litter birth variation.

References

Anderson LL 1975. Embryonic and placental development during prolonged inanition in the pig. American Journal Physiology 229, 1687–1694.

Ashworth CJ 1991. Effect of pre-mating nutritional status and post-mating progesterone supplementation on embryo survival and conceptus growth in gilts. Animal Reproduction Science 26, 311–321.

Atinmo T, Pond WG and Barnes RH 1974. Effect of maternal energy vs. protein restriction on growth and development of progeny in swine. Journal of Animal Science 39, 703–711.

Baidoo SK, Aherne FX, Kirkwood RN and Foxcroft GR 1992. Effect of feed intake during lactation and after weaning on sow reproductive performance. Canadian Journal of Animal Science 72, 911–917.

Ball RO, Samuel RS and Moehn S 2008. Nutrient requirements of prolific sows. Advances in Pork Production 19, 223–236.

Battaglia FC 2000. Glutamine and glutamate exchange between the fetal liver and the placenta. Journal of Nutrition 130, 974–977.

Bee G 2004. Effect of early gestation feeding, birth weight, and gender of progeny on muscle fiber characteristics of pigs at slaughter. Journal of Animal Science 82, 826–836.

Biensen NJ, Wilson ME and Ford SP 1998. The impact of either a Meishan or Yorkshire uterus on Meishan or Yorkshire fetal and placental development to days 70, 90, and 110 of gestation. Journal of Animal Science 76, 2169–2176.

Buitrago JA, Maner JH, Gallo JT and Pond WG 1974. Effect of dietary energy in gestation on reproductive performance of gilts. Journal of Animal Science 39, 47–52.

Cerisuelo A, Sala R, Gasa J, Chapinal N, Carrion D, Coma J and Baucells MD 2008. Effects of extra feeding during mid-pregnancy on gilts productive and reproductive performance. Spanish Journal of Agricultural Research 6, 219–229.

Christenson RK 1993. Ovulation rate and embryonic survival in Chinese Meishan and white crossbred pigs. Journal of Animal Science 71, 3060–3066.

Cromwell GL, Hall DD, Clawson AJ, Combs GE, Knabe DA, Maxwell CV, Noland PR, Orr DE Jr and Prince TJ 1989. Effects of additional feed during late gestation on reproductive performance of sows: a cooperative study. Journal of Animal Science 67, 3–14.

DeMarco V, McCain MD, Strauss D, Chakrabarti R and Neu J 1997. Characterization of glutamine synthetase transcript, protein, and enzyme activity in the human placenta. Placenta 18, 541–545.

Dwyer CM, Stickland NC and Fletcher JM 1994. The influence of maternal nutrition on muscle fiber number development in the porcine fetus and on subsequent postnatal growth. Journal of Animal Science 72, 911–917.

Dyck GW, Palmer WM and Simaraks S 1980. Progesterone and luteinizing hormone concentration in serum of pregnant gilts on different levels of feed consumption. Canadian Journal of Animal Science 60, 877–884.

Ferguson EM, Slevin J, Edwards SA, Hunter MG and Ashworth CJ 2006. Effect of alterations in the quantity and composition of the pre-mating diet on embryo survival and foetal growth in the pig. Animal Reproduction Science 96, 89–103.

Flynn NE, Meininger CJ, Haynes TE and Wu G 2002. The metabolic basis of arginine nutrition and pharmacotherapy. Biomedicine and Pharmacotherapy 56, 427–438.

Ford SP 1995. Control of blood flow to the gravid uterus of domestic livestock species. Journal of Animal Science 73, 1852–1860.

Ford SP 1997. Embryonic and fetal development in different genotypes in pigs. Journal of Reproduction and Fertility 52, 165–176.

Ford SP, Vonnahme KA and Wilson ME 2002. Uterine capacity in the pig reflects a combination of uterine environment and conceptus genotype effects. Journal of Animal Science 80, 66–73.

Foxcroft G 2008. Hyper-prolificacy and acceptable postnatal development – a possible contradiction. Advances in Pork Production 19, 205–211.

Foxcroft GR, Dixon WT, Novak S, Putman CT, Town SC and Vinsky MD 2006. The biological basis for prenatal programming of postnatal performance in pigs. Journal of Animal Science 84, 105–112.

Gatford KL, Ekert JE, Blackmore K, De Blasio MJ, Boyce JM, Owens JA, Campbell RG and Owens PC 2003. Variable maternal nutrition and growth hormone treatment in the second quarter of pregnancy in pigs alter semitendinosus muscle in adolescent progeny. British Journal of Nutrition 90, 283–293.

Gondret F, Lefaucheur L, Louveau I, Lebret B, Pichodo X and Le Cozler Y 2005. Influence of piglet birth weight on postnatal growth performance, tissue lipogenic capacity and muscle histological traits at market weight. Livestock Production Science 93, 137–146.

Herpin P, Damon M and Le Dividich J 2002. Development of thermoregulation and neonatal survival in pigs. Livestock Production Science 78, 25–45.

Jindal R, Cosgrove JR, Aherne FX and Foxcroft GR 1996. Effect of nutrition on embryonal mortality in gilts: association with progesterone. Journal of Animal Science 74, 620–624.

Kim SW, Wu G and Baker DH 2005. Amino acid nutrition of breeding sows during gestation and lactation. Pig News Inform 26, 89–99.

Kim SW, Hurley WL, Wu G and Ji F 2009. Ideal amino acid balance for sows during gestation and lactation. Journal of Animal Science 87, 123–132.

Kirkwood RN, Baidoo SK and Aherne FX 1990. The influence of feeding level during lactation and gestation on the endocrine status and reproductive performance of second parity sows. Canadian Journal of Animal Science 70, 1119–1126.

Kongsted AG 2005. A review of the effect of energy intake on pregnancy rate and litter size-discussed in relation to group-housed non-lactating sows. Livestock Production Science 97, 13–26.

Lawlor PG, Lynch PB, O'Connell MK, McNamara L, Reid P and Stickland NC 2007. The influence of over feeding sows during gestation on reproductive performance and pig growth to slaughter. Archives of Animal Breeding 50 (special issue), 82–91.

Lehninger AL, Nelson DL and Cox MM 1993. Principles of Biochemistry, 2nd edition. Worth Publishers, New York.

Liao CW and Veum TL 1994. Effects of dietary energy intake by gilts and heat stress from days 3 to 24 or 30 after mating on embryo survival and nitrogen and energy balance. Journal of Animal Science 72, 2369–2377.

Lund MS, Puonti M, Rydhmer L and Jensen J 2002. Relationship between litter size and perinatal and pre-weaning survival in pigs. Animal Science 74, 217–222.

Mahan DC 1998. Relationship of gestation protein and feed intake level over a five-parity period using a high-producing sow genotype. Journal of Animal Science 76, 533–541.

Mateo RD, Wu G, Bazer FW, Park JC, Shinzato I and Kim SW 2007. Dietary L-arginine supplementation enhances the reproductive performance of gilts. Journal of Nutrition 137, 652–656.

McPherson RL, Ji F, Wu G, Blanton JR Jr and Kim SW 2004. Growth and compositional changes of fetal tissues in pigs. Journal of Animal Science 82, 2534–2540.

Merks JWM 2000. One century of genetic change in pigs and the future needs. In The challenge of genetic change in animal production (ed. WG Hill, SC Bishop, B McGuirk, JC McKay, G Simm and AJ Webb), BSAS occasional publication no. 27, 8–19. British Society of Animal Science, Edinburgh, UK.

Miller HM, Foxcroft GR and Aherne FX 2000. Increasing food intake in late gestation improved sow condition throughout lactation but did not affect piglet viability or growth rate. Animal Science 71, 141–148.

Musser RE, Davis DL, Tokach MD, Nelssen JL, Dritz SS and Goodband RD 2006. Effects of high feed intake during early gestation on sow performance and offspring growth and carcass characteristics. Animal Feed Science and Technology 127, 187–199.

National Research Council (NRC) 1988. Nutrients requirements of swine, 9th edition. National Academic of Science, Washington, DC.

Neu J 2001. Glutamine in the fetus and critically ill low birth weight neonate: metabolism and mechanism of action. Journal of Nutrition 131, 2585–2589.

Nissen PM, Danielsen VO, Jorgensen PF and Oksbjerg N 2003. Increased maternal nutrition of sows has no beneficial effects on muscle fiber number or postnatal growth and has no impact on the meat quality of the offspring. Journal of Animal Science 81, 3018–3027.

Noblet J, Close WH, Heavens RP and Brown D 1985. Studies on the energy metabolism of the pregnant sow. I. Uterus and mammary tissue development. British Journal of Nutrition 53, 251–265.

Pere MC and Etienne M 2000. Uterine blood flow in sows: effects of pregnancy stage and litter size. Reproduction Nutrition Development 40, 369–382.

Petters RM, Johnson BH, Reed ML and Archibong AE 1990. Glucose, glutamine and inorganic phosphate in early development of the pig embryo in vitro. Journal of Reproduction and Fertility 89, 269–275.

Pluske JR, Williams IH and Aherne FX 1995. Nutrition of the neonatal pig. In The neonatal pig: development and survival (ed. MA Varley), pp. 187–235. CAB International, Wallingford, UK.

Pond WG, Yen JT, Maurer RR and Christenson RK 1981. Effect of doubling daily energy intake during the last two weeks of pregnancy on pig birth weight, survival and weaning weight. Journal of Animal Science 52, 535–541.

Pond WG, Maurer RR, Mersmann HJ and Cummins S 1992. Response of fetal and newborn piglets to maternal protein restriction during early or late pregnancy. Growth Development and Aging 56, 115–127.

Prime GR, Varley MA and Symonds HW 1988. The effect of food intake during lactation and early pregnancy on plasma progesterone concentrations and prolificacy in multiparous sows. Animal Production 46, 499 [abstract].

Prunier A and Quesnel H 2000a. Nutritional influences on the hormonal control of reproduction in female pigs. Livestock Production Science 63, 1–16.

Prunier A and Quesnel H 2000b. Influence of the nutritional status on ovarian development in female pigs. Animal Reproduction Science 60–61, 185–197.

Quesnel H, Pasquier A, Mounier AM and Prunier A 1998. Influence of feed restriction during lactation on gonadotropic hormones and ovarian development in primiparous sows. Journal of Animal Science 76, 856–863.

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

Quesnel H, Boulot S, Serriere S, Venturi E and Martinat-Botté F 2010. Post-insemination level of feeding does not influence embryonic survival and growth in highly prolific gilts. Animal Reproduction Science 120, 120–124.

Quiniou N, Dagorn J and Gaudré D 2002. Variation of piglets' birth weight and consequences on subsequent performance. Livestock Production Science 78, 63–70.

Ramaekers P, Kemp B and van der Lende T 2006. Progenos in sows increases number of piglets born. Journal of Animal Science 84, 394 [abstract].

Redmer DA, Wallace JM and Reynolds LP 2004. Effect of nutrient intake during pregnancy on fetal and placental growth and vascular development. Domestic Animal Endocrinology 27, 199–217.

Rehfeldt C and Kuhn G 2006. Consequences of birth weight for postnatal growth performance and carcass quality in pigs as related to myogenesis. Journal of Animal Science 84, 113–123.

Reynolds LP and Redmer DA 2001. Angiogenesis in the placenta. Biology of Reproduction 64, 1033–1040.

Reynolds LP, Ford SP and Ferrell CL 1985. Blood flow and steroid and nutrient uptake of the gravid uterus and fetus of sows. Journal Animal Science 61, 968–974.

Reynolds LP, Killilea SD and Redmer DA 1992. Angiogenesis in the female reproductive system. FASEB Journal 6, 886–892.

Roberts J and Deen J 1995. Conformance quality in pig production. The Compendium on Continuing Education for the Practicing Veterinarian 17, 1308–1311.

Schoknecht PA, Newton GR, Weise DE and Pond WG 1994. Protein restriction in early pregnancy alters fetal and placental growth and allantoic fluid proteins in swine. Theriogenology 42, 217–226.

Self JT, Spencer TE, Johnson GA, Hu J, Bazer FW and Wu G 2004. Glutamine synthesis in the developing porcine placenta. Biology of Reproduction 70, 1444–1451.

Sladek SM, Magness RR and Conrad KP 1997. Nitric oxide and pregnancy. American Journal Physiology – Regulatory Integrative and Comparative Physiology 272, 441–463.

Sterling LG and Cline TR 1986. The effect of energy level in late gestation and lactation on the sow and litter: growth and reproductive performance. Journal of Animal Science 63, 115 [abstract].

Tribout T, Caritez JC, Gogué J, Gruand J, Billon Y, Bouffaud M, Lagant H, Le Dividich J, Thomas F, Quesnel H, Guéblez R and Bidanel JP 2003. Estimation, par utilisation de semence congelée, du progrès génétique réalisé en France entre 1977 et 1998 dans la race porcine Large White: Résultats pour quelques caractères de reproduction femelle. Journées de la Recherche Porcine en France 35, 285–292.

Van den Brand H, Soede NM and Kemp B 2006. Supplementation of dextrose to the diet during the weaning to estrus interval affects subsequent variation in within-litter piglet birth weight. Animal Reproduction Science 91, 353–358.

Van Den Brand H, Soede NM, Schrama JW and Kemp B 1998. Effects of dietary energy source on plasma glucose and insulin concentration in gilts. Journal of Animal Physiology and Animal Nutrition 79, 27–32.

Van Den Brand H, Van Enckevort LCM, Van Der Hoeven EM and Kemp B 2009. Effects of dextrose plus lactose in the sows diet on subsequent reproductive performance and within litter birth weight variation. Reproduction in Domestic Animals 44, 884–888.

Wang C, Delcros JG, Cannon L, Konate F, Carias H, Biggerstaff J, Gardner RA and Phanstiel O IV 2003. Defining the molecular requirements for the selective delivery of polyamine conjugates into cells containing active polyamine transporters. Journal of Medicinal Chemistry 46, 5129–5138.

Wilson ME, Biensen NJ, Youngs CR and Ford SP 1998. Development of Meishan and Yorkshire littermate conceptuses in either a Meishan or Yorkshire uterine environment to day 90 of gestation and to term. Biology of Reproduction 58, 905–910.

Wolf J, Žáková E and Groeneveld E 2008. Within-litter variation of birth weight in hyperprolific Czech Large White sows and its relation to litter size traits, stillborn piglets and losses until weaning. Livestock Science 115, 195–205.

Wu G 2009. Amino acids: metabolism, functions, and nutrition. Amino Acids 37, 1–17.

Wu G and Morris SM Jr 1998. Arginine metabolism: nitric oxide and beyond. Biochemical Journal 336, 1–17.

Wu G, Meier SA and Knabe DA 1996a. Dietary glutamine supplementation prevents jejunal atrophy in weaned pigs. Journal of Nutrition 126, 2578–2584.

Wu G, Bazer FW, Tuo W and Flynn SP 1996b. Unusual abundance of arginine and ornithine in porcine allantoic fluid. Biology of Reproduction 54, 1261–1265.

Wu G, Ott TL, Knabe DA and Bazer FW 1999. Amino acid composition of the fetal pig. Journal of Nutrition 129, 1031–1038.

Wu G, Bazer FW, Wallace JM and Spencer TE 2006. Board-invited review: intrauterine growth retardation: implications for the animal sciences. Journal of Animal Science 84, 2316–2337.

Wu G, Pond WG, Flynn SP, Ott TL and Bazer FW 1998. Maternal dietary protein deficiency decreases nitric oxide synthase and ornithine decarboxylase activities in placenta and endometrium of pigs during early gestation. Journal of Nutrition 128, 2395–2402.

Wu G, Bazer FW, Cudd TA, Meininger CJ and Spencer TE 2004. Maternal nutrition and fetal development. Journal of Nutrition 134, 2169–2172.

Wu G, Bazer FW, Burghardt RC, Johnson GA, Kim SW, Li XL, Satterfield MC and Spencer TE 2010. Impacts of amino acid nutrition on pregnancy outcome in pigs: mechanisms and implications for swine production. Journal of Animal Science 88, 195–204.

Wu G, Bazer FW, Davis TA, Jaeger LA, Johnson GA, Kim SW, Knabe DA, Meininger CJ, Spencer TE and Yin Y-L 2007. Important roles for the arginine family of amino acids in swine nutrition and production. Livestock Science 112, 8–22.

Zak LJ, Cosgrove JR, Aherne FX and Foxcroft GR 1997a. Pattern of feed intake and associated metabolic and endocrine changes differentially affect postweaning fertility in primiparous lactating sows. Journal of Animal Science 75, 208–216.

Zak LJ, Xu X, Hardin RT and Foxcroft GR 1997b. Impact of different patterns of feed intake during lactation in the primiparous sow on follicular development and oocyte maturation. Journal of Reproduction and Fertility 110, 99–106.