Amino Acids (2014) 46:1605–1623
DOI 10.1007/s00726-014-1725-z

INVITED REVIEW

Improving amino acid nutrition to prevent intrauterine growth restriction in mammals

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Received: 1 February 2014 / Accepted: 6 March 2014 / Published online: 23 March 2014

Abstract Intrauterine growth restriction (IUGR) is one of the most common concerns in human obstetrics and domestic animal production. It is usually caused by placental insufficiency, which decreases fetal uptake of nutrients (especially amino acids) from the placenta. Amino acids are not only building blocks for protein but also key regulators of metabolic pathways in fetoplacental development. The enhanced demands of amino acids by the developing conceptus must be met via active transport systems across the placenta as normal pregnancy advances. Growing evidence indicates that IUGR is associated with a reduction in placental amino acid transport capacity and metabolic pathways within the embryonic/fetal development. The positive relationships between amino acid concentrations in circulating maternal blood and placental amino acid transport into fetus encourage designing new therapies to prevent or treat IUGR by enhancing amino acid availability in maternal diets or maternal circulation. Despite the positive effects of available dietary interventions, nutritional therapy for IUGR is still in its infancy. Based on understanding of the underlying mechanisms whereby amino acids promote fetal growth and of their dietary requirements by IUGR, supplementation with functional amino acids (e.g., arginine and glutamine) hold great promise for preventing fetal growth restriction and improving health and growth of IUGR offspring.

Keywords Amino acids · Fetus · Intervention · IUGR · Nutrition · Placenta · Pregnancy

Abbreviations

AGA	Appropriate for gestational age
BCAA	Branched-chain amino acids
eNOS	Endothelial nitric oxide synthase
IUGR	Intrauterine growth restriction
mTOR	Mammalian target of rapamycin
NBW	Normal birth weight
NO	Nitric oxide
NRC	National research council
ODC	Ornithine decarboxylase
SGA	Small for gestational age

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Introduction

Application of genetic selection and assisted reproductive technologies has greatly increased litter size in multiparous species (e.g., pig and rat) and multiple fetal pregnancies in women over the past two decades (Blickstein 2005; Wu et al. 2006). However, uterine capacity limits embryonic survival and growth (Bazer et al. 2009), as well as provision of nutrients from mother to fetus (Wu et al. 2013a). Fetal undernutrition results in impaired fetal growth and

has consequences on negatively impacting the neonatal survival and growth of the offspring with intrauterine growth restriction (IUGR) (Gootwine et al. 2007) in humans (Blickstein and Kalish 2003), sheep (Freetly and Leymaster 2004), as well as other mammals including dogs, pigs, rabbits, and rats (Wootton et al. 1983; Wu et al. 2006). In clinical medicine, fetuses with an estimated fetal weight below 10th percentile for gestational age are often defined as IUGR (American College of Obstetricians and Gynecologists 2001). However, this simple definition has limitations, as many infants with clinical evidence of IUGR have birth weights within the range of 10 and 90 percentile (Cecconi et al. 2011). Infants who are classified as small for gestational age (SGA) are those who are smaller in size than normal for the gestational age, which is commonly defined as a weight below the 10th percentile for the gestational age. Note that not all fetuses that are SGA suffer from IUGR and may be constitutionally small. Thus, IUGR and SGA are related but not synonymous. Intrauterine growth restriction results in babies born as SGA, namely, all IUGR infants are SGA. However, not all SGA infants are pathologically IUGR.

IUGR is one of the most common concerns in human obstetrics and domestic animal production (Wu et al. 2006). Available evidence suggests that risk of fetal death or perinatal mortality and morbidity is markedly increased in IUGR fetuses. A prevalence of $\sim$8 % in the general population, 52 % of stillbirths, 10 % of neonatal mortality and up to 72 % of unexplained fetal deaths can be linked to IUGR (Froen et al. 2004; Mandruzzato et al. 2008). It has also been reported that IUGR has stunting effects on neonatal adjustment, postnatal growth and development, food/feed utilization efficiency, body composition (Wu et al. 2006; Wang et al. 2008a, 2010, 2013a; Liu et al. 2013a), and is associated with the onset of cardiovascular and metabolic diseases in adulthood, such as type 2 diabetes (Park et al. 2008). IUGR is caused by maternal, placental and fetal factors (Faraci et al. 2011), e.g. maternal nutritional status, placental insufficiency, fetal umbilical uptake of nutrients. Results of several studies provide a clear indication that changes in placental transport and metabolism of nutrients (especially amino acids) play a critical role in the pathogenesis of IUGR (Lin et al. 2012; Wu et al. 2008). Proper nutrition can help mothers to reach their genetic potential, which lead to increased litter size without changing average fetal birth weight. However, there are currently few nutritional attempts at preventing or treating IUGR in both humans and animals gestating multiple fetuses. Paradoxically, maternal dietary protein supplementation during pregnancy to improve the growth of IUGR fetuses resulted in an increased risk for SGA delivery and increased perinatal mortality rates (Say et al. 2003). Recently, improved nutrition of amino acids, which have versatile metabolic functions, has become an attractive therapeutic option in ameliorating IUGR, especially when fetuses fail to achieve their growth potential (Brown et al. 2011; Gao et al. 2012; Raimondi et al. 2012; Washburn et al. 2013a, b; Ren et al. 2012; Wu et al. 2013b).

This review will discuss amino acid metabolism during pregnancy and the perinatal period. Then, we will consider fetoplacental amino acid transport and utilization in those pregnancies affected by IUGR. In addition, possible mechanisms responsible for improving fetal or neonatal growth through supplementation with amino acids to maternal diets will be explored. Finally, we will propose new amino acid interventions beneficial for preventing and/or treating IUGR.

Benefits of amino acids in pregnancy and neonatal growth

During pregnancy, umbilical vein, allantoic fluid and amniotic fluid serve as a nutritional reservoir of amino acids and other nutrients. Meanwhile, the developing embryo receives additional amino acids in the form of histotroph, which is a complex mixture of secreted molecules created within uterine lumen (Bazer et al. 2012). Amino acids represent one kind of the major nutrients for fetal and neonatal life, and are essential precursors for development and survival of the conceptus (Avagliano et al. 2012; Rezaei et al. 2013). Because of a suboptimal intrauterine environment, mammals suffer 20–50 % embryonic and fetal loss during gestation, with most of the prenatal losses (more than two-thirds) occurring during the peri-implantation period of pregnancy (Bazer et al. 2012; Wu et al. 2010). In the pregnant ovine model, amounts of arginine, glutamine, glutamate and proline in uterine fluids increased 3- to 23- fold during days 10–16 of gestation (Gao et al. 2009b), due to enhanced expression of transporters for arginine (SLC7A2B) and other amino acids by uterine epithelia (Gao et al. 2009a). Compared with its maternal plasma level, an unusual abundance of the arginine family of amino acids was also discovered in porcine and ovine allantoic fluid during early pregnancy, when the fetal-placental growth is most rapid (Gao et al. 2012; Wu et al. 1996). However, most of the amino acids are not synthesized by blastocysts. A significant fetal growth restriction was observed when mouse blastocysts were maintained in a culture medium lacking arginine, lysine and histidine for 5 days (Gwatkin 1966). The findings indicate that these basic amino acids in the uterine lumen are required for blastocyst expansion and implantation in vivo. Arginine, which is metabolized to nitric oxide and polyamines, activates the mTOR signaling pathway and

protein synthesis in porcine trophectoderm cells (Kong et al. 2012). Arginine and leucine can also stimulate the AKT1-MTOR/FRAP1-RPS6K-RPS6 cell signaling pathways to increase proliferation and migration of ovine trophectoderm cells during the peri-implantation period (Kim et al. 2011a, b).

During the perinatal period, amino acids are also crucial for neonatal growth and development. There is almost no placental growth after day 70 of gestation in pigs (Knight et al. 1977). Thus, porcine uterine uptake of amino acids during late gestation largely reflects amino acid utilization by the fetus other than by the placenta (Wu et al. 2013a). Uterine uptake of amino acids is increased substantially between days 90 and 114 of gestation to support the rapid growth of the fetus (Wu et al. 1999), while glutamine concentrations in amniotic fluid decrease dramatically after achieving a peak value at day 45 of gestation (Lin et al. 2012; Wu et al. 1995). It appears that glutamine is a limiting factor for maximum fetal growth during the late stage of gestation. The amount of glutamine in the basal maternal diet (2 kg/day) is inadequate for fetal growth and development in swine. Thus, supplementing glutamine to the swine diet during late gestation enhances fetal growth and litter birth weight (Wu et al. 2011).

Glutamine and its metabolite, glutamate, also have a beneficial role in stimulating neonatal growth. They are the most abundant amino acids in sow's milk in both free and peptide-bound forms (Haynes et al. 2009; Lei et al. 2012). Of note, the concentration of free glutamine increases to the greatest extent among all free amino acids as lactation progresses (Wu and Knabe 1994). This is consistent with the report that glutamine promotes small intestine growth and muscle protein synthesis in neonates (Wang et al. 2008b; Xi et al. 2011). The underlying mechanisms involve mTOR cell signaling, mitogen-activated protein kinase, and inhibition of autophagy (Wu 2013). Because of a lower rate of endogenous arginine synthesis in IUGR piglets, the effect of arginine supplementation to the diets for lactating sows was greater for low-birth-weight piglets than those NBW littermates, as indicated by a relatively greater increase in postnatal growth rate (Kim and Wu 2009).

Fetoplacental transport and utilization of amino acids

The fetus receives amino acids and other nutrients from the mother via the umbilical vein, in contrast to the embryo which is nourished by uterine secretions (Battaglia and Meschia 1988; Wu et al. 2012a). Fetal growth depends upon not only the provision of nutrients but also the fetal endocrine status (Harding 2001; Wu et al. 2004a). The placenta acts as a predominant interface between mother and fetus in that this organ supplies nutrients and oxygen from mother to fetus, while carrying metabolic wastes (e.g., carbon dioxide and ammonia) from fetus to mother (Avagliano et al. 2012; Regnault et al. 2005). Most amino acids are delivered from the maternal circulation into the fetal circulation via active transport systems across the placenta. Higher concentrations of free amino acids are present in the human placenta than in maternal or fetal plasma (Philipps et al. 1978). The concentrations of most amino acids in porcine umbilical venous plasma are higher than those in maternal plasma, especially functional amino acids (e.g., glutamine, glycine and arginine) (Lin et al. 2012). Also, most amino acids exhibit a positive relationship between fetal and maternal concentrations in normal pregnancies (Cetin et al. 1996), suggesting that an increase in concentrations of amino acids in maternal plasma can lead to an elevation of their availabilities in the fetus. Even though concentrations of amino acids in maternal plasma are not changed, an increase in uteroplacental blood flows can augment their transport to the fetal plasma (Satterfield et al. 2010).

Two classes of amino acid transport systems have been identified in both the apical (maternal) and basal (fetal) facing membranes of trophoblast in the placenta: Na^+-dependent amino acid transporters and Na^+-independent amino acid transporters (Avagliano et al. 2012; Regnault et al. 2005). Amino acid transport systems are either highly specific or have a broad specificity for a group of amino acids. For example, one transporter can transfer a certain kind of amino acids (e.g., system A can transfer neutral amino acids, like alanine, serine, proline and glutamine) (Novak et al. 1996). In contrast, other transport systems have overlapping substrate specificity. This means that the same amino acid can be transported by multiple transporters (e.g. leucine can be transferred by both transport system L and $b^{0,+}$) (Cariappa et al. 2003). Thus, the total transport rate of a certain amino acid depends on its concentration in the maternal plasma (Regnault et al. 2002), placental amino acid transport capacity (related to the total placental surface area) (Teasdale and Jean-Jacques 1985), as well as the abundance, affinity and activity of transport systems (Christensen 1990). In addition, the possible interaction and compensation between different transport systems should be assessed. Furthermore, a combination of several factors can regulate the uptake and utilization of amino acids across the maternal–fetal interface, including concentrations in maternal uterine plasma, placental histotoxicity, and placental vascularity (Avagliano et al. 2012; Lewis et al. 2013).

During prenatal development, the umbilical cord is the connection between the developing fetus/embryo and the placenta. The left lobe of the fetal liver receives amino acids from the nutrient-rich umbilical vein, while the right lobe of the fetal liver takes up amino acids from both the

umbilical vein and the portal vein (Haugen et al. 2004). Also, amino acids shuttle between the fetal liver and placenta, suggesting that fetal tissue can release amino acids into fetal circulation. Thus, the net fetal uptake of amino acids from the placenta is less than the total appearance of amino acids in the fetal circulation (Brown et al. 2011). The presence of interconversion of some amino acids [e.g., serine to glycine (Cetin et al. 1991) and glutamate to glutamine (Vaughn et al. 1995)] increases the uptake of serine and glutamate by the placenta from the fetus. There are reports that maternal serine does not directly cross the placenta into the fetus in an ovine model, and instead serine is utilized within uteroplacental tissues for the synthesis of glycine, which is delivered partially into fetal circulation (Moores et al. 1993). Whether or not this view is correct needs to be confirmed. Glycine is one of the most abundant amino acids in the porcine umbilical vein (Lin et al. 2012), ovine uterine artery (Kwon et al. 2003), as well as bovine uterine fluids from cyclic cows (Hugentobler et al. 2007) and gestating sows (Zhou et al. 2014). Except for serine and glutamate in the ovine placentome, it appears that all other amino acids are transported from the placenta into the fetus in normal pregnancies (Brown et al. 2011; Rozance et al. 2009).

The enhanced demands for amino acids by the developing conceptus must be met via an increase in amino acid transport capacity as normal pregnancy advances (Wu et al. 2013a). Uterine uptake and placental delivery of amino acids may reflect amino acid utilization by both fetus and placenta. For most amino acids in the fetal circulation, disposal can occur via two routes (Brown et al. 2011): (1) absorption by fetal tissues for metabolism (oxidation or conversion to non-protein nitrogenous substances) and protein accretion (the balance between protein synthesis and degradation); (2) flux into the placenta via the umbilical arteries for both oxidation and nitrogenous compounds production. These amino acids are delivered and exchanged between the maternal and fetal circulation to meet the demand of the expansion of maternal tissues, the development of the placenta, and the rapid growth of the fetus.

Amino acid metabolism in IUGR

Using temporal proteomic approaches, our previous studies have shown continuous impairment of intestinal, liver and muscle development in piglets with IUGR during gestation and neonatal periods (Liu et al. 2013a; Wang et al. 2008a, 2010, 2013a). Dynamic alterations in the tissue proteomes related to amino acid metabolism may be one of the major mechanisms responsible for abnormal utilization of these nutrients and impaired fetal development in IUGR fetuses. When compared with normal pregnancies, metabolism of amino acids in both maternal and fetal circulation is markedly different in pregnancies with IUGR. Specifically, maternal plasma concentrations of most amino acids in IUGR pregnancies are much higher than those in the women carrying fetuses that are classified as appropriate for gestational age (AGA) pregnancies (Economides et al. 1989). In contrast, lower fetal concentrations of most amino acids are observed in the umbilical cord of IUGR fetuses, compared with NBW fetuses (Cetin et al. 1996; Lin et al. 2012), suggesting the impaired transport of amino acids from maternal to fetal circulation in IUGR pregnancies. As a result, intramuscular concentrations of many free amino acids (including arginine and glutamine) are lower in IUGR fetuses than in NBW fetuses (Sales et al. 2013; Wu et al. 2008). Furthermore, maternal protein restriction or hypercholesterolemia (Bhasin et al. 2009), as well as the fetal alcohol syndrome caused by heavy drinking during pregnancy (Ramadoss et al. 2008), may also reduce the concentrations of amino acids in fetal plasma, thereby leading to IUGR and postnatal growth retardation of IUGR offspring.

Amino acids represent up to 88 % of total nitrogen, and constitute the nitrogen requirements for both the placenta and the fetus (Wu et al. 1999). Rates of fetal amino acid accretion into protein increase rapidly as pregnancy advances. For several amino acids (arginine, alanine, aspartate/asparagine, glutamate/glutamine, leucine, lysine and proline), nitrogen concentration increases progressively from day 60 to 114 of gestation in fetal pigs (Wu et al. 1999). On the basis of utilization of amino acids for protein synthesis, the maternal supply of amino acids differs both quantitatively and qualitatively with advancing gestation. Arginine, containing four nitrogen atoms per molecule, is the most abundant nitrogen carrier in fetus, while glutamine is the most abundant nitrogen supplier in porcine umbilical vein during late gestation (Table 1) (Lin et al. 2012). Thus, the rate of fetal glutamine accretion is the greatest throughout the gestation in pigs (Wu et al. 1999). Notably, reduced amounts of amino acids (especially for arginine and glutamine) were delivered to the IUGR fetuses during late gestation when compared to the normal body weight (NBW) fetuses (Table 1), resulting in inadequate amounts of amino acids for either protein accretion or synthesis of non-protein nitrogenous compounds.

Reductions in the flow of blood from the placenta into the fetus and in rates of placental amino acid transport are major factors contributing to the development of IUGR in mammals (Wu et al. 2006). This notion is consistent with the suggestion that placental insufficiency is one of the most common causes of IUGR (Valsamakis et al. 2006). Indeed, reduced expression and/or reduced activities of several amino acid transport systems have been reported

Table 1 Amino acid (AA) nitrogen in the umbilical vein plasma of NBW and IUGR fetuses and in maternal plasma of gestating gilts

AA	Gestational age (days)	AA Nitrogen in plasma (mg/L)		
		Maternal	Fetal-NBW	Fetal-IUGR
Nutritionally nonessential AA				
Ala	90	7.45 ± 0.01	10.30 ± 1.27*	10.28 ± 1.01
	110	7.21 ± 0.52	10.45 ± 0.67*	11.00 ± 0.84
Asn	90	1.40 ± 0.03	1.85 ± 0.14	1.62 ± 0.31
	110	1.32 ± 0.22	2.02 ± 0.17*	2.05 ± 0.45
Asp	90	0.21 ± 0.01	0.99 ± 0.01*	1.02 ± 0.01
	110	0.22 ± 0.01	0.59 ± 0.03*, §	0.57 ± 0.03
Glu	90	3.54 ± 0.11	7.06 ± 0.50*	7.47 ± 0.71
	110	3.67 ± 0.04	2.51 ± 0.25*	2.40 ± 0.17
Gly	90	14.43 ± 1.26	11.91 ± 1.30*	10.45 ± 0.67
	110	16.67 ± 0.70	10.90 ± 0.76*	11.42 ± 1.27
Ser	90	2.07 ± 0.04	6.70 ± 0.69*	5.94 ± 0.25
	110	2.23 ± 0.11	4.86 ± 0.49*, §	6.30 ± 0.91
Conditionally essential AA				
Arg	90	11.65 ± 0.11	9.47 ± 0.78*	6.67 ± 0.34#
	110	12.05 ± 0.67	6.56 ± 0.95*, §	5.27 ± 0.56#
Cystine	90	0.64 ± 0.06	1.15 ± 0.22*	1.01 ± 0.11
	110	0.50 ± 0.06	0.78 ± 0.11*	1.06 ± 0.31
Gln	90	8.43 ± 0.17	25.91 ± 2.24*	21.32 ± 1.68#
	110	7.82 ± 0.11	27.96 ± 1.15*	24.20 ± 1.29#
Pro	90	4.37 ± 0.03	4.64 ± 0.42	3.78 ± 0.22#
	110	4.24 ± 0.13	4.36 ± 0.25	4.47 ± 0.38
Tyr	90	1.65 ± 0.18	1.23 ± 0.08*	1.23 ± 0.18
	110	1.81 ± 0.15	1.64 ± 0.14§	1.76 ± 0.22
Nutritionally essential AA				
His	90	2.86 ± 0.08	3.03 ± 0.34	2.10 ± 0.21#
	110	3.11 ± 0.13	3.78 ± 0.50§	4.16 ± 1.22
Ile	90	1.32 ± 0.11	1.92 ± 0.01*	1.30 ± 0.14#
	110	1.47 ± 0.08	1.41 ± 0.08§	1.44 ± 0.24
Leu	90	2.56 ± 0.22	2.89 ± 0.38	1.44 ± 0.24#
	110	2.84 ± 0.08	3.32 ± 0.29	2.94 ± 0.70
Lys	90	5.15 ± 0.08	8.66 ± 1.82*	8.49 ± 0.98
	110	5.71 ± 0.42	6.81 ± 1.20§	7.09 ± 1.26
Met	90	0.45 ± 0.01	0.87 ± 0.08*	0.77 ± 0.04
	110	0.52 ± 0.06	0.69 ± 0.10	0.70 ± 0.22
Phe	90	1.36 ± 0.01	0.99 ± 0.17*	0.92 ± 0.04
	110	1.40 ± 0.01	1.55 ± 0.14§	1.61 ± 0.24
Thr	90	1.69 ± 0.01	5.06 ± 0.66*	5.35 ± 0.48
	110	2.00 ± 0.18	2.72 ± 0.03*, §	3.15 ± 0.36
Trp	90	1.76 ± 0.06	0.84 ± 0.11*	0.76 ± 0.11
	110	1.88 ± 0.22	1.04 ± 0.11*	1.09 ± 0.14
Val	90	3.15 ± 0.24	4.43 ± 0.90	4.16 ± 0.43
	110	3.35 ± 0.15	4.59 ± 0.56*	4.27 ± 0.63
Total protein AA				
	90	76.17 ± 1.36	109.87 ± 5.14	96.90 ± 4.17#
	110	80.02 ± 2.08	98.53 ± 8.03	96.96 ± 5.42

Calculated from Lin et al. (2012). Values are mean ± SEM. $n = 8$ gilts for each gestational age, or 8 fetuses from 8 gilts (1 NBW fetus and 1 IUGR fetus from each gilt)

* Different from the corresponding maternal value ($P < 0.05$)

Different from the Fetal-NBW group ($P < 0.05$)

§ Different from the value for day 90 of gestation ($P < 0.05$)

for the IUGR (Casanello and Sobrevia 2002; Jansson et al. 1998; Kavitha et al. 2014; Norberg et al. 1998; Wu et al. 2008) or the SGA (Shibata et al. 2008) placenta when compared to AGA pregnancies. These observations, together with morphological changes (decreased placental surface area and fewer blood vessels) in the placenta (Coan et al. 2010; Pomorski et al. 2012), help to explain a lower capacity of placental amino acid transport in IUGR than in NBW fetuses. Maternal infusions of a solution enriched in essential amino acids lead to increased umbilical uptake of some amino acids [e.g., branched-chain amino acids (BCAA)] to the IUGR fetus (Jozwik et al. 2004). However, concentrations of other amino acids (e.g., threonine, histidine, and lysine) in the fetal circulation remain low (Paolini et al. 2003; Ronzoni et al. 2002), indicating the presence of competition for the same transporter across the placenta among the co-infused amino acids. Recently, strong evidence has shown that a failure of placental amino acid transport occurs prior to the development of IUGR and is considered as a factor directly contributing to the restriction of fetal growth. The time course of alterations in placental and fetal growth, as well as placental amino acid transport, has been investigated in a pregnant rat IUGR model induced by maternal protein malnutrition. No significant change in placental or fetal growth, but reduction in placental amino acid transport, was observed in response to a low protein diet at 19 days of gestation. However, both fetal/placental weight and amino acid transport activity decreased at 21 days of gestation (Jansson et al. 2006). These data suggest that down-regulation of key placental amino acid transport systems play an important role in the pathogenesis of IUGR. Although a temporal relationship exists between the development of IUGR and reduced amino acid availability in the fetus, it is possible that fetal growth restriction occurs before the presence of decreased amino acid transport (Nathanielsz 2006). Integration of research on uterine biology at molecular, cellular, and tissue levels will provide a more comprehensive perspective to explore the underlying mechanism for IUGR.

Development of an amino acid–based strategy for prevention and treatment of IUGR

Optimal maternal nutrition during pregnancy plays a critical role in the regulation of placenta and fetal growth and development. Maternal suboptimal nutrition or undernutrition may reduce nutrient supply to the fetus, resulting in IUGR or low birth weight, thereby influencing lifelong health of the newborn (Belkacemi et al. 2010). More attentions have been paid to placental function and development. The placenta serves as a nutrient sensor, regulating expression of nutrient transporters in response to changes in the ability of the placenta to obtain nutrients from the maternal blood (Jansson and Powell 2007). Enhancement of placental growth and development via nutritional intervention is considered as an effective solution to improving pregnancy outcomes (Wu et al. 2010).

During pregnancy there is an increased demand for nutrients to enable the placenta and fetus to grow in a well-coordinated manner. Adequate placental vascular growth and placental function can enable maternal provision of adequate oxygen and amino acids to the fetus. In contrast, impaired placental vascularization may result in insufficient transfer of amino acids from the placenta to fetuses, leading to IUGR, as well as increased rates of perinatal morbidity and mortality (Wu et al. 2004a). Some amino acids (e.g. arginine, cysteine, glutamine, proline, etc.) are classified as conditionally essential amino acids because the rates of their synthesis are lower than the rates of their utilization under some circumstances (Reeds 2000). Although the body has the capacity to produce these conditionally essential amino acids, their provision from maternal diets may be inadequate to meet maximum fetal growth and development. Therefore, it is necessary to supplement deficient amino acids in the diets of pregnant mothers. A recommendation of dietary amino acid requirements is also needed to provide technical information necessary for implementing nutritional needs at different developmental stages. Such data are now available to guide development of optimal amino acid ratios in a gestation diet for swine (Li et al. 2011; Wu 2014). In order to overcome farrowing difficulties and appetite reduction during lactation, feed intake is restricted to prevent excessive bodyweight gain throughout gestation under current practice in the swine industry. This feeding regimen results in insufficient provision of amino acids for both mother and fetus. Furthermore, due to a lack of knowledge on amino acid nutrition, the National Research Council (NRC 1998) recommended little or no dietary intake of some amino acids (e.g., arginine, glutamine and glutamate) by gestating and lactating sows (Table 2). Recently, a considerable number of studies have indicated that supplementation of the maternal diet with specific amino acids (e.g., arginine and glutamine) improves fetal survival and pregnancy outcome (Wu et al. 2013b). Considering these functions of amino acids, together with restricted feeding programs, feed wastage and gestation days, NRC (2012) suggests higher requirements of all nutritionally essential and conditionally essential amino acids to meet gestational needs and the demands of lactation (Table 2). In humans, no data on amino acid requirements by pregnant and lactating women are available at the present time. Some therapeutic options, such as supplementation with high amounts of protein to pregnant women, actually resulted

Table 2 National Research Council (NRC)-recommended requirements of essential amino acids by gestating and lactating sows

	Gestating sows			Lactating sows	
	NRC (1998)	NRC (2012)		NRC (1998)	NRC (2012)
Body weight at breeding or post-farrowing (kg)	175		165	175	175
Anticipated sow weight change (kg)[a]	40		60	−10	−7.7
Anticipated litter size[b]	12		13.5	10	11
Days of gestation	0–114	<90	>90	–	–
Lactation length (days)	–	–	–	21	21
Estimated feed intake (kg/day)	1.88	2.21[c]	2.61[c]	4.61	5.95[c]
Daily weight gain (g)[d]	–	539	481	200	230
Dry matter (%)	90	90	90	90	90
Total basis (g/day)[e]					
Arginine	0.0	5.7	9.1	22.4	28.2
Histidine	3.3	3.9	5.7	17.5	21.1
Isoleucine	5.9	6.4	9.4	25.0	29.6
Leucine	8.6	9.9	16.5	48.6	59.5
Lysine	10.3	11.0	17.5	44.9	52.6
Methionine	2.6	3.1	5.1	11.3	14.2
Sulfur amino acids (methionine + cysteine)	6.9	7.5	12.0	21.7	29.0
Phenylalanine	5.6	6.1	9.8	23.9	29.0
Phenylalanine + tyrosine	9.6	11.0	17.4	49.8	60.5
Threonine	8.3	8.6	13.2	28.8	35.3
Tryptophan	2.0	2.0	3.4	8.2	9.9
Valine	6.8	8.1	12.9	38.4	45.7

Data are recommended by National Research Council (NRC 1998, 2012). The dietary amino acid requirements are estimated from the gestation or lactation models

[a] Weight gain for the gestating sow includes maternal tissue and products of conception

[b] Anticipated mean birth weight of piglets is 1.40 kg

[c] Assumes 5 % feed wastage

[d] Body weight gain for gestating sows or for nursing pigs by lactating sows

[e] Total amino acid requirements are expressed on an as-fed basis for a corn- and soybean meal-based diet

in a decrease in fetal growth and an increase in risk for preterm and SGA delivery (Brown et al. 2011; Say et al. 2003). High maternal intake of dietary protein seems to be toxic to the fetus, while dietary supplementation with some amino acids (e.g., arginine and glutamine) results in beneficial perinatal outcomes (Wu et al. 2010). These findings suggest that supplementation with functional amino acids, but not total protein per se, could be an attractive potential strategy to prevent or treat IUGR.

Circulating maternal concentration of amino acid is one of the major factors contributing to the placental amino acid profile and ultimately determining the provision of amino acids from the mother to the fetus (Li et al. 2010; Mateo et al. 2007; Wu et al. 1998). Thus, maternal nutritional approaches (e.g. parenteral administration or dietary supplementation) are effective in increasing the availability of amino acids in the fetus and, therefore, prevent IUGR. Among all mammalian species, pigs suffer from the most severe naturally occurring IUGR (Wu et al. 2006) and high rates of embryonic death during peri-implantation period and early gestation. Amino acids and other nutrients play a vital role in embryonic and fetal survival at this developmental stage. Later on, fetal losses may result from inadequate uterine capacity and placental insufficiency after implantation (Webel and Dziuk 1974), which is extremely critical for a pregnant mother with multiple fetuses. The fetus grows most rapidly during late gestation (the third trimester equivalent of human pregnancy). Evidence shows little or no placental growth during the last trimester (e.g., after day 70 of gestation in pigs) (Knight et al. 1977). This means all amino acids from maternal circulation will be largely utilized for fetal growth and development during late gestation, and it will be another important period for regulating fetal growth and preventing IUGR via an amino acid-based strategy. In response to acute amino acid infusion directly into the fetal circulation during late gestation, IUGR sheep exhibited a decrease in protein breakdown and an increase in net protein accretion, thus enhancing fetal growth rates (Brown et al. 2012). Even during the neonatal period, amino acids also offer great promise for treating IUGR offspring and improving their health and well-being in humans and other mammals. In support of these views, emerging findings indicate beneficial roles for supplementation with an individual amino acid or their combination in promoting embryonic/fetal growth and preventing or treating IUGR in several mammalian species (Table 3).

Table 3 Examples of amino acid strategies for preventing or treating IUGR

References	Amino acid	Species	Supplementation			Pregnant outcome or growth performance
			Method	Period	Amount	
Brown et al. (2012)	MAA[a]	Sheep	I.V. injection	at d 132 of gestation (3-h infusions)	Not reported	Suppressed fetal protein breakdown rates; increased leucine oxidation rate by only 25 %; increased protein accretion rates by 150 % in IUGR
Hultman et al. (2007)	Taurine	Rat	Water	d 18–23 of gestation	2 % in drinking water	IUGR animals (50 %) from mother received additional taurine displayed catch-up at 12 wk of age, and they increased fat depots and reduced insulin sensitivity
Lassala et al. (2009)	Arg-HCl and Cit	Sheep	I.V. injection	d 135 of gestation	155 μM Arg or Cit/kg BW	Half-life of citrulline in plasma was twice that of arginine in ewes
Lassala et al. (2010)	Arg-HCl	Sheep	Jugular injection	d 60 of gestation to term	155 μM Arg/kg BW 3 times daily	Enhanced birth weights of lambs by 21 % compared with saline-infused underfed ewes, but no difference compared with control-fed ewes
Lassala et al. (2011)	Arg-HCl	Sheep	I.V. injection	d 100–121 of gestation	345 μM Arg-HCl/kg BW 3 times daily	Reduced lambs born dead by 23 %; increased lambs born alive by 59 %; enhance the birth weights of quadruplets by 23 % without affecting maternal BW
Liu et al. (2011)	Taurine	Rat	Diet	d 12 of gestation to term	300 mg/kg BW/day	Improved brain cortex structures induced by IUGR; decreased brain cell apoptosis
Mateo et al. (2007)	Arg-HCl	Pig	Diet	d 30–114 of gestation	1.0 % in maternal diet or 16.6 g Arg per sow/day	Increased the number of pigs born alive by 22 % and live litter birth weight by 24 %; increased of live-born piglets by 2 per litter
Raimondi et al. (2012)	AAF[a]	Human	Milk replacer	d 2 of age till weaning	Start at 1 mL every 2 h, with daily increments of 16 mL/kg	No difference in body weight between AAF and SPF group at days 21 and 28, as well as 12-month of age. AAF rescued VLBW IUGR neonates with severe feeding intolerance
Sieroszewski et al. (2004)	Arg	Human	Oral ADM.	around wk 32 of gestation (treat for 20 days)	3 g/day	Estimated fetal weight increased by 60 % compared to control group. The percentage of IUGR newborns was 44 % lower in arginine group than in control group
Vosatka et al. (1998)	Arg	Rat	Water	d 9–21 of gestation	0.2 and 2 % in water	Exposure to hypoxia resulted in a 30 % reduction in fetal weights; Arg prevented reduction in fetal weight
Wang et al. (2012b)	Arg	Pig	Milk replacer	d 7–14 of age	0.6 % in milk replacer, or 0.418 g Arg/kg BW per d	Increased ADG, DMI SI weight and by 47.3, 21.4 %, and 73.2 %, decreased the diarrhea rate by 61.5 % compared with IUGR piglets fed the control diet
Wu et al. (2010)	Arg-HCl and Gln	Pig	Diet	d 30–114 of gestation	0.4 % Arg + 0.6 % Gln, or 8 g Arg and 12 g Gln to a 2-kg basal diet per day	Increased litter size by 1.4 per litter and live-born litter birth weight by 15 %; reduced variation in birth weights of live-born piglets by 24 %
Wu et al. (2011)	Gln	Pig	Diet	d 90–114 of gestation	1 % Gln, or 20 g Gln to a 2-kg basal diet per day	Increased average birth weight and litter birth weight of live-born piglets; reduced the number of IUGR piglets, variation in birth weight, and preweaning mortality of live-born piglets by 39, 33, and 46 %, respectively
Xiao and Li (2005)	Arg	Human	I.V. injection	wk 33, receive arg for 7 days	20 g/day	Mean birth weight was higher in arg group than in control group, but lower than in the normal pregnancy
Zeng et al. (2008)	Arg-HCl	Rat	Diet	d 1–7 of gestation, or full pregnancy	1.3 % in maternal diet	Enhanced embryonic survival; increased litter size by 30 % at term birth

Table 3 continued

References	Amino acid	Species	Supplementation			Pregnant outcome or growth performance
			Method	Period	Amount	
Zeng et al. (2012)	NCG	Rat	Diet	throughout pregnancy	0.1 % in maternal diet	Increased litter size, live-born pup number, litter birth weight, and litter birth weight of live-born rats by 13, 12, 14 and 14 %, respectively

AAF amino acid formula, *ADM.* administration, *ADG* average daily gain, *BW* body weight, *d* day, *DMI* dry matter intake, *MAA* mixed amino acid, *NCG N*-carbamoylglutamate, *IUGR* intrauterine growth restriction, *I.V.* injection: intravenous injection, *SI* small intestine, *SPF* standard preterm formula, *VLBW* very low birth weight, *wk* week

[a] The composition of formula is not provided

The arginine family of amino acids

The arginine family of amino acids, including arginine, asparagine, aspartate, citrulline, glutamate, glutamine, ornithine, and proline, is usually interconvertible through inter-organ metabolism in most mammals, including humans, mice, rats and swine (Wu et al. 2007). Fetal fluids, such as amniotic fluid and allantoic fluid, serve as amino acids-rich reservoirs for fetal growth and development. By analyzing porcine conceptuses at different gestational ages, an unusual abundance of the arginine family of amino acids was discovered in amniotic fluid and allantoic fluid during early gestation, when placental growth is most rapid (Wu et al. 1996). Glutamine is the most abundant amino acid in amniotic fluid, and accounts for more than 40 % of the total α-amino acid nitrogen on day 45 of gestation (Wu et al. 1996). The concentrations of arginine and ornithine are approximately 50 times higher in porcine allantoic fluid on day of 40 of gestation (Wu et al. 1996), compared to the maternal plasma at the same period (Wu et al. 1995). Similar results have been reported for ovine fetal allantoic fluid (Kwon et al. 2003).

Recently, epidemiological and metabolomic studies provide novel insights into alterations in amino acid profile in IUGR fetuses and infants (Table 4). Remarkable changes in the arginine family of amino acids (e.g., arginine, asparagine, ornithine, citrulline and glutamine) were reported in the amniotic fluid of IUGR fetuses and in the plasma of IUGR neonates in women (Ivorra et al. 2012; Tea et al. 2012) and other animals, including pigs (He et al. 2011; Lin et al. 2012; Wu et al. 2008), rabbits (van Vliet et al. 2013), and rats (Alexandre-Gouabau et al. 2011). All these results indicate a crucial role for the arginine family of amino acids in conceptus growth and development. Furthermore, these functional amino acids could serve as potential biomarkers for designing effective strategies to diagnose, prevent, and treat IUGR in mammalian species.

Arginine

Arginine is the most abundant amino acid nitrogen carrier in tissue protein, and is involved in versatile biochemical pathways, including (1) synthesis of nitric oxide (NO) and polyamines, (2) activation of mTOR pathway, and (3) stimulation of brown adipose tissue development (Wu et al. 2013b). Specifically, NO and polyamines are synthesized from arginine via NO synthase (NOS) and ornithine decarboxylase (ODC), respectively (Wu et al. 2012b). Both NO and polyamines are key regulators of placental angiogenesis, nutrient metabolism, and embryogenesis that regulate fetoplacental blood flow, as well as embryonic and fetal growth (Dai et al. 2013; Wu et al. 2004a). Inhibition of endothelial NO synthase (eNOS) in the mother or the

Table 4 Epidemiological and animal studies reveal alterations in amino acid profile between IUGR and control NBW fetuses

References	Species	Developmental stage	Compartments observed	Alterations in amino acid profile		IUGR criterion	Note
				Higher in IUGR	Lower in IUGR		
Alexandre-Gouabau et al. (2011)	Rat	From birth to weaning	Plasma	His[a], carnitine	Arg, His[a], Ile, Leu, Met, Phe, Pro, Trp, Tyr, Val	NP	IUGR induced by maternal protein restriction
Cosmi et al. (2013)	Women	At birth	Umbilical vein	Phe	Ile, Pro, Trp, Val	Body weight below the 10th percentile for GA	IUGR from twin pregnancy with/without abnormal Umbilical artery Doppler
Favretto et al. (2012)	Women	At birth	Umbilical vein	Glu, His, Ile, Met, Phe, Pro, Thr, Trp, Val	–	Single pregnancy and neonatal weight of <10th percentile	Only healthy women undergoing cesarean section were selected
He et al. (2011)	Pig	d 21 of suckling period	Serum and Jejunum	Thr	Ala, creatine, Gln, Glu, Phe, Taurine, Tyr, Val	Body weight below the 10th percentile for GA	Naturally occurred IUGR
Ivorra et al. (2012)	Women	At delivery	Umbilical cord	Cit, Phe	Ala, Gln, Pro	Body weight below the 10th percentile for GA (<2.5 kg)	Low birth weight newborns form healthy mothers
Lin et al. (2012)	Pig	d 90 and 110 of gestation (term at d 114)	Umbilical vein	Carnitine, creatine, pyroglutamic acid	Arg, Cit, Gln, His, Hy-Pro, Ile, Leu, Pro, Tyr, Trp, Val	Body weight <10th percentile (<2 SD) of the mean for population	Naturally occurred IUGR
Parimi et al. (2004)	Rat	At birth	Plasma	Gly, Ser, Lys	His	NP	IUGR induced by maternal protein restriction
Story et al. (2011)	Women	wk 32[b]	Brain	–	NAA:Creatine and NAA:Choline	Estimated fetal weight below the 10th percentile for GA	Abnormal Umbilical artery Doppler was categorized in terms of disease severity
Tea et al. (2012)	Women	At birth	Umbilical cord	Gln, Glu	Ala, Ile, Methylhistidine, Thr, Tyr, Val	GA <32 weeks and/or a birth weight <1.5 kg	Perinatal asphyxia or major fetal pathology were excluded
van Vliet et al. (2013)	Rabbit	d 30 of gestation (term at day 31)	Brain	–	Asn, His, Lys, NAA, NAAG, Orn	NP	IUGR induced by uteroplacental vessels ligation

d day, *GA* gestational age, *NAA* *N*-acetylaspartate, *NAAG* *N*-acetylaspartylglutamic acid, *NP* not provided, *wk* week

[a] Plasma histidine decreased at birth, but elevated at days 5 and 22 after birth in IUGR pups

[b] IUGR fetuses delivered at week 21–37 of gestation, while control fetuses at week 35–43 of gestation

conceptus causes IUGR in eNOS knockout mice (Hefler et al. 2001; Kulandavelu et al. 2012), because eNOS is essential for augmenting fetoplacental vascularity, and umbilical blood flow during late gestation (Kulandavelu et al. 2013). Arginine was reported to reverse the fetal growth restriction caused by NOS deficiency, when this amino acid was supplemented at the dose of 21 mg/kg per day to pregnant rats (Helmbrecht et al. 1996). Due to the lack of arginase activity, arginine is not metabolized to form polyamines in the porcine placenta, where proline is utilized as the source of ornithine for ODC via proline oxidase and ornithine aminotransferase (Wu et al. 2005). Reducing polyamine synthesis by inhibition of placental ODC activity also decreased placental weight and placental/fetal growth (Ishida et al. 2002).

On the basis of its multiple functions, arginine is now considered a conditionally nutritional essential amino acid for pigs (NRC 2012). Compelling evidence shows that arginine is a nutritionally essential amino acid for the maximal growth of neonates (Wu et al. 2004b). Interestingly, maternal supply of arginine to the porcine IUGR fetus is continuously lower than that for their NBW littermates throughout late gestation (Lin et al. 2012). Thus, arginine has been proposed to improve fetal weight gain and promote fetal growth and development (Wu et al. 2013b). In pigs, feeding a corn- and soybean meal-based diet supplemented with 1.0 % arginine–HCl during middle to late gestation (between day 30 to term of gestation) enhanced litter birth weight by 24 %, as well as litter size and live-born piglets by two (Mateo et al. 2007). Similar results were reported for arginine supplementation during early pregnancy in gilts (Li et al. 2014) and sows (Bérard and Bee 2010), when placental growth is most rapid. Dietary supplementation with 1 % arginine to sows between days 14 and 28 gestation increased the number of fetuses and fetal skeletal muscle development on day 75 of gestation (Bérard and Bee 2010) and the percentage of piglets born alive at parturition (Ramaekers et al. 2006). In addition, dietary supplementation with 0.1 % *N*-carbamoylglutamate, an analog of N-acetyl-glutamate [an allosteric activator of arginine synthesis (Wu et al. 2004b)], or with 1.3 % L-arginine–HCl to pregnant rats improved embryo implantation and survival, enhanced litter size, the number of surviving embryos, and litter birth weight of all live-born rats through the PI3K/PKB/mTOR/NO signaling pathway (Zeng et al. 2008, 2012).

Either parenteral administration of 345 mmol arginine–HCl/kg body weight 3 times daily to multiparous Booroola Rambouillet ewes between days 100 and 121 of gestation (Lassala et al. 2011) or intravenous administration of 155 μmol arginine–HCl/kg body weight 3 times daily to undernourished Suffolk ewes between day 60 of pregnancy and parturition (Lassala et al. 2010) has been reported to reduce the percentage of lambs born dead and to enhance fetal survival and the number of live-born lambs. The beneficial effect of arginine administration on ameliorating fetal growth restriction is associated with increases in uterine and maternal circulating levels of the arginine family of amino acids (arginine, glutamate, glutamine, proline and ornithine) and a decrease in maternal plasma concentration of ammonia (Lassala et al. 2011; Zeng et al. 2008). Similarly, beneficial effects of arginine supplementation on pregnancy outcomes have been reported for underfed or overfed ewes (Satterfield et al. 2012, 2013) or in ewes carrying multiple fetuses (Lassala et al. 2011; McCoard et al. 2013).

Guided by the findings from animal studies, arginine has been used to treat IUGR in human medicine (Shen and Hua 2011). The efficacy of L-arginine therapy for IUGR can be based on biometric measurements (e.g., fetal weight) using an ultrasound evaluation. The fetal weight and birth weight of the newborns from pregnant women with IUGR fetuses who received 3 g/day arginine orally for 20 days showed a greater increase in fetal growth, as compared with the untreated group (Sieroszewski et al. 2004). Likewise, pregnant women whose fetuses were diagnosed with IUGR were treated with intravenous arginine administration in combination with other supplemental amino acids or conventional treatment during gestation. An acceleration of fetal development, improved birth weight of IUGR fetuses, and reduced incidence of SGA newborns were also reported in the arginine group, compared with the conventionally treated group (Shen and Hua 2011; Xiao and Li 2005). The underlying mechanisms for the beneficial effects of arginine to ameliorate fetal mortality and IUGR include: (1) improved placental function by reduced expression of placental apoptosis gene (Shen and Hua 2011; Lei et al. 2011); (2) stimulation of maternal growth hormone secretion (de Boo et al. 2008; Lassala et al. 2010); and (3) modulation of the placental NO and polyamine synthetic pathways (Lassala et al. 2011), thereby affecting uteroplacental blood flow and increasing the delivery of oxygen and nutrients to the fetus. Furthermore, arginine has been demonstrated to stimulate placental protein synthesis (Kong et al. 2012) and improve small intestine development (Wang et al. 2012b) via the mTOR signaling pathway. However, some recent studies failed to replicate the positive effects of arginine. For example, compared with the placebo group, oral administration of 14 g/day of arginine during pregnancy had no effect on fetal growth in pregnant women with severe vascular IUGR (fetal abdominal circumference less than or equal to the 3rd percentile) (Winer et al. 2009). The rationale for the use of this arginine dose is not clear. Similarly, dietary supplementation with 0.8 % arginine between days 0 and 25 of gestation decreased uterine weight, litter size, total fetal

weight and concentrations of some hormones, compared with the control group (Li et al. 2010). These results emphasize the importance of choosing an appropriate dose of supplemental arginine and an appropriate period for arginine supplementation to achieve desirable effects of arginine in animal reproduction and clinical medicine.

Citrulline

Citrulline is synthesized from glutamine, glutamate and proline in the small intestine of most mammals, including humans, mice, rats, and pigs (Wu and Morris 1998). Quantitatively, a very small amount of citrulline is generated from arginine by constitutive NOS in animals. In sheep, fetal urea production was impaired in IUGR induced by placental embolization during late gestation (de Boo et al. 2007). The conversion of citrulline into arginine is a potentially effective pathway to restore whole-body NO production when arginine availability is insufficient (Bryk et al. 2008; Wu and Meininger 2000). Results of recent studies indicate that an increase in arginine concentration in the fetal plasma brought about by maternal intravenous infusion of citrulline reflected increased arginine availability in the fetus (Lassala et al. 2009). Thus, citrulline provision is highly effective in enhancing NO production by placental tissues and the delivery of maternal nutrients to fetuses. Moreover, intravenous administration of 155 mmol/kg body weight of citrulline to pregnant ewes is more effective than the same dose of arginine in sustaining an elevated concentration of arginine in both maternal and fetal circulations, because the half-life of citrulline is approximately twice that of arginine in gestating sheep (Lassala et al. 2009). This is likely true for humans.

Glutamine

Glutamine plays a prominent role in fetal carbon and nitrogen metabolism and is the most abundant free amino acid in porcine fetal umbilical venous plasma (Lin et al. 2012; Wu et al. 1995). In pigs, the fetal:maternal ratio of plasma glutamine is greater than 2 throughout pregnancy and exhibits the highest value among all free amino acids, whereas the opposite is true for branched-chain amino acids (BCAA) (Wu et al. 1995), suggesting that the placenta synthesizes glutamine from BCAA and release glutamine into the fetal circulation (Wu et al. 1995). Direct evidence supporting this view was provided by Self et al. (2004). Rates of glutamine accretion in fetal pigs, which represents minimal glutamine requirement by the fetus, increase progressively from day 40 to 114 of gestation. When uterine blood flow and uterine arterial–venous differences in plasma are taken into consideration, uterine uptake of glutamine to support the rapid growth of the fetus during days 110 to 114 of gestation is the most predominant among all amino acids and accounts for 170 % of fetal glutamine accretion in gestating swine (Wu et al. 1999). These results indicate that glutamine is actively metabolized by the fetus and may serve as a regulator of metabolic pathways besides protein accretion. Like arginine, glutamine also activates the mTOR signaling pathway to stimulate protein synthesis in placental cells (Kim et al. 2013).

Supplementing 1 % glutamine to a corn- and soybean meal-based diet for gestating sows during late pregnancy (from day 90 to 114 of gestation) markedly reduced incidence of IUGR piglets, variation in birth weight, and preweaning mortality of live-born piglets by 39, 33, and 46 %, respectively, without altering total number of live-born piglets (Wu et al. 2011). Moreover, its combination with arginine can regulate protein synthesis more efficiently and economically by activating production of polyamines and the mTOR signaling pathway (Wu et al. 2011). In addition, dietary supplementation with 0.6 % glutamine plus 0.4 % arginine decreased concentrations of ammonia in the maternal plasma, suggesting an improved efficiency in the utilization of dietary protein by gestating gilts receiving glutamine and arginine supplementation. Also, the dietary supplementation with glutamine and arginine to gilts increased litter birth weight for live-born piglets by 15 %, while reducing variation in birth weight and the number of IUGR piglets simultaneously (Wu et al. 2010). Taken together, glutamine is an effective amino acid to support the maximum survival, growth, development, productivity and performance of swine. Similarly, supplementing glutamine to the diet for lactating sows increased concentrations of glutamine in the plasma, skeletal muscle, and milk, as well as milk production (Manso et al. 2012; Wu et al. 2011). It is possible that supplemental glutamine may spare BCAA (substrates for glutamine production) for metabolic utilization and activation of the mTOR signaling pathway (Curi et al. 2005; Li et al. 2009).

Branched-chain amino acids (BCAA)

BCAA (leucine, isoleucine, and valine) have a positive effect on protein synthesis in skeletal muscle by activating the mTOR signaling pathway and decreasing rates of protein degradation (Davis et al. 2002). Also, BCAA donate the amino group for synthesis of glutamine in mammals, as noted above. In pigs, the reduced concentration of leucine in the umbilical vein (Lin et al. 2012) and the decreased concentration of valine in the jejunum (He et al. 2011) are associated with abnormal energy metabolism in IUGR piglets. In addition, placental transport and fetal utilization of BCAA were drastically altered by IUGR. Using stable

isotope techniques, transport and utilization of leucine were investigated in an ovine model of IUGR induced by exposure to heat stress. Uteroplacental utilization, fetal disposal rate, flux between placenta and fetus, and intra-fetal oxidation of leucine were all reduced in the IUGR group, compared with the control (Ross et al. 1996). Moreover, activity of the amino acid transport system L, which is responsible for leucine transport, was also decreased in the IUGR placenta (Jansson et al. 1998; Roos et al. 2007). The decreased placental transport of BCAA in IUGR may explain the reduction in BCAA availability in the fetus. Interestingly, fractional rates of protein synthesis and its response to feeding are unaffected by IUGR in newborn pigs (Davis et al. 1997), indicating the possibility of accelerating lean mass growth in the IUGR fetus/neonate through dietary intervention. The trajectory of muscle development and growth, including cell division and protein accretion, is down-regulated in IUGR offspring. Reduced muscle mass occurs in human (Padoan et al. 2004) and porcine (Wu et al. 2008) IUGR fetuses. In the porcine IUGR model, the number of primary fibers did not differ between IUGR and NBW fetuses on day 60 of gestation, while the total number of muscle fiber was decreased in the IUGR group on days 90 and 110 of pregnancy. The mean diameter of the *longissimus dorsi* muscle fiber was continuously low, and the muscle proteome involved in metabolic pathways was markedly altered as a result of IUGR throughout the mid and late gestation (Wang et al. 2013a). Furthermore, reduced lean mass and impaired muscle development persist after birth in IUGR offspring, because muscle fiber number is fixed at birth (Thorn et al. 2011; Yates et al. 2012). BCAA supplementation during prenatal and postnatal period has been proposed as a nutritional therapy to stimulate muscle development and lean mass growth in the IUGR fetus/neonate (Zheng et al. 2009). Frequent feeding should be considered to achieve maximum catch-up growth in IUGR offspring, due to its role in sustaining insulin concentrations in plasma to stimulate tissue protein synthesis (Davis et al. 1997). Leucine-rich diets have recently been used to minimize reductions in placental and fetal growth and to improve protein synthesis and body composition in tumor-bearing pregnant mice (Viana and Gomes-Marcondes 2013). Further studies with animal models are needed to elucidate the response of protein accretion to BCAA intervention and its underlying mechanism.

Other amino acids

Amino acids involved in one-carbon metabolism

Compelling evidence indicates that IUGR is associated with altered regulation of gene expression (Park et al. 2008; Del Curto et al. 2013). Moreover, epigenetic alterations in early embryos and the unfavorable effects of IUGR on offspring can last for generations via covalent modifications of DNA and core histones (Wang et al. 2012a). Maternal nutrition will alter the epigenetic status of the fetal genome and expression of imprinted genes (Wu et al. 2004a). Maternal amino acids, such as glycine, serine, histidine, and methionine, are key components of one-carbon metabolism that participate in provision of methyl donors for DNA synthesis and methylation (Locasale 2013). Alterations of enzymes in maternal and fetal one-carbon metabolism during pregnancy increase the risk for the development of uteroplacental insufficiency, which can lead to IUGR (Furness et al. 2008). In addition, uteroplacental insufficiency can affect hepatic one-carbon metabolism and subsequent DNA methylation, resulting in persistent changes of hepatic gene expression in the postnatal IUGR rat (MacLennan et al. 2004). Methyl donors supplemented to maternal diets regulate CpG methylation in early life, and the methylation patterns will strongly influence the susceptibility to adult diseases (Waterland and Jirtle 2004). Thus, it is necessary to determine whether maternal amino acids would influence methylation of genes critical for placental growth and fetal programming. Amino acids involved in one-carbon metabolism, such as glycine [a conditionally essential for embryonic and fetal growth and development (Wang et al. 2013b)], have the potential to improve epigenetic modifications to prevent or treat IUGR. These investigations will allow for a better understanding of mechanisms responsible for fetal programming and genome imprinting.

Aromatic amino acids

Aromatic amino acids (such as phenylalanine, tyrosine, histidine and tryptophan) are precursors of neurotransmitters, regulating neurological functions during embryonic and fetal development. A growing body of evidence has already demonstrated that these amino acids in fetal fluids and tissues are affected to different extents by IUGR (Table 4). Alterations of these amino acids are proposed to exacerbate neuronal viability (van Vliet et al. 2013) of IUGR fetuses and may have a permanent effect on the physiological and feeding behavior during postnatal life (Alexandre-Gouabau et al. 2011; Lin et al. 2012). Research on dynamic changes of these aromatic amino acids in the conceptus is expected to provide a molecular mechanism and potential biomarkers for the early diagnosis of IUGR-related abnormal neurodevelopment (Wu et al. 1995). At present, little is known about effects of dietary supplementation with aromatic amino acids on conceptus survival or growth in any species.

Taurine

Taurine has potent anti-oxidative functions in animals (Schaffer et al. 2014). An adequate supply of taurine appears to be vital for the growth of the fetus and is crucial for β-cell development and insulin action. Taurine is a β-amino acid that is not incorporated into proteins, and is regarded as a nutritionally essential amino acid for fetus and neonate due to the inadequate capacity of fetal synthesis (Hayes and Sturman 1981). Therefore, placental transfer is the primary source of taurine during fetal life. However, placental transport capacity for taurine is reduced in IUGR due to changes in Na^+-dependent transport activity, resulting in a dramatic decline of fetal taurine concentrations (Norberg et al. 1998; Roos et al. 2004). Nevertheless, maternal taurine supplementation has positive effects on fetal growth and development. For example, in a study involving pregnant rats, oral administration of taurine at a dose of 300 mg/kg/d beginning on day 12 after conception till term could alleviate the damage to the fetal brain caused by IUGR (Liu et al. 2011). The underlying mechanisms include a decrease in brain cell apoptosis to improve brain ultra-structure (Liu et al. 2011) and activation of the protein kinase A signaling pathway to increase expression of neurotrophic factors (Liu et al. 2013b), thus promoting brain development in the IUGR fetus. Meanwhile, supplementing taurine in the maternal diet during late pregnancy (day 18 to parturition) could markedly enhance postnatal growth of offspring with both NBW and IUGR (Liu et al. 2013b). However, only 50 % of IUGR, particularly female, displayed catch-up growth at 12 weeks of age after taurine supplementation. The accelerated postnatal growth may be associated with adult obesity and insulin resistance in both IUGR and NBW offspring, suggesting the determinant role of altered availability of fetal taurine in postnatal insulin sensitivity and fat accumulation (Hultman et al. 2007).

Concluding remarks and perspectives

Inadequate placental transfer of amino acids from mother to fetus is a major factor contributing to IUGR in mammals. Despite several available methods for treating IUGR, nutritional therapy is still in its infancy. Amino acids are not only building blocks for protein but also key regulators of metabolic pathways in fetoplacental development. These nutrients play a major role in promoting fetal growth in IUGR more effectively than hormonal strategies when metabolic responses to hormones are limited (Brown et al. 2012). Fetal growth depends on maternal nutritional, metabolic and endocrine status, which are all affected by dietary uptake of nutrients. The positive relationships between circulating maternal amino acid concentrations and placental amino acid transport into the fetus encourage the development of new therapies to prevent or treat IUGR by enhancing amino acid levels in maternal diet or maternal circulation. Caution should be taken to recognize that the link between maternal nutrition and fetal growth is indirect. A large margin of safety for fetal development is allowed within the maternal–fetal supply line (Harding 2001). Depending on maternal adaptation to the environment (including diet), a relatively large change in dietary intakes of amino acids by gestating mothers may have little impact on amino acid availability in the fetal circulation. For example, Baggs ewes were able to maintain fetal amino acid concentrations in the face of a maternal limited nutrition by adapting well to the harsh conditions (Jobgen et al. 2008). Therefore, the beneficial effects of maternal amino acid administration rely on the capacity and efficiency of placental transport systems responsible for nutrient transfer between mother and fetus. Due to incomplete knowledge about the multi-factorial events in IUGR (Lin et al. 2011; Moco et al. 2013), innovative mechanistic studies are required to develop new amino acid-based strategies to improve fetal growth and survival. Furthermore, increased placental vascularity, but adverse fetal outcome, observed in gilts supplemented with arginine between days 0 and 25 of gestation (Li et al. 2010) highlights the necessity to fully understand the cellular and molecular mechanisms by which amino acids regulate metabolic pathways and embryonic/fetal growth. If future interventions through administration of amino acids are given to mother with IUGR or IUGR offspring, balance among dietary amino acids, acid–base balance, and alterations of related metabolic pathways must be evaluated to improve the efficiency of nutrient utilization (Mateo et al. 2008). In view of the multiple functions of amino acids in the fetus, we propose to design an optimal amino acid pattern in maternal diets as an effective therapeutic strategy for IUGR intervention (Wu 2014; Wu et al. 2014). Capitalizing on the beneficial roles of amino acids in nutrition holds great promise for preventing and treating IUGR, as well as improving the growth, health, and well-being of IUGR offspring.

Acknowledgments This work was supported by the Natural Science Foundation of China (no. 30810103902, 30972156, 31129006, 31272449, and 31272450), and Texas A&M AgriLife Research (H-8200).

Conflict of interest The authors declare that they have no conflict of interests.

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