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Review:

Within-litter variation in birth weight: impact of nutritional status in the sow*

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Abstract: Accompanying the beneficial improvement in litter size from genetic selection for high-prolificacy sows, within-litter variation in birth weight has increased with detrimental effects on post-natal growth and survival due to an increase in the proportion of piglets with low birth-weight. Causes of within-litter variation in birth weight include breed characteristics that affect uterine space, ovulation rate, degree of maturation of oocytes, duration of time required for ovulation, interval between ovulation and fertilization, uterine capacity for implantation and placentation, size and efficiency of placental transport of nutrients, communication between conceptus/fetus and maternal systems, as well as nutritional status and environmental influences during gestation. Because these factors contribute to within-litter variation in birth weight, nutritional status of the sow to improve fetal-placental development must focus on the following three important stages in the reproductive cycle: pre-mating or weaning to estrus, early gestation and late gestation. The goal is to increase the homogeneity of development of oocytes and conceptuses, decrease variations in conceptus development during implantation and placentation, and improve birth weights of newborn piglets. Though some progress has been made in nutritional regulation of within-litter variation in the birth weight of piglets, additional studies, with a focus on and insights into molecular mechanisms of reproductive physiology from the aspects of maternal growth and offspring development, as well as their regulation by nutrients provided to the sow, are urgently needed.

Key words: Within-litter variation, Pig, Mortality, Morbidity, Growth, Sow nutrition
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1 Introduction

Over the last few decades, selection for highly prolific sows has resulted in an increase in litter size (Quiniou *et al.*, 2002); however, this is positively related to a substantial increase in pre- and post-natal mortality before weaning (Johnson *et al.*, 1999) due to greater within-litter variation in birth weights characterized by a higher proportion of low-birth-weight piglets in the litter (Milligan *et al.*, 2002a; Quesnel *et al.*, 2008; Kapell *et al.*, 2011). There is a tendency for the proportion of runt piglets to be higher in litters in which birth weights of piglets are highly variable (van der Lende and Dejager, 1991). While small piglets are at greater risk of death than their larger littermates (Winters *et al.*, 1947; Sharpe, 1966; Quiniou *et al.*, 2002), survival of all piglets increases when there is reduced variation in birth weights of piglets within a litter (van der Lende and Dejager, 1991). At the same time, heterogeneity in birth weights of piglets among

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ORCID: Jun-jun WANG, http://orcid.org/0000-0001-9427-3824 and within litters increases management costs in modern all-in-all-out swine production systems (Quiniou *et al*., 2002). Though some highly related factors such as genetic merit, oocyte quality, uterine capacity, and placental efficiency have been documented, the underlying mechanisms responsible for the high variability in birth weights within litters are unclear.

The aim of this review is to summarize the negative effects resulting from within-litter variation in birth weights, causative factors, and possible strategies for improving overall survival of piglets in large litters.

2 Negative effects of within-litter variation in birth weight of piglets

2.1 Pre-weaning mortality

Pre-weaning mortality is the major problem associated with improving prolificacy of sows. Approximately 15%–20% of piglets born do not survive to weaning (Fahmy and Bernard, 1971; Quiniou *et al*., 2002), and low birth weight is a primary contributor to poor survival to weaning (Winters *et al*., 1947; Pomeroy, 1960; Sharpe, 1966; Fahmy and Bernard, 1971; Bereskin *et al*., 1973; Pettigrew *et al*., 1986). Pre-weaning survival of piglets lighter than 0.45 kg was significantly lower than that of piglets weighing 1.6 kg or more (18% vs. 97%) (Fahmy and Bernard, 1971). Further, there is considerable evidence that high variation in birth-weight distribution in litters negatively skews the distribution in birth weights with the majority of piglets having birth weights well below the mean birth weight of the litter (Milligan *et al*., 2002b). In fact, there is a linear relationship between piglet survival and coefficient of variation for within-litter birth weight, and a curvilinear relationship between average birth weight and mortality of piglets (Fahmy and Bernard, 1971). Although there is also a favorable correlation between pre-weaning survival and within-litter variation in birth weight from the genetic perspective (Knol *et al*., 2002; Kapell *et al*., 2011), it is worth emphasizing that the adverse effects of high variation in birth weight on piglet survival are mainly due to an increase in the proportion of small piglets (Milligan *et al*., 2002a) since normal variation in birth weight has little effect on piglet survival in healthy litters (Milligan *et al*., 2001).

2.1.1 Intra-uterine growth restriction and susceptibility to infection and disease

Low-birth-weight piglets in litters with high variation in birth weights experience intra-uterine growth restriction (IUGR), usually resulting in physiological dysfunctions and an increase in neonatal morbidity and mortality (Wootton *et al*., 1983; Aucott *et al*., 2004). In addition, IUGR neonates are more susceptible to infection or environmental changes due to an ineffective immune system (Cromi *et al*., 2009; Zhong *et al*., 2012), and IUGR animals have abnormal differences in size and histopathology of the thymus (Cromi *et al*., 2009). Consistently, overexpression of heat shock protein 70 (Hsp70) associated with impaired cellular immunity was observed in the intestine (Zhong *et al*., 2010) and liver (Li *et al*., 2012) of IUGR neonates, suggesting that immune function is altered widely in IUGR piglets. There is growing evidence that elevated Hsp70 reduces proliferation and impairs nuclear factor-kappa B (NF-κB) signaling for cell survival (Wei *et al*., 1995; Ran *et al*., 2004).

2.1.2 IUGR and hyperammonemia

Abnormal metabolism of ammonia must be taken into consideration as a cause for morbidity or mortality of small piglets (Wu G. *et al*., 2010). We detected an abnormally high activity of glutamate oxaloacetate transaminase in the liver of IUGR fetuses compared with normal fetuses at Day 110 of gestation, this enzyme being responsible for the generation of ammonia from glutamate (Liu *et al*., 2013). High levels of expression of glutamate dehydrogenase 1, coupled with reduced levels of carbomoyphosphate synthase 1 to degrade it, result in the accumulation of ammonia, which increases the risk of hyperammonemia in low-birth-weight piglets and low-birth-weight human infants (Batshaw and Brusilow, 1978). This condition severely threatens survival of the neonate. Moreover, IUGR fetuses both at Days 90 and 110 of gestation had higher concentrations of ammonia in umbilical vein plasma than normal fetuses (Lin *et al*., 2012), which may account for poor survival and development of IUGR fetuses. The rate of protein degradation in the IUGR fetus may be higher than that in the normal-weight fetus.

2.1.3 IUGR and insufficient colostrum intake

For low-birth-weight piglets, intake of colostrum is delayed and inadequate (Le Dividich *et al*., 1998; Quesnel *et al*., 2012), leading to a poor acquisition of passive immunity and a poor nutritional status, thereby increasing the incidence of death or poor growth performance of piglets during lactation (Rooke and Bland, 2002; Le Dividich *et al*., 2005). This is because colostrum is the most important source of highly digestible compounds for neonates, including glucose, fat, protein, immunoglobulins, hormones, and growth factors (Le Dividich *et al*., 2005) required to meet demands for energy of piglets and support maturation of the digestive and immune systems (Walzem *et al*., 2002; Politis and Chronopoulou, 2008). In addition, low-birth-weight neonates that have low energy reserves are at greater risk of being inadvertently crushed by the sow when she lies down (Fahmy and Bernard, 1971), as well as an inability to prevent chilling due to impaired thermogenic mechanisms (Le Dividich, 1999).

2.2 Pre-weaning growth performance

Differences in birth weights among piglets are also related to differences in pre-weaning growth performance within litters, which are mainly due to remarkable differences in both milk intake and efficiency of utilization of nutrients by littermates. Colostrum/milk intake is affected by both vitality of the piglet at birth and within-litter competition to access a teat as the teat order for suckling develops within the first 24 h after birth and is then maintained (McBride, 1963). Vigorous piglets prefer the anterior teats (Fraser *et al*., 1979; Thompson and Fraser, 1986), while small piglets are at a disadvantage in fighting to gain possession of these more productive anterior teats compared with their larger siblings since the teat order is a dominance hierarchy (Pond and Houpt, 1978; Auldist and King, 1995). However, per kg body weight, milk consumption does not appear to differ between IUGR and normal-weight piglets (Rezaei *et al*., 2011). Offspring that obtain milk from anterior and middle mammary glands (MGs) grow faster than those suckling posterior MG (Puppe and Tuchscherer, 1999; Kim *et al*., 2000). Besides the greater amount of colostrum and milk from anterior and middle MGs (Gill and Thomson, 1956), we reported that components in colostrum and milk secreted by anterior and posterior MGs are also distinctive (Wu W.Z. *et al*., 2010) in having proteins that are beneficial to passive immunity, intestinal development, and epithelial integrity; they include immunoglobulins and haptoglobin in colostrum and lactoferrin in milk from anterior MG, which are more abundant in anterior and middle MGs compared with posterior MG. In addition, piglet body weight and stimulation through suckling intensity to the MG strongly determine milk production (King *et al*., 1997).

The inefficient utilization of nutrient was reported for small piglets (Rezaei *et al*., 2011) owing to physiological immaturity at birth, especially severe dysfunction in several organs, including the intestine (Wang X.Q. *et al*., 2014b), liver (Liu *et al*., 2013), and skeletal muscle (Wang T. *et al*., 2013). Additionally, concentrations of key proteins involved in growth and development were reduced, while there was an abundance of proteins associated with oxidative stress, proteolysis, and ATP hydrolysis in the small intestine, liver, and muscle of low-birth-weight piglets (Wang *et al*., 2008). Impaired development and dysfunction of those organs and tissues that play vital roles in digestion, absorption, and metabolism of dietary nutrients (Jobgen *et al*., 2006) could permanently decrease postnatal growth performance and efficiency of nutrient utilization in piglets. Therefore, these overall capacity differences in intake and utilization efficiency of nutrients among piglets may partly explain why differences in body weight at birth are often maintained or even increase throughout the period of lactation.

2.3 Post-weaning growth and meat quality

In litters in which there is a high variability among piglets regarding birth weight, growth rates among those offspring are desynchronized. Litters with more variability in piglet weight at birth have more variable weaning weights (Thompson and Fraser, 1986; Milligan *et al*., 2001; 2002b), since birth weight, absolute body-weight gain during lactation and weight at weaning are highly correlated (Quiniou *et al*., 2002). As an unfavorable consequence, the time for pigs within a litter to achieve slaughter weight is variable, with an additional three weeks being required for small piglets to reach 25 kg compared with their heavier littermates (76 and 55 d, respectively) (Quiniou *et al*., 2002). These differences can result in an increase in feed and management costs for lighter pigs due to the longer time and increased feed required for them to reach the required minimum commercial slaughter weight.

The distribution of muscular fiber type for IUGR piglets is affected negatively (Widdowson, 1971; Wigmore and Stickland, 1983; Wu *et al.*, 2006) as both secondary and total muscle fibers are reduced in number (Wigmore and Stickland, 1983; Wang T. *et al.*, 2013) for small fetuses, which, in turn, adversely affects growth rate and post mortem quality of meat. The reduction in number of muscular fibers and the larger diameters for those fibers for IUGR piglets result in greater amounts of intramuscular lipids and decreased meat tenderness at slaughter (Gondret *et al.*, 2005), leading to a decrease in meat quality and economic losses.

3 Causes for within-litter variation in birth weight

Knowledge of the underlying mechanisms responsible for various distributions in birth weights of piglets within litters has important implications for the prevention of small neonates and is crucial for enhancing the efficiency of livestock production and animal health. Growth and development of the fetus involve numerous complex biological events that can be influenced by genetics, epigenetics, maternal maturity, state of maternal nutrition, and environmental temperatures (Redmer *et al.*, 2004). These factors affect implantation and placentation by the conceptus, angiogenesis within the uterus and placenta, utero-placental efficiency of transport of nutrients, and activities of fetal metabolic pathways (Bell and Ehrhardt, 2002; Fowden *et al.*, 2005; Reynolds *et al.*, 2006). All of those events may be influenced by breed characteristics that include maturity of ovulated oocytes, duration of ovulation, implantation and placentation capacity, available uterine space for implantation and placentation, size and efficiency of the placenta, as well as nutritional provision and environmental influences on the sow (Wu *et al.*, 2006).

3.1 Duration of ovulation and oocyte maturation

The duration of ovulation, known as the time interval between ovulation of the first and the last follicle in a sow, and follicular diversity are believed to be associated with diversity in embryonic development during early pregnancy (Pope *et al.*, 1990). Furthermore, the sequence of oocyte release during ovulation might contribute to differences in embryonic development with later-ovulated oocytes (42 h after human chorionic gonadotropin (hCG) injection) producing less-developed embryos at Day 4 of pregnancy, compared with earlier-ovulated oocytes (39 h after hCG injection); not surprisingly, the less-developed Day 4 embryos became the smaller blastocysts within a litter at Day 12 of gestation (Xie *et al.*, 1990). In terms of hormone levels being key predictors of embryonic development, the more-developed blastocysts synthesize estradiol sooner than their contemporaries (Geisert *et al.*, 1982a; Pope *et al.*, 1988), while less-developed embryos at Day 12 of gestation contained less estradiol, less total protein, and less acid phosphatase activity (Xie *et al.*, 1990), which might influence elongation and implantation of blastocysts. At the same time, the duration of ovulation in Meishan sows is 2 h versus 6 h for Large White sows, and this shorter interval was associated with less morphological variation and increased embryonic survival in litters of Meishan gilts (Bazer *et al.*, 1988). Moreover, when later-ovulated follicles were removed, the diversity in embryonic morphology was reduced concomitantly, mainly through eliminating less-developed embryos (Pope *et al.*, 1988). Further, duration of ovulation is related to the pattern of ovulation, since the distribution of follicular development and oocyte maturation are both skewed with a majority of mature follicles and oocytes (e.g. 70%) being ovulated during a short period of time and the rest (e.g. 30%) being ovulated during the following 2–6 h (Pope *et al.*, 1990).

In contrast, Soede *et al.* (1992) concluded that embryonic diversity was not related to the duration of ovulation, at least up to 3 h, as they observed no significant differences in numbers of nuclei or numbers of cell cycles about 100 h after ovulation between Groups A and B (duration of ovulation was (1.8±0.6) and (4.6±1.7) h in Groups A and B, respectively). The reasons for these differences in results may include the maturation and quality of oocytes, as well as endocrine status of the sows. It is clear that embryonic diversity throughout at least the first 12 d of gestation is predetermined by factors that involve follicular development and oogenesis (Pope *et al.*, 1990; Xie *et al.*, 1990). Furthermore, oocyte maturation and quality can affect embryonic development and hormone secretion by the conceptus ultimately affecting the endocrine status of the uterus (Bazer *et al.*, 2014). More studies are warranted to gain further insight into relationships between duration of ovulation and variations in embryonic development, although a body of evidence supports the view that the oocytes of later-ovulated follicles could be progenitors of small embryos.

3.2 Implantation capability of conceptuses and position within the uterus

The relationship between the fetal-placental growth and location within the uterus is evident. Pig fetuses from the ovarian end of the horn were approximately 10% heavier than those located at the middle or near end of the cervix (Waldorf *et al.*, 1957; Perry and Rowell, 1969; Wise *et al.*, 1997), and similar results have been described in rabbits (Rosahn and Greene, 1936). The effects of location within the uterine horn on fetal piglet weight are more notable during the last one-third of gestation when the demand for transfer of nutrients from the maternal system across the placenta to the fetus is greatest. Kim *et al.* (2013) concluded that fetal weight decreased linearly from the utero-tubal junction to the cervix between Days 102 and 112 of gestation. It is postulated that vascular density within the placenta varies from uterine horn to cervix, that blood flow increases from the cervical to the oviductal end of each uterine horn in gilts during early pregnancy (Ford *et al.*, 1982), and that implantation sites with less than three blood vessels were associated with poor development of the fetus which increased fetal weight variation within the litter. Moreover, it has been observed that there is considerable diversity in development of conceptuses prior to implantation within litters (Anderson, 1978; Geisert *et al.*, 1982a), which may contribute to differences in timing and capacity to establish adequate surface area for implantation and placentation, since elongation of the conceptus during the peri-implantation period of pregnancy is critical to implantation and depends on the conceptus achieving a specific stage of differentiation and development (Anderson, 1978; Stroband and van der Lende, 1990; Blomberg *et al.*, 2010).

3.3 Placental efficiency

Maternal nutrition during gestation, especially the amount of nutrients provided to each conceptus, has been regarded as a major cause for within-litter variation in birth weight of piglets currently born to sows. Fetuses acquire nutrients from the maternal system via the utero-placental circulation and umbilical vein throughout gestation (Kiserud and Acharya, 2004), and transfer of nutrients from mother to fetus is impaired in pregnancies with reduced blood flow in piglets which exhibit signs of IUGR (Reynolds *et al.*, 2006; Kim *et al.*, 2013). Furthermore, the composition of nutrients, gases, and other molecules in the umbilical vein blood is different between normal and IUGR fetuses. Previous results from our laboratory indicated lower circulating concentrations of glucose, amino acids of the arginine family, such as arginine and glutamine, and branched-chain amino acids (valine, leucine, and isoleucine), but increased concentrations of ammonia in umbilical vein plasma during late gestation in IUGR, compared with normal fetuses (Lin *et al.*, 2012). It is clear that the transport of nutrients by the placenta of IUGR fetuses is altered and directly impairs fetal development (Wu *et al.*, 2008).

3.4 Available uterine space

Increase in ovulation rates for gilts and sows during the past decades is a positive response to continuous selective breeding; however, as the number of conceptuses that survive during the post-implantation period greatly exceeds uterine capacity, there is a decrease of available uterine surface area for the development of each placenta. Therefore, there is a peak in post-implantation conceptus deaths between Days 30 and 50 of gestation when uterine surface area is insufficient (Knight *et al.*, 1977; Vonnahme *et al.*, 2002). As gestation progresses, the negative effects of limited uterine space on fetal development also increase (Vonnahme *et al.*, 2002). The great within-litter variation in birth weight and increased proportion of small piglets born to the highly prolific sows as used today are likely related, in part, to intra-uterine crowding from at least the end of the first month of gestation (Foxcroft *et al.*, 2006), especially when there are more than 14 fetuses present within the uterus (Webel and Dziuk, 1974). Moreover, intra-uterine crowding can alter the pattern of development of fetal muscle fibers in the immediate post-implantation period (Foxcroft *et al.*, 2007), when mesenchymal stem cells of the embryo undergo differentiation for myogenesis, adipogenesis or mesenchymal cells (Cossu and Borello, 1999; Du *et al.*, 2010). Detrimental effect of uterine crowding on fetal development (Town *et al.*, 2004) is considered to be associated with insufficient development of placental vascularity (Argente *et al.*, 2008), while a poor vascular supply and reduced uterine space limit development of offspring that thereby experience a deficit in nutrient availability before birth (Argente *et al.*, 2006; Foxcroft *et al.*, 2007). This subsequently increases within-litter variation in birth weight that is associated with greater post-natal death of piglets.

3.5 Breed characteristics

There is a body of evidence implying that genetic merit does exert considerable effects on litter homogeneity, as fetal genotype determines placental and endometrial vascularity during the last one-third of gestation (Biensen *et al.*, 1998). Convincing data revealed that development of Meishan conceptuses was more uniform between Days 8 and 14 of gestation (Bazer *et al.*, 1988), and within-litter variation in birth weight was lower in Meishan litters than in Large White litters (Lee and Haley, 1995). Differences in growth patterns for placentas and uterine capacity (Père and Etienne, 2000) between the two breeds can account for a large portion of the significant differences in birth-weight distribution. The Meishan placentas are smaller at farrowing (Wilson *et al.*, 1998), while vascular density progressively increases between Days 90 and 110 of gestation with constant placental size. In contrast, Large White placental size progressively increased during late gestation, while vascular density remained constant (Biensen *et al.*, 1998; Wilson *et al.*, 1998). Hence, endometrial surface area per Meishan placenta decreased and competition among fetuses reduced simultaneously, which is associated with the high degree of uniformity in birth weight within litters of Meishan sows.

Within-litter variation in birth weight is also affected by parity, with older sows with greater parity often having less uniform litters as well as a higher proportion of low-birth-weight piglets (Damgaard *et al.*, 2003; Quesnel *et al.*, 2008; Wientjes *et al.*, 2012). Pettigrew *et al.* (1986) also reported that birth weights of piglets from primiparous sows were more uniform. Litter size is positively correlated with parity, reaching the highest level between parities 3–5 (Dewey *et al.*, 1995; Hughes, 1998). However, negative effects of parity on litter homogeneity may be related to its effects on litter size, which is positively related to within-litter variation in birth weight especially in litters with more than a total of 16 piglets born (Quiniou *et al.*, 2002; Quesnel *et al.*, 2008; 2014). An opposite view held by Pettigrew *et al.* (1986) is that the apparent increase in piglet birth weight standard deviation associated with increased litter size was far from enough to explain the impacts of parity on litter uniformity. Moreover, variation in birth weight is greater in older parity sows after correction for the total number of piglets born and excluding the effects of litter size (Wientjes *et al.*, 2012). It has been postulated that the decrease in litter uniformity in older parity sows may result from deterioration in quality of follicles/oocytes with aging as reported for women (Broekmans *et al.*, 2009), suggesting that litter uniformity in birth weight can also be affected solely by parity.

It follows that within-litter variation in birth weight is an integrated trait influenced by many factors. Additionally, these factors can interact with each other. Thus, studies focusing on within-litter variation in birth weight are in their infancy, and more studies are needed to clarify mechanisms and develop strategies to decrease IUGR in modern sows.

4 Strategies to decrease within-litter variation in birth weight

Pregnancy outcome is influenced by interactions between nutrition and genetics (Wu *et al.*, 2006). For specific breeds in swine production, the sow's nutrition is attracting the most research interest with a promise of decreasing within-litter variation in birth weight. Since there are three critical stages associated with conceptus/fetus survival and development throughout gestation, nutritional strategies that focus on pre-ovulation, peri-implantation and late gestation periods are expected to increase developmental homogeneity of oocytes and/or conceptuses, and decrease variations in the capability of conceptuses to undergo successful implantation and placentation, so that the birth weights of newborn piglets are more uniform. Improving litter uniformity is expected to increase the number of piglets born alive, as well as survival of piglets pre- and post-weaning and their growth performance after weaning.

4.1 Nutrition related to follicle/oocyte maturity

There is evidence that events during oogenesis influence survival and development of swine embryos (Pope *et al.*, 1990), since oocyte maturity may be a determinant of uniformity in embryonic development, and subsequently, within-litter variation in birth weight (van der Lende *et al.*, 1990). Therefore, nutritional strategies directed at sows prior to mating hold great promise to decrease within-litter variation in birth weight.

4.1.1 Energy intake

Energy intake should be regarded as the intake of lipids, carbohydrate, and amino acids in diets, as well as the ratios of these nutrients. Thus, knowledge of nutrient metabolism is essential to understand the utilization and function of dietary energy. Energy is critical for reproductive performance in swine. Sows fed low-energy diets during the weaning-to-estrus interval exhibit lower ovulation rates (Zak *et al.*, 1997; van den Brand *et al.*, 2000), smaller follicle size and fail to exhibit strong signs of estrous behavior (Prunier *et al.*, 1993). However, modestly high-energy diets for sows pre-mating have positive impacts on embryonic survival (Ferguson *et al.*, 2006) and litter homogeneity (Ashworth *et al.*, 1999). Blastocysts recovered at Day 12 of gestation from gilts on a high level of feed intake pre-mating (3.5 kg/d) exhibited a lower within-litter standard deviation in blastocyst surface area, compared with blastocysts from gilts fed a maintenance diet pre-mating (1.15 kg/d), indicating that increasing pre-mating feed intake can reduce within-litter variability in blastocyst size at Day 12 of pregnancy (Ashworth *et al.*, 1999). In addition, variation in body weight was less for sows fed 150 g/d dextrose-supplemented diets, compared with sows fed general diets during the weaning-to-estrus interval (van den Brand *et al.*, 2006). Similar results were obtained in response to dietary supplementation with dextrose plus lactose from the last week of gestation until sows were inseminated (van den Brand *et al.*, 2009).

4.1.2 Energy and insulin/IGF-1

Within-litter variation in birth weight reduced through dietary manipulation during the follicular phase of the estrous cycle (van den Brand *et al.*, 2006; 2009) is likely due to improved follicle and oocyte development associated with changes in concentrations of metabolic hormones such as insulin-like growth factor-1 (IGF-1) and insulin (Yang *et al.*, 2000; Ferguson *et al.*, 2003). Development of follicles and oocytes is improved owing to higher concentrations of insulin (Matamoros *et al.*, 1990; Tokach *et al.*, 1992; van den Brand *et al.*, 1998; 2000; Ziecik *et al.*, 2002) or IGF-1 in plasma (Ferguson *et al.*, 2003). The underlying mechanism by which insulin increases follicular development is possibly due to an increase in luteinizing hormone (LH) pulsatility (Cox *et al.*, 1987) or LH production (Adashi *et al.*, 1981), and a higher LH pulse frequency (van den Brand *et al.*, 2000).

4.1.3 Energy source

Effects of feeding level on reproductive performance depend on dietary energy. Follicle quality or oocyte maturation can be stimulated by carbohydrate-rich diets, but decreased by fat-rich diets (van den Brand *et al.*, 2006), which can be explained partially by different ingredients in feed that affect different reproductive hormones (van den Brand *et al.*, 2000). Feeding a carbohydrate-rich diet during and after lactation increases the pre-ovulatory LH peak and circulating concentrations of progesterone in comparison with feeding a fat-rich diet (Kemp *et al.*, 1995). On the other hand, plasma insulin levels increase more rapidly in gilts fed dextrose than fat, which results in a significant difference in plasma insulin at 24 min after feeding (van den Brand *et al.*, 1998). Furthermore, feeding a high fiber diet during the estrous cycle tends to increase embryonic survival and decrease the proportion of IUGR fetuses at Day (27±2) of gestation (Ferguson *et al.*, 2006). This may be due to a longer time for energy or some fiber-related metabolites to enhance oocyte quality or follicular development.

4.1.4 Vitamin A/retinol

Vitamins function as micronutrients with extensive participation in metabolic processes. Alterations in dietary retinol could improve pregnancy outcome by decreasing both the incidence of low-birth-weight piglets and within-litter variation in birth weight (Whaley *et al.*, 2000; Antipatis *et al.*, 2008). Treatment of sows with vitamin A at weaning increased subsequent litter size through decreased embryonic mortality (Coffey and Britt, 1993) and synchronous development of embryos (Pope *et al.*, 1990). Whaley *et al.* (2000) found that embryonic development was more advanced and more uniform when dietary supplementation with 1×10^6 IU vitamin A (retinyl palmitate) was provided from Day 15 after the second estrus until mating at the third estrus. Similarly, more embryos with greater uniformity were obtained at Day 11 of gestation from gilts treated with vitamin A before mating (Whaley *et al.*, 1997). Positive effects of vitamin A are considered to be associated with enhanced maturation of oocytes (Robertson, 1997; Robertson *et al.*, 1997) and, consequently, enhanced embryonic development (Besenfelder *et al.*, 1996). Further, concentrations of progesterone, IGF-1, and prostaglandin F2-α (PGF2-α) in follicular fluid were greater in vitamin-A-treated than in control gilts. Effects of vitamin A on follicle maturation were suggested to be through an IGF-1 stimulatory mechanism, since IGF-1 produced by granulosa cells plays a key role in the resumption of oocyte meiosis (Hammond *et al.*, 1991) and increases both proliferation and progesterone synthesis and secretion by granulosa cells (Giudice, 1992).

4.2 Nutrition related to the peri-implantation period of pregnancy

Maternal recognition of pregnancy and conceptus implantation are the most important biological events associated with the establishment of pregnancy (Perry *et al.*, 1976). Estrogen secreted by pig conceptuses is the major signal for maternal recognition of pregnancy at approximately Day 11 of gestation (Dhindsa and Dziuk, 1968; Perry *et al.*, 1973; Bazer and Thatcher, 1977; Flint *et al.*, 1979), which coincides with the time of conceptus elongation (Heap *et al.*, 1979; Geisert *et al.*, 1982b). Moreover, the morphological transition of conceptuses from spherical to tubular and filamentous forms occurs between Days 10 and 12 (Geisert *et al.*, 1982b; Bazer and Johnson, 2014).

Implantation is a gradual process starting as early as Day 13 when elongation of the conceptus is underway and is well advanced by Day 18 of gestation (Perry *et al.*, 1976), which is a determinant for establishing sufficient uterine surface area for placentation and subsequent nutrient transport for piglet survival and development (Geisert *et al.*, 2014; Bazer and Johnson, 2014). It should be emphasized that establishment of pregnancy (conceptus elongation and implantation) also involves maternal uterine pro-inflammatory and immune responses (Geisert *et al.*, 2014), due to a number of cytokines released or stimulated by the elongating conceptuses, such as NF-κB (Hayden and Ghosh, 2012) and interleukin 1β (IL-1β) (Ross *et al.*, 2003; Blomberg *et al.*, 2005). In order to avoid rejection by the immune response, an increase in expression of both IL1B and estrogen by individual conceptuses counter-balances stimulation of the pro-inflammatory and immune response within the uterus (Geisert *et al.*, 2014); thus elongating conceptus can attach across the uterine luminal epithelial surface successfully.

As stated above, elongation of pig conceptuses is triggered by the conceptus achieving a specific stage of differentiation and development within the uterus (Bazer *et al.*, 2014). Thus, it is a maternal event and has never been achieved *in vitro* (Anderson, 1978; Stroband and van der Lende, 1990; Blomberg *et al.*, 2010; Bazer, 2013). However, various stages of conceptus development (spherical, tubular and filamentous) can be observed prior to and during the time of trophoblast elongation within the same litter (Anderson, 1978; Geisert *et al.*, 1982a), leading to remarkable differences in timing, position, and area of implantation, and, thereafter, various states of survival and development. It is worth noting that pre-implantation embryonic losses are considered to make up the largest proportion of prenatal losses in pigs (Wiseman *et al.*, 1998), suggesting that this is a key period to regulate embryonic survival and development during the implantation window and to affect placentation.

4.2.1 L-Arginine

Dietary supplementation with 0.4% or 0.8% L-arginine between Days 14 and 25 of gestation increased number of viable fetuses per litter by 2 on Day 25 compared with a control group (Li *et al.*, 2014). This positive result is consistent with the presence of unusually high concentrations of amino acids in the arginine family in porcine allantoic fluid at the stage of blastocyst expansion and implantation *in vivo* (Wu *et al.*, 1996; Gao *et al.*, 2012) and of an increase in endometrial angiogenesis between Days 13 and 18 of gestation (Keys *et al.*, 1986). Furthermore, arginine stimulates the AKT1-mTOR/FRAP1-RPS6K-RPS6 cell signaling pathways to increase proliferation and migration of porcine (Kong *et al.*, 2012) and ovine (Kim *et al.*, 2011) trophectoderm cells during peri-implantation period. The positive impact of L-arginine supplementation during the peri-implantation period of pregnancy is due in part to the production of NO, since this is crucial for embryonic development and implantation (Maul *et al.*, 2003; Wang X.Q. *et al.*, 2014a). Putrescine, which is a product of arginine catabolism in maternal tissues (Wu *et al.*, 2009), can also stimulate protein synthesis in porcine placental cells (Kong *et al.*, 2014). Of note, dietary supplementation of 0.8% L-arginine between Day 0 and Day 25 of gestation reduced litter size, uterine weight, total number of fetuses, number of corpora lutea and total fetal weights significantly at Day 25 (Li *et al.*, 2010). Even though there was increased vascularity of the uterus due to arginine supplementation, its administration too early (from onset of estrus) interfered with normal ovulation, which decreased production of progesterone and estrone (Li *et al.*, 2010). From these aspects, dietary supplementation with L-arginine during the peri-implantation period is expected to promote survival and synchronize development of embryos within a litter.

4.2.2 Retinol/vitamin A

Providing a vitamin A-deficient diet for 100 d prior to mating and during the first month of pregnancy increased the uniformity of birth weights and showed a tendency to decrease the incidence of low-birth-weight piglets (Antipatis *et al.*, 2008). Moreover, sows on vitamin A-deficient diets did not experience a reduction in fetal survival and growth at Day 30 of pregnancy (Ashworth and Antipatis, 1999), perhaps due to a compensatory increase in the abundance of retinol binding protein (RBP) (Antipatis *et al.*, 2008). Since pig conceptuses secrete RBP prior to onset of elongation and throughout the peri-implantation period, RBP could be an important component of the uterine secretions for early embryonic development (Harney *et al.*, 1990; Schweigert *et al.*, 1999). Thus, elevated levels of RBP in gilts deficient in vitamin A can account for positive outcomes of piglets having low within-litter variation in birth weight.

It is well documented that progesterone is required to maintain pregnancy and circulating concentrations of progesterone can be modulated by feed intake. Sows receiving high ((2.8±0.02) kg/d) nutrient intake, compared with a low ((1.5±0.01) kg/d) nutrient intake, from Day 0 to Day 9 of pregnancy had higher embryonic survival at Day 10 of pregnancy ((92±3)% vs. (77±3)%) (Athorn *et al.*, 2013), which may be due to higher concentrations of blood progesterone in response to adequate feed intake. Progesterone synthesis is likely to be impaired when dietary intake of nutrients (particularly amino acids) and energy is insufficient.

4.3 Nutrition related to fetal growth during late gestation

Approximately 90% of fetal growth occurs during the last one-third of pregnancy. This period of pregnancy is characterized by a high incidence of limitations on fetal development and increased within-litter variation in fetal weight. The weight variation among piglets in each litter increased from Day 45 to Day 60 of gestation (Kim *et al.*, 2009). After implantation, the placenta is the only organ through which nutrients, waste and respiratory gases are exchanged between the sow and conceptus (Faber and Thornburg, 1983). The size and capacity of the placenta for nutrient transfer play key roles in determining the prenatal growth of the fetus and hence affect birth weight directly (Redmer *et al.*, 2004). Placentation that occurs during early pregnancy is one of the most important developmental events (Boshier, 1969; King *et al.*, 1982), since it is tightly associated with embryonic survival (Reynolds and Redmer, 2001). Extensive angiogenesis occurs in both the maternal uterus and fetal placenta during placentation, and umbilical blood flow increases during the same time (Reynolds *et al.*, 1984; Reynolds and Redmer, 1992; 1995). It has been reported that early embryonic mortality increases as placental vascular development decreases (Meegdes *et al.*, 1988; Reynolds and Redmer, 1995). Therefore, adequately balanced diets provided to sows and functional nutrients available for placental transport are two major factors affecting uniformity of piglets in a litter during late gestation. Supplementation of diets with functional amino acids (e.g. arginine and glutamine) holds great promise for preventing fetal growth restriction (Wu *et al*., 2013a; Lin *et al*., 2014).

4.3.1 L-Arginine/*N*-carbamyl-L-glutamate

Amino acids in the arginine family (arginine, glutamine, glutamate, proline, aspartate, asparagine, citrulline, and ornithine) have been studied extensively given their prominent effects in improving litter size (Greenberg *et al*., 1997; Hazeleger *et al*., 2007; Mateo *et al*., 2007; Gao *et al*., 2012; Li *et al*., 2014). At the same time, dietary supplementation with 25.5 g/d L-arginine from Day 77 of pregnancy until term reduced within-litter variation in birth weight of live-born piglets by 20.6% and 25.4% in arginine and control groups, respectively (Quesnel *et al*., 2014). Dietary supplementation with 0.1% *N*-carbamyl-L-glutamate (NCG) from Day 90 of gestation also increased litter size born alive and total litter weight for piglets born alive (Liu *et al*., 2012).

L-Arginine is an important precursor for the synthesis of NO and polyamines (Wu and Morris, 1998; Wu *et al*., 2007; Blachier *et al*., 2011), both of which play key roles in placental growth and angiogenesis (Wu *et al*., 2006). Similarly, NCG stimulates expression of vascular endothelial growth factor (Liu *et al*., 2012) associated with vasculogenesis and angiogenesis (Hanahan, 1997; Arroyo and Winn, 2008). Subsequently, NCG increases blood flow and placental efficiency (McCrabb and Harding, 1996; Gardner *et al*., 2001), as well as the provision of nutrients to fetuses. Therefore, nutrient partitioning among fetuses is less variable as is within-litter variation in birth weight of piglets. However, there are other reports that do not indicate positive effects of dietary supplementation with L-arginine during mid-gestation to term on within-litter uniformity (Mateo *et al*., 2007; Gao *et al*., 2012). These different findings may be explained by differences in the total amounts of dietary L-arginine and other amino acids consumed by gestating pigs (Wu *et al*., 2013b; 2013c).

As previously mentioned, either dextrose supplementation during the weaning-to-estrus interval or 1% L-arginine supplementation during the last one-third of gestation can reduce within-litter variation in birth weights (van den Brand *et al*., 2006; Quesnel *et al*., 2014). Unexpectedly, combined supplies of dextrose beginning one week before insemination and L-arginine during the last one-third of pregnancy in sow diets had no obvious beneficial effects on within-litter variation in birth weight, compared with control groups (Quesnel *et al*., 2014). This was postulated to be correlated with complex interactions between different nutrients. High levels of glucose can affect amino acid metabolism and, therefore, may not be beneficial for embryonic and fetal survival, growth, or development. Thus, consideration must be given to interactions among different nutrients when manipulating maternal diets during gestation.

4.3.2 Glutamine

As a member of the arginine family of amino acids, glutamine plays a key role in many metabolic processes, such as cell proliferation, differentiation, and embryonic development (Petters *et al*., 1990; Wu *et al*., 2011). Concentrations of glutamine are highest among amino acids in fetal tissues and maternal placenta (Self *et al*., 2004), and there are increased concentrations of glutamine in allantoic fluid in the second third of gestation (Wu *et al*., 1996), which highlights the importance of glutamine during that stage of rapid placental and fetal growth.

Within-litter variation in weight of piglets can also be reduced by dietary supplementation with glutamine (Wu *et al*., 2010). Sows fed a basal gestational diet supplemented with mixture of 8 g L-arginine and 12 g L-glutamine had reduced within-litter variation in birth weight either on the basis of total piglets or live-born piglets, and the proportion of runt piglets was decreased. It would be of interest to determine whether dietary supplementation with L-glutamate, which is the immediate precursor of L-glutamine (Rezaei *et al*., 2013b) and is another functional amino acid (Wu, 2010), can enhance fetal growth and reduce birth-weight variation among piglets.

4.3.3 Branched chain amino acids

Branched chain amino acids (BCAAs), including leucine, isoleucine, and valine, have received growing attention owing to their emerging functional importance (Lei *et al*., 2012; 2013). These amino acids are substrates for the synthesis of glutamate and arginine, and, therefore, alanine, citrulline, arginine, and proline in pigs (Rezaei *et al.*, 2013a) and ruminant species (Wu *et al.*, 2014). Data from our laboratories suggest that dietary supplementation with BCAAs throughout pregnancy can reverse IUGR in a rat model of malnutrition (Zheng *et al.*, 2009). In litters derived from BCAA-supplemented gestating sows, weights of piglets and placentas increase by 18.4% and 18.0%, respectively, and litter size is also increased. Furthermore, BCAA treatment increased IGF-1 in embryonic liver, estrogen receptor-α and progesterone receptor in the uterus, and IGF-II in placentas, all of which are beneficial to survival and growth of the conceptus. There was also enhanced expression of two key enzymes (fructose-1,6-biphosphatase and phosphoenolpyruvate carboxykinase) involved in gluconeogenesis in embryonic livers. These positive findings indicate that BCAAs have important roles in enhancing positive pregnancy outcomes.

Fetal growth is affected by the nutritional, metabolic and endocrine status of the maternal system which is affected by dietary intake of nutrients (Lin *et al.*, 2014). Moreover, nutrient requirements of sows are distinct at different stages of gestation (Kim *et al.*, 2013). Therefore, more studies to gain insight into the molecular mechanism for the role of maternal nutrients on fetal programming are necessary for designing innovative nutrient-balanced gestational diets that enhance the homogeneity of birth weight of piglets.

4.4 Genetic selection

Litter size, directly related to productivity, has been considered as a key factor in genetic selection. As a result, the total number of piglets at birth has been significantly improved in past decades (Southwood and Kennedy, 1991; Estany and Sorensen, 1995). However, this practice has also increased the neonatal mortality of piglets owing to the increased percentage of low-birth-weight pigs (Lund *et al.*, 2002). To avoid this situation, scientists have started to test whether litter size at Day 5 (LS5) after birth can be used to reduce the neonatal mortality while not decreasing the litter size at birth. Recent results from 42807 Landrace and 33225 Yorkshire sows showed a significant genetic and phenotypic improvement in the total number of piglets at birth and neonatal survival (Nielsen *et al.*, 2013), as well as litter size at weaning (Su *et al.*, 2007; EAAP, 2011) by using LS5 as an index of genetic selection. Therefore, this criterion has been extended for use in the Danish Landrace and Yorkshire breeding program since 2004 (Nielsen *et al.*, 2013). At the same time, a maternal line selected on litter size at weaning in rabbits for 21 generations improved the number of progeny born alive and litter size at weaning, compared with selection on litter size at birth (García and Baselga, 2002), suggesting that it is effective in both promoting litter size at birth and survival rate during lactation (Savietto *et al.*, 2014). Additionally, it is feasible to select for within-litter uniformity in birth weight (Damgaard *et al.*, 2003; Kapell *et al.*, 2011) to improve piglet survival (Canario *et al.*, 2010). A selection experiment on within-litter birth-weight variation in rabbits yielded a favorable response and decreased pre-weaning morbidity (Garreau *et al.*, 2004). Collectively, genetic selection by combining litter uniformity at birth, survival rate during lactation, and litter size at weaning holds a promise of improving pig productivity.

5 Summary and perspectives

Currently, special attention is given to within-litter variation in birth weight, as a distinct problem in modern highly prolific sows. Heterogeneity is a problem mainly for piglets with low birth weight that have suffered from IUGR (Foxcroft *et al.*, 2006), which is associated with high pre-weaning mortality, variable weights at weaning, and poor growth performance post-weaning, resulting in lower production efficiency and economic losses. Furthermore, within-litter homogeneity in birth weight may also be related to a decrease in stillbirths (Damgaard *et al.*, 2003; Canario *et al.*, 2006). In this context, the development of strategies that reduce within-litter variation in birth weight or unfavorable traits that are negatively related to piglet survival is essential for sustaining the pig industry. Since the degree of heterogeneity within litters increases as a response to selection for litter size (Johnson *et al.*, 1999), genetic selection on litter size should be accompanied by selection on piglet survival traits (losses from birth to weaning and the minimal birth weight in the litter, which are proposed as potential traits for a selection against piglet mortality) and birth-weight traits (Wolf *et al.*, 2008). On the other hand, identifying the physiological and biochemical mechanisms responsible for variation in litter birth weight and optimizing maternal nutrition to support requirements for growth and development of conceptuses is essential. Research focused on regulation of litter homogeneity is in its infancy, and therefore, more researches are essential to better understand the cellular and molecular mechanisms by which certain nutrients regulate metabolic pathways and embryonic/fetal development. It should also be borne in mind that nutrient interactions (e.g. ratios of amino acids, carbohydrate, and fatty acids) affect within-litter variation in birth weight. Finally, gestating swine requires not only proteinogenic amino acids that cannot be synthesized in animal cells but also proteinogenic and possibly non-proteinogenic amino acids that can be synthesized in the body to support their maximum reproductive performance (Wang W.W. *et al*., 2013; Wu, 2014). These synthesizable, functional amino acids include L-arginine, L-glutamine, L-proline, and glycine (Wang W.W. *et al*., 2014; Wu, 2013) to improve anti-oxidative capacity, immunity, health, well-being, and tissue protein synthesis in gestating mammals (e.g. pigs).

Compliance with ethics guidelines

Tao-lin YUAN, Yu-hua ZHU, Meng SHI, Tian-tian LI, Na LI, Guo-yao WU, Fuller W. BAZER, Jian-jun ZANG, Feng-lai WANG, and Jun-jun WANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：母猪营养状态对仔猪初生重窝内变异的影响

概　要：本综述旨在总结仔猪初生重窝内变异对仔猪健康、生长及生产管理造成的不利影响、形成因素、以及改善窝内变异的措施。在现代化高产母猪养殖中，仔猪初生重窝内变异程度及低初生重猪的比例大幅增加，导致新生期存活率、生长性能大大降低。初生重窝内变异的影响因素包括母猪排卵率、卵子质量、排卵持续时间、胚胎附植能力、子宫容积、胎盘体积和效率等；品种差异对仔猪初生重的均匀度也有很大影响。在妊娠的三个关键阶段（断奶–配种间隔期、妊娠早期和妊娠后期）进行针对性的营养调控有望一定程度上提高窝内初生重均匀度。目前已被报道的包括：在配种前母猪日粮中添加葡萄糖或者维生素A，妊娠后期添加谷氨酰胺均可改善仔猪初生重均匀度，精氨酸以及支链氨基酸也有提高仔猪初生重一致性的潜能。但总体而言，目前相关研究相对较少、潜在的分子机制仍不明确，需要大量深入的研究来加深对妊娠期母体与胎儿发育过程相关生物学事件、营养素作用机制的理解，为制定出更加科学有效的母猪饲喂措施提供理论基础。

关键词：窝内变异；猪；死亡率；发病率；生长性能；母猪营养