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Developmental origins of metabolic disorders: The need for biomarker candidates and therapeutic targets from adequate preclinical models

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ABSTRACT

The investigation on obesity and associated disorders have changed from an scenario in which genome drove the phenotype to a dynamic setup in which prenatal and early-postnatal conditions are determinant. However, research in human beings is difficult due to confounding factors (lifestyle and socioeconomic heterogeneity) plus ethical issues. Hence, there is currently an intensive effort for developing adequate preclinical models, aiming for an adequate combination of basic studies in rodent models and specific preclinical studies in large animals. The results of these research strategies may increase the identification and development of contrasted biomarkers and therapeutic targets.

1. Introduction

Currently, nutrition-related disorders (obesity, metabolic syndrome and diabetes) are in the focus of intense research and debate. First, the appearance of obesity and associated conditions like diabetes is linked to other non-communicable disorders; e.g. cardiovascular disease. In fact, 50% of deaths caused by diabetes are related to cardiovascular disease (primarily heart disease and stroke; [1]). Second, obesity and associated disorders were traditionally reported in adult individuals of wealthy populations from high-income countries. However, in recent years, the global changes in lifestyle and dietary patterns have modified the distribution of the diseases and therefore obesity and diabetes affect both children and adults of different socioeconomic classes in both developed and developing countries [2]. Hence, obesity was declared a global pandemic by the World Health Organization (WHO) in 2005, when the affected population reached 400 million of adults and at least 2.6 million of people were dying each year as a result of being overweight or obese. Furthermore, WHO predicted that around 2.3 billion adults would be overweight and 700 million would be obese by 2015 (http://www.who.int/features/factfiles/obesity/en/index.html). This prediction was not too much inaccurate since in the last year, 2014, around 1.9 billion of adults were reported to be overweight and 600 million to be obese (http://www.who.int/mediacentre/factsheets/fs311/en/). These data mean that 39% of adults are overweight and 13% are obese; of them, 9% are affected by diabetes. Diabetes caused 1.5 million deaths in 2012; more than 80% of them occurring in low- and middle-income countries (http://www.who.int/mediacentre/factsheets/fs312/en/).

Moreover, the problem is aggravated by the causal relationship among nutrition-related diseases and other non-communicable diseases (i.e. renal, immune, inflammatory and reproductive disorders, and cancer [3–7]). Hence, the epidemics is becoming a major worldwide public health problem since it does not only affects directly life-quality and wellbeing of individuals but also constitutes a strong economic challenge to health-care systems and governmental administrations. Thus, there is an urgent need to tackle the situation, by both increasing research in the area and developing adequate strategies for prevention and treatment.

The studies performed in the last decades have changed substantially the vision of the causal factors of obesity and associated disorders. We have moved from a gene-centric static perspective, in which genome drove the phenotype with secondary

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influence of lifestyle and nutrition, to a much more holistic and dynamic approach in which environmental, parental, prenatal and early-postnatal conditions are strongly determinants of postnatal development and homeostasis and therefore health status and disease risks. In this scenario, the development of proteomics and other "-omics" during the last years is giving a complimentary tool that may help to accurately elucidate the condition and identify therapeutic targets [8–13].

2. The Developmental Origins of Health and Disease (DOHaD)

The DOHaD concept points out that prenatal and early-postnatal conditions (mainly nutrition and lifestyle) determine growth, life-time fitness/obesity and the risks for non-communicable diseases via epigenetic changes induced during development (reviewed in Ref. [14]). In all the mammalian species, foetal development is dependent on adequate transfer of oxygen and nutrients from the mother to the foetus via the placenta. Inadequate maternal conditions (e.g. deficiency or excess in food intake or hypoxia) and/or metabolic disturbances (e.g. obesity, metabolic syndrome or diabetes) and insufficient placental function may affect the supply of oxygen and nutrients to the foetuses. Hence, such conditions may affect foetal development and may compromise homeostasis, metabolism and health of the offspring throughout life, and even may affect subsequent generations (transgenerational programming [15]).

In case of maternal food-intake excess, obesity and metabolic disorders, the excess in the supply of nutrients induces an excessive development of the foetuses. At birth, in situations of maternal overnutrition, neonates are frequently large-for-gestational age (LGA) and obese, having high amounts of body fat; moreover, they can manifest macrosomia with severe enlargement of heart, liver and spleen [16].

In case of maternal food intake deficiencies or hypoxia and in case of placental insufficiency, the shortage in the supply of oxygen and nutrients to the foetuses causes deficiencies in their development. The neonates are small-for-gestational-age (SGA), with reduced body-weight at birth as a consequence of a process known as intrauterine growth restriction (IUGR). In humans, the incidence of IUGR infants ranges between 7 and 15% depending on sociodemographic issues [17]. Classically, IUGR has been associated with maternal malnutrition but, currently, 60% of IUGR offspring are identified as mainly caused by placental insufficiency [18,19].

Maternal obesity and metabolic disorders may also cause IUGR [20–22], mainly due to vascular alterations affecting the placental development and function and causing foetal hypoxia [23]. Women with alterations in glucose and lipid metabolism may also develop hypertensive disorders in pregnancy (HDP). HPD includes a spectrum of disorders varying, according to severity, from chronic pre-existing hypertension and gestational hypertension to preeclampsia and eclampsia. Occurrence of HDP usually induces IUGR and SGA [24].

SGA offspring, depending on the severity of IUGR, may be predisposed to high neonatal morbidity and mortality rates, with early death or life-long alterations in their development, health and welfare [25]. In offspring with extreme IUGR, deficiencies of development are unavoidable and viability of the neonate is strongly compromised, causing death. In less-critical IUGR, the central nervous system functionality is assured but the functionality of the other organs can be severely affected. Hence, health and welfare of these IUGR offspring is compromised by gastrointestinal (alterations in development and function of the intestine, which predispose to feeding intolerance and digestive disorders), metabolic (inadequate liver development, which is essential for the metabolism of glucose, amino-acids, proteins, lipids and vitamins), respiratory (abnormalities in the airways and lungs, causing impaired respiratory function), renal (compromising homeostasis and causing hypertension) and immune disfunctions (immune depression and high susceptibility to infection) [26–30].

At adulthood, both LGA and SGA phenotypes are affected by different health complications, such as obesity, metabolic, and cardiovascular pathologies [25,31–34].

The profound implications of these disorders in perinatal survival and lifelong performance and health have boosted research efforts. The perspective on future research is based on three pillars: the complete understanding of the underlying biology of the disease, the availability of contrasted biomarkers for diagnosis, and the assessment of preventive and curative treatments. These three keystones would allow the improvement of both individualised healthcare and wide population strategies focussed on diagnostic and treatment.

3. The usefulness of animal models for the screening of adequate biomarker candidates and therapeutic targets

Biomarkers are essential tools for delineating adequacy or inadequacy of biological processes (for allowing early and accurate diagnosis) and the spectrum of biological effects of intervention strategies (for developing optimal dosage and treatment strategies). However, the a priori discovery of biomarker candidates in patient populations is difficult due to the inherent high variability of data caused by a plethora of confounding factors (including genetic, lifestyle and socioeconomic heterogeneity, as well as co-morbidities and their treatments, to name but a few). In addition, research in human beings is obviously limited by ethical issues.

Hence, preclinical studies in animal models are an important source of biomarker candidates for the systematic analysis of pregnancy disturbances and for the efficacy and safety evaluations of new treatments. The translation from basic research into practice is a long, often inefficient and costly process. The choice of appropriate animal models with adequate features is critical for the success of translational research.

Models in experimental studies on obesity and metabolic disorders have been traditionally based on laboratory rodents, especially rats and mice [35–38]. The rodents need little space, are relatively inexpensive to maintain, easy to manage, have a short life cycle, have a sequenced genome and are easily modified by genetic engineering. However, rodents are the election model for studies on a concrete mechanism but there are also certain severe limitations. The main constraints are the marked differences with humans in cell and tissue biology, metabolic and endocrine routes, and developmental patterns and physiology of organs and systems [39,40]. Moreover, placentation of rodents is a very specific evolutive strategy of these species and show large differences when compared to humans [41]. Hence, findings in rodents are very different from those in human patients in many diseases and developmental areas. Different large animal species overcome these limitations and offer numerous profitable characteristics for the discovery and testing of biomarkers.

In brief, housing and management of large animals are well-developed, behavioural patterns are diurnal and body size allows application of imaging techniques and serial sampling of large amounts of blood and tissues. Moreover, pathways regulating appetite, energy balance and adipogenesis in large animals are more similar to humans than in rodents. Finally, in the last years, the genomic analysis is well-advanced and it is possible to obtain targeted gene mutations for specific models.

The most prominent large animal model for translational studies in nutritional and metabolic disorders is the pig [42,43]. At the same time, the mammalian species with the highest rate of IUGR is the swine with an average incidence of 15–20% [44,45].

Modern swine production is mainly based on large farms (in Europe, USA, Brazil, China and other countries in South-East Asia) generating "value-for-money" products with optimised productivity and efficiency. Genetic, nutritional and reproductive strategies are main tools in modern pig production. A main approach to improve profitability consists of increasing the number of piglets born per litter (prolificacy). Nevertheless, a higher litter size limits the available uterine space for placental development and, hence, compromises placental function and causes IUGR in some of the littermates. In fact, highly-prolific sows are characterised by a high number of piglets in the litter but also by a high incidence of SGA piglets, also known as low-birth-weight (LBW) piglets [45,46]. Incidence of IUGR and LBW piglets may be also increased by maternal nutritional deficiencies [47].

Piglets affected by IUGR have a similar health status to IUGR infants (mainly characterised by gastrointestinal and metabolic disfunctions) and are therefore largely used for translational studies. Proteomics and other "-omic" techniques have been used in the last years to empower classical studies and get a more holistic picture of critical points like foetal homeostasis [48], and liver [49,50] and intestinal function [49,51,52] in neonates.

Moreover studies on incidence and pre- and postnatal consequences of IUGR and developmental programming are of highly translational value for biomedical research, but are also crucial in animal production; results will optimise animal health and welfare, as well as profitability and sustainability of the productive systems [53].

4. Processes and biomarkers of maternal and foetal metabolism

Glucose, free fatty acids (FFAs), lipids and amino acids are essential for adequate foetal development. The foetus obtains them mostly from maternal supply. Early pregnancy is characterised by hyperphagia and increased lipogenesis, which causes fat accumulation, whilst late pregnancy is characterised by reduced intake but accelerated breakdown of the previously accumulated fat depots (lipolysis; [16]). Maternal lipolysis during the last trimester of pregnancy is important for foetal development, as it produces FFA and glycerol, which, in the maternal liver, are converted into triglycerides, ketone bodies and glucose that are transferred to the foetus [54]. Hence, common biomarkers of pregnancy and foetal development are maternal fasting blood glucose, triglycerides, total cholesterol, VLDL-cholesterol, LDL-cholesterol, HDL-cholesterol, and pregnancy associated protein-A (PAPP-A) [55]. Other biomarkers may be focused on placental transporters mediating the transfer of amino acids, glucose (GLUTs), and fatty acids (FATPs) [56].

A good example is the foetal uptake of amino acids, which needs to be performed through two active transporter processes. The first, known as system A transporter (SNAT1, SNAT2 and SNAT4), facilitates the uptake of small non-essential neutral amino acids (e.g. alanine, glycine and serine) against their concentration gradient by simultaneously transporting sodium into the cell [57,58]. The second, known as system L transporter (LAT1 and LAT2), facilitates exchange of non-essential amino acids for essential amino acids (e.g. leucine and phenylalanine) against their concentration gradient, independently of sodium [59].

Glucose crosses the placenta via facilitated transport, mainly by GLU1 [60], and is generally considered to be the main energy source for developing foetuses [61]. A certain degree of maternal insulin resistance is a physiological state during pregnancy in order to facilitate the supply of glucose to the feto-placental unit, which is necessary for adequate foetal development. However, in case of women affected by severe insulin resistance and hyperglycaemia (either by pre-existing diabetes or pre-diabetes or by gestational diabetes mellitus; GDM), the foetuses are exposed to high intrauterine concentrations of glucose; their development, as a consequence, is accelerated and the result is macrosomia. Diabetes also alters the expression and activity of the human placental GLUT1 glucose transporter, increasing placental glucose transport even in the absence of maternal hyperglycaemia and contributing to macrosomia and other consequences [62].

In the same way, cholesterol and triglycerides increase in maternal plasma throughout pregnancy. Cholesterol is essential for cell proliferation, tissue development and endocrine homeostasis of the growing foetus, and triglycerides are a key energy source for foetal growth and development. The FFAs taken up by the placenta and transported to the foetus originate predominantly from maternal non-esterified fatty acids (NEFAs) and from esterified fatty acids contained in triglycerides (TGs) carried by lipoproteins; the FFAs, after being oxidised in the maternal liver as ketone-bodies, represent an alternative fuel source for the foetus. Maternal TGs have been suggested as the primary source of fatty acids because of their substantial increase in late gestation compared to NEFAs [63].

Some essential fatty acids (EFA) must be obtained from food, since humans and other mammals cannot synthesise them due to the lack of the required desaturase enzymes. Among the EFA, two polyunsaturated fatty acid (PUFA) are very important: alpha-linolenic acid (ALA; with a double bond three carbon atoms, also called omega-3 fatty acid) and linoleic acid (LA; with a double bond six carbon atoms, also called omega-6 fatty acid). Some PUFA (LC-PUFA) of both omega-3 (eicosapentaenoic acid = EPA and docosahexaenoic acid = DHA) and omega-6 type (gamma-linolenic acid = GLA and arachidonic acid = AA) are conditionally essential; e.g. during pregnancy (reviewed in [64]). Mammals have a limited ability to synthesise them and, in case of increased need during gestation, they have to obtain them from food.

During pregnancy, maternal LC-PUFAs are transferred to the foetus, either associated to triglycerides or, in a minor proportion, as FFAs. Selective placental uptake of LC-PUFAs via plasma membrane fatty acid-binding proteins results in higher LC-PUFA concentrations in the foetal than in the maternal circulation. During the last third of pregnancy, AA and DHA are the principal maternal LC-PUFAs. AA determines adequate foetal growth and development but also postnatal metabolism, while DHA is indispensable for the development of the central nervous system and essential for cognitive and visual functions. Both DHA and EPA are important for immune functions. Adequate LC-PUFA supply is also necessary during early postnatal development (i.e. during lactation, [65]).

In case of pregnancies affected by obesity and/or metabolic disorders causing hyperlipidaemia, and usually dyslipidaemia, the foetuses are exposed to high intrauterine concentrations of FFAs and lipids, which also induce accelerated foetal development. During recent years, dietary supplementation of obese pregnant women with PUFAs, mainly omega-3, principally if they develop any component of metabolic syndrome or its complications, has increased in popularity [64,66].

However, the benefit-to-risk ratio of increasing PUFAs intake during pregnancy has not been completely established. It is known that excessive dietary PUFA may – especially in pregnancies with metabolic syndrome or diabetes – have inhibitory effects on desaturase and elongase enzymes, lowering the synthesis of LC-PUFA. Excess dietary PUFAs may also enhance peroxidation and may reduce antioxidant capacity, impairing foetal homeostasis (reviewed in Ref. [66]). Furthermore, the information on the adaptation in placental LC-PUFA metabolism in response to metabolic syndrome is limited and contradictory. Nevertheless, due to the increasing prevalence of nutrition-related diseases (obesity, metabolic syndrome and diabetes), dietary supplementation with PUFA is more widely used, although the risks may exceed the benefits since the assessment is still scarce. This is therefore a good example of the need for preclinical studies in animal models and, in this sense, lipids metabolism in pregnant females and foetuses are very similar in humans and pigs [67]. The occurrence of disorders like dyslipidemia strongly modifies availability and metabolism of lipids at the fetoplacental unit [68], affecting viability and developmental trajectory of the conceptuses [69].

5. Processes and biomarkers of feto-placental development and IUGR

The adequate supply of nutrients and oxygen to the foetus depends on adequate maternal availability but also on adequate placental transfer. Hence, foetal development depends on efficient placental function. Placental efficiency is primarily determined by its ample development (adequate interdigitation of placenta and endometrium to increase exchange surface, vascular dilation and angiogenesis; [45]), which favours blood flow and exchange of nutrients and oxygen with the conceptus.

Placental insufficiency is currently considered a main factor for pregnancy complications, as described previously [18]. In case of impaired placental function, several placental-secreted proteins, hormones, mRNAs and miRNAs molecules crossing the maternal-foetal barrier may be used as specific biomarkers since they are measurable in the maternal circulation [70–72].

In normal pregnancies, vascular dilation and neoangiogenesis are signalled by proangiogenic factors secreted by the placenta (placental growth factor, PlGF, and vascular endothelial growth factor, VEGF). Vasodilatation and angiogenesis are primarily driven by nitric oxide (NO) and its endothelial constitutive synthase (eNOS or NOS3) which can be found both at the trophoblast, the cells that adhere to and penetrate the uterine endometrium at implantation, and at the extravillous trophoblast, inducing vasodilatation and angiogenesis in maternal cells during the implantation process [73–75]. During the post-implantation period and early placental development, NO and NOS3 are hypothesised to be involved in tissue remodelling, immunosuppression, and vasoregulation [76]. In consequence, a decreased NO bioavailability is recognised to be involved in the pathogenesis of IUGR [77]. Concomitantly, imbalances in the levels of angiogenic regulators, which cause insufficient placental and foetal blood-flow, compromise the supply of oxygen. Insufficient supply of oxygen causes hypoxia and oxidative stress at the feto-placental unit [78]. These facts are also predisposing for cardiovascular disorders at juvenile and adult stages. Overall, these considerations highlight the necessity of adequate biomarkers.

Among the different candidate biomarkers, different authors are addressing the usefulness of asymmetric dimethylarginine (ADMA), an endogenous amino acid derived from proteolytic breakdown of arginine-methylated proteins [79], which by competition with arginine, the substrate of NOS, antagonises the production of NO. ADMA is used in adult individuals with cardiovascular risk and, currently, is being proposed a reliable marker to identify both SGA and LGA subjects at higher risk of health disturbances [80].

This knowledge also provides specific therapeutic targets. There are several amino acids which are precursors of NO; not only arginine but also ornithine, leucine, glutamine, and proline. These amino acids also regulate synthesis of polyamines and proteins; thus, besides favouring placental development and nutrient transfer, also support conceptus development. The results obtained under experimental conditions in swine suggest that amino acids supplementation may be a promising strategy to reduce the incidence of IUGR offspring [81–84], although some of the findings have been conflicting and make necessary further specific studies.

It is well-known that IUGR foetuses are able to modify their metabolic regulation in order to ensure a better use of the scarce nutrients that they have. The mechanism is based on displaying insulin resistance, which allows them to take advantage of the scarce supply of glucose that they are receiving. However, on the other hand, high levels of insulin increase the synthesis of NO inhibitors [85], prejudicing utero-placental blood-flow [86] and reducing the supply of oxygen and nutrients to the foetuses. In fact, IUGR foetuses have a state of low-grade inflammation affecting immune cell proliferation and serum cytokines, as well as an increased susceptibility to infection [87]. In consequence, the use of markers of systemic inflammation, like tumour necrosis factor α (TNFα) and interleukin-6 (IL-6), is also a promising field of study [88].

6. Concluding remarks

The intense research on the causes and mechanisms implicated in the current epidemics of obesity and associated non-communicable disorders has addressed the substantial role of environmental, parental, prenatal and early-postnatal conditions in the development of disease. The individuals, during prenatal and early postnatal development, undertake epigenetic changes in the structure and function of some of their organs and systems. These changes may lead to metabolic disorders at juvenile period and adulthood and may be transferred to subsequent generations by transgenerational inheritance.

The perspective on future research is based on three pillars: the complete understanding of these processes, the availability of contrasted biomarkers for diagnosis and the assessment of preventive and curative treatments. Such research makes necessary interventional procedures, either to affect foetal development and metabolism or to sample the feto-placental unit, which cannot be conducted in humans because of ethical issues.

Hence, preclinical studies in animal models are an important source of biomarker candidates that can be useful for the systematic analysis of pregnancy disturbances and for the efficacy and safety evaluation of new treatments. However, the results need to be translational; hence, the studies have to be performed in adequate animal models. Rodents are the species of election for basic research, but the translational value of large animal models is becoming increasingly recognised in the last years. Further work is however needed to increase the awareness of researchers and medical doctors on the amenability of large animal models. Moreover, the use of large animals implies ethical issues and social repudiation, such that active explanation and promoting of ethical experimentation to the society need to be undertaken.

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References

[1] N.J. Morrish, S.L. Wang, L.K. Stevens, J.H. Fuller, H. Keen, Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes, Diabetologia 44 (2) (2001) S14–S21.
[2] L. Chen, D.J. Magliano, P.Z. Zimmet, The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives, Nat. Rev. Endocrinol. 8 (2011) 228–236.
[3] G.M. Reaven, Y.D. Chen, Role of insulin in regulation of lipoprotein metabolism in diabetes, Diab. Metab. Rev. 4 (1988) 639–652.
[4] S.M. Grundy, H.B. Brewer, J.I. Cleeman, S.C. Smith, C. Lenfant, Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/

American Heart Association conference on scientific issues related to definition, Arterioscler. Thromb. Vasc. Biol. 24 (2004) e13–e18.
[5] R.H. Eckel, S.M. Grundy, P.Z. Zimmet, The metabolic syndrome, Lancet 365 (9468) (2005) 1415–1428.
[6] R. Kahn, J. Buse, E. Ferrannini, M. Stern, The metabolic syndrome: time for a critical appraisal joint statement from the American Diabetes Association and the European Association for the Study of Diabetes, Diab. Care 28 (9) (2005) 2289–2304.
[7] R. Olufadi, C.D. Byrne, Clinical and laboratory diagnosis of the metabolic syndrome, J. Clin. Pathol. 61 (6) (2008) 697–706.
[8] N.M. Page, C.F. Kemp, D.J. Butlin, P.J. Lowry, Placental peptides as markers of gestational disease, Reproduction 123 (4) (2002) 487–495.
[9] R. Shankar, F. Cullinane, S.P. Brennecke, E.K. Moses, Applications of proteomic methodologies to human pregnancy research: a growing gestation approaching delivery? Proteomics 4 (7) (2004) 1909–1917.
[10] S.D. Ferrara, G. Viel, Functional-omics in intrauterine growth restriction: novel insights into child development, Exp. Rev. Proteomics 9 (4) (2012) 355–357.
[11] Z. Miao, M. Chen, H. Wu, H. Ding, Z. Shi, Comparative proteomic profile of the human placenta in normal and fetal growth restriction subjects, Cell Physiol. Biochem. 34 (5) (2014) 1701–1710.
[12] M.D. Ruis-González, M.D. Cañete, J.L. Gómez-Chaparro, N. Abril, R. Cañete, J. López-Barea, Alterations of protein expression in serum of infants with intrauterine growth restriction and different gestational ages, J. Proteomics 119 (2015) 169–182.
[13] A. Dessì, C. Pravettoni, F. Cesare Marincola, A. Schirru, V. Fanos, The biomarkers of fetal growth in intrauterine growth retardation and large for gestational age cases: from adipocytokines to a metabolomic all-in-one tool, Exp. Rev. Proteomics 12 (3) (2015) 309–316.
[14] M.E. Symonds, S.P. Sebert, M.A. Hyatt, H. Budge, Nutritional programming of the metabolic syndrome, Nat. Rev. Endocrinol. 5 (11) (2009) 604–610.
[15] A. Gonzalez-Bulnes, C. Ovilo, S. Astiz, Transgenerational inheritance in the offspring of pregnant women with metabolic syndrome, Curr. Pharm. Biotechnol. 15 (1) (2014) 13–23.
[16] E. Herrera, H. Ortega-Senovilla, Disturbances in lipid metabolism in diabetic pregnancy—are these the cause of the problem? Best Pract. Res. Clin. Endocrinol. Metab. 24 (4) (2010) 515–525.
[17] Z. Ergaz, M. Avgil, A. Ornoy, Intrauterine growth restriction—etiology and consequences: what do we know about the human situation and experimental animal models? Reprod. Toxicol. 20 (3) (2005) 301–322.
[18] R. Saffery, Epigenetic change as the major mediator of fetal programming in humans: are we there yet? Ann. Nutr. Metab. 64 (3–4) (2014) 203–207.
[19] H.J. Schröder, Models of fetal growth restriction, Eur. J. Obstet. Gynecol. Reprod. Biol. 110 (2003) S29–S39.
[20] E.A. Nohr, B.H. Bech, M.J. Davies, M. Frydenberg, T.B. Henriksen, J. Olsen, Prepregnancy obesity and fetal death: a study within the Danish National Birth Cohort, Obstet. Gynecol. 106 (2) (2005) 250–259.
[21] E.A. Nohr, B.H. Bech, M. Vaeth, K.M. Rasmussen, T.B. Henriksen, J. Olsen, Obesity, gestational weight gain and preterm birth: a study within the Danish National Birth Cohort, Paediatr. Perinat. Epidemiol. 21 (1) (2007) 5–14.
[22] E.A. Nohr, M. Vaeth, B.H. Bech, T.B. Henriksen, S. Cnattingius, J. Olsen, Maternal obesity and neonatal mortality according to subtypes of preterm birth, Obstet. Gynecol. 110 (5) (2007) 1083–1090.
[23] H.P. Li, X. Chen, M.Q. Li, Gestational diabetes induces chronic hypoxia stress and excessive inflammatory response in murine placenta, Int. J. Clin. Exp. Pathol. 6 (4) (2013) 650–659.
[24] J.M. Roberts, G. Pearson, J. Cutler, M. Lindheimer, Summary of the NHLBI Working Group on research on hypertension in pregnancy, Hypertension 41 (3) (2003) 437–445.
[25] M.G. Ross, M. Desai, Developmental programming of offspring obesity, adipogenesis, and appetite, Clin. Obstet. Gynecol. 56 (3) (2013) 529–536.
[26] R. D'Inca, M. Kloareg, C. Gras-Le Guen, I. Le Huërou-Luron, Intrauterine growth restriction modifies the developmental pattern of intestinal structure, transcriptomic profile, and bacterial colonization in neonatal pigs, J. Nutr. 140 (5) (2010) 925–931.
[27] M. Baserga, C. Bertolotto, N.K. Maclennan, J.L. Hsu, T. Pham, G.S. Laksana, R.H. Lane, Uteroplacental insufficiency decreases small intestine growth and alters apoptotic homeostasis in term intrauterine growth retarded rats, Early Hum. Dev. 79 (2004) 93–105.
[28] C. Liu, G. Lin, X. Wang, T. Wang, G. Wu, D. Li, J. Wang, Intrauterine growth restriction alters the hepatic proteome in fetal pigs, J. Nutr. Biochem. 24 (6) (2012) 954–959.
[29] P.T. Sangild, Uptake of colostral immunoglobulins by the compromised newborn farm animal, Acta Vet. Scand. 98 (2003) 105–122.
[30] K. Pike, J. Jane Pillow, J.S. Lucas, Long term respiratory consequences of intrauterine growth restriction, Semin. Fetal Neonatal Med. 17 (2) (2012) 92–98.
[31] P. Hovi, S. Andersson, J.G. Eriksson, A.L. Jarvenpaa, S. Strang-Karlsson, O. Makitie, E. Kajantie, Glucose regulation in young adults with very low birth weight, N. Engl. J. Med. 356 (20) (2007) 2053–2063.
[32] L. Ibañez, A. Lopez-Bermejo, L. Suarez, M.V. Marcos, M. Diaz, F. de Zegher, Visceral adiposity without overweight in children born small for gestational age, J. Clin. Endocrinol. Metab. 93 (6) (2008) 2079–2083.
[33] M.J. Heerwagen, M.R. Miller, L.A. Barbour, J.E. Friedman, Maternal obesity and fetal metabolic programming: a fertile epigenetic soil, Am. J. Physiol. Regul. Integr. Comp. Physiol. 299 (3) (2010) R711–R722.
[34] W.H. Tam, R.C. Ma, X. Yang, A.M. Li, G.T. Ko, A.P. Kong, T.T. Lao, M.H. Chan, C.W. Lam, J.C. Chan, Glucose intolerance and cardiometabolic risk in adolescents exposed to maternal gestational diabetes: a 15-year follow-up study, Diab. Care 33 (6) (2010) 1382–1384.
[35] J.A. Armitage, P.D. Taylor, L. Poston, Experimental models of developmental programming: consequences of exposure to an energy rich diet during development, J. Physiol. 565 (1) (2005) 3–8.
[36] J. Speakman, C. Hambly, S. Mitchell, E. Krol, Animal models of obesity, Obes. Rev. 8 (s1) (2007) 55–61.
[37] M. Schroeder, L. Shbiro, O. Zagoory-Sharon, T.H. Moran, A. Weller, Toward an animal model of childhood-onset obesity: follow-up of OLETF rats during pregnancy and lactation, Am. J. Physiol. Regul. Integr. Comp. Physiol. 296 (2) (2009) R224–R232.
[38] C.S. Rosenfeld, Animal models to study environmental epigenetics, Biol. Reprod. 82 (3) (2010) 473–488.
[39] U. Neitzke, T. Harder, A. Plagemann, Intrauterine growth restriction and developmental programming of the metabolic syndrome: a critical appraisal, Microcirculation 18 (4) (2011) 304–311.
[40] U. Neitzke, T. Harder, K. Schellong, K. Melchior, T. Ziska, E. Rodekamp, J.W. Dudenhausen, A. Plagemann, Intrauterine growth restriction in a rodent model and developmental programming of the metabolic syndrome: a critical appraisal of the experimental evidence, Placenta 29 (3) (2008) 246–254.
[41] A. Moffett, C. Loke, Immunology of placentation in eutherian mammals, Nat. Rev. Immunol. 6 (8) (2006) 584–594.
[42] M.E. Spurlock, N.K. Gabler, The development of porcine models of obesity and the metabolic syndrome, J. Nutr. 138 (2) (2008) 397–402.
[43] A. Bähr, E. Wolf, Domestic animal models for biomedical research, Reprod. Domest. Anim. 47 (4) (2012) 59–71.
[44] C.J. Ashworth, A.M. Finch, K.R. Page, M.O. Nwagwu, H.J. McArdle, Causes and consequences of fetal growth retardation in pigs, Reprod. Suppl. 58 (2001) 233–246.
[45] G. Wu, F.W. Bazer, J.M. Wallace, T.E. Spencer, Board-invited review: intrauterine growth retardation: implications for the animal sciences, J. Anim. Sci. 84 (9) (2006) 2316–2337.
[46] G.R. Foxcroft, W.T. Dixon, S. Novak, C.T. Putman, S.C. Town, M.D.A. Vinsky, The biological basis for prenatal programming of postnatal performance in pigs, J. Anim. Sci. 84 (13) (2006) E105–12.
[47] C.C. Metges, I.S. Lang, U. Hennig, K.P. Brüssow, E. Kanitz, M. Tuchscherer, W. Otten, Intrauterine growth retarded progeny of pregnant sows fed high protein: low carbohydrate diet is related to metabolic energy deficit, PLoS One 7 (2) (2012) e31390.
[48] F. Chen, T. Wang, C. Feng, G. Lin, Y. Zhu, G. Wu, G. Johnson, J. Wang, Proteome differences in placenta and endometrium between normal and intrauterine growth restricted pig fetuses, PLoS One 10 (11) (2015) e0142396.
[49] J. Wang, L. Chen, D. Li, Y. Yin, X. Wang, P. Li, L.J. Dangott, W. Hu, G. Wu, Intrauterine growth restriction affects the proteomes of the small intestine: liver, and skeletal muscle in newborn pigs, J. Nutr. 138 (1) (2008) 60–66.
[50] C. Liu, G. Lin, X. Wang, T. Wang, G. Wu, D. Li, J. Wang, Intrauterine growth restriction alters the hepatic proteome in fetal pigs, J. Nutr. Biochem. 24 (6) (2013) 954–959.
[51] X. Wang, W. Wu, G. Lin, D. Li, G. Wu, J. Wang, Temporal proteomic analysis reveals continuous impairment of intestinal development in neonatal piglets with intrauterine growth restriction, J. Proteome Res. 9 (2) (2010) 924–935.
[52] P. Jiang, P.T. Sangild, Intestinal proteomics in pig models of necrotising enterocolitis, short bowel syndrome and intrauterine growth restriction, Proteomics Clin. Appl. 8 (9–10) (2014) 700–714.
[53] N. Oksbjerg, P.M. Nissen, M. Therkildsen, H.S. Møller, L.B. Larsen, M. Andersen, J.F. Young, Meat science and muscle biology symposium: in utero nutrition related to fetal development, postnatal performance, and meat quality of pork, J. Anim. Sci. 91 (3) (2013) 1443–1453.
[54] E. Herrera, H. Ortega-Senovilla, Lipid metabolism during pregnancy and its implications for fetal growth, Curr. Pharm. Biotechnol. 15 (1) (2014) 24–31.
[55] H.A. Parlakgumus, P.C. Aytac, H. Kalaycı, E. Tarim, First trimester maternal lipid levels and serum markers of small-and large-for-gestational age infants, J. Matern. Fetal Neonatal Med. 27 (1) (2014) 48–51.
[56] S. Lager, T.L. Powell, Regulation of nutrient transport across the placenta, J. Pregnancy 2012 (1798) 27.
[57] T. Jansson, Amino acid transporters in the human placenta, Pediatr. Res. 49 (2) (2001) 141–147.
[58] M. Desforges, K.J. Mynett, R.L. Jones, S.L. Greenwood, M. Westwood, C.P. Sibley, J.D. Glazier, The SNAT4 isoform of the system A amino acid transporter is functional in human placental microvillous plasma membrane, J. Physiol. 587 (2009) 61–72.
[59] F. Verrey, System L: heteromeric exchangers of large, neutral amino acids involved in directional transport, Pflugers Arch. 445 (5) (2003) 529.
[60] T. Jansson, M. Wennergren, N.P. Illsley, Glucose transporter protein expression in human placenta throughout gestation and in intrauterine growth retardation, J. Clin. Endocrinol. Metab. 77 (6) (1993) 1554–1562.
[61] H.J. Shelley, J.M. Bassett, R.D. Milner, Control of carbohydrate metabolism in the fetus and newborn, Br. Med. Bull. 31 (1975) 37–43.
[62] K. Gaither, A.N. Quraishi, N.P. Illsley, Diabetes alters the expression and activity of the human placental GLUT1 glucose transporter, J. Clin. Endocrinol. Metab. 84 (2) (1999) 695–701.
[63] P. Haggarty, Fatty acid supply to the human fetus, Annu. Rev. Nutr. 30 (2010) 237–255.

[64] J.A. Greenberg, S.J. Bell, W.V. Ausdal, Omega-3 fatty acid supplementation during pregnancy, Rev. Obstet. Gynecol. 1 (2008) 162–169.
[65] D.L. Hachey, Benefits and risks of modifying maternal fat intake in pregnancy and lactation, Am. J. Clin. Nutr. 59 (2) (1994) 454S–463S.
[66] M.L. Jones, P.J. Mark, B.J. Waddell, Maternal dietary omega-3 fatty acids and placental function, Reproduction 147 (5) (2014) R143–R152.
[67] H.L.S. Walsh, R.J. Martin, Influence of genetic obesity on maternal and fetal serum and lipoprotein lipids in swine, Int. J. Obes. 12 (1988) 49–57.
[68] A. Gonzalez-Bulnes, L. Torres-Rovira, C. Ovilo, S. Astiz, E. Gomez-Izquierdo, P. Gonzalez-Añover, P. Pallares, M.L. Perez-Solana, R. Sanchez-Sanchez, Reproductive, endocrine and metabolic feto-maternal features and placental gene expression in a swine breed with obesity/leptin resistance, Gen. Comp. Endocrinol. 176 (2012) 94–101.
[69] L. Torres-Rovira, S. Astiz, P. Gonzalez-Añover, P. Pallares, S. Perez-Garnelo, M. Perez-Solana, R. Sanchez-Sanchez, A. Gonzalez-Bulnes, Intake of high saturated-fat diets disturbs steroidogenesis, lipid metabolism and development of obese-swine conceptuses from early-pregnancy stages, J. Steroid Biochem. Mol. Biol. 139 (2014) 130–137.
[70] U.D. Anderson, M.G. Olsson, K.H. Kristensen, B. Åkerström, S.R. Hansson, Review: biochemical markers to predict preeclampsia, Placenta 33 (2012) S42–7.
[71] D.M. Morales-Prieto, S. Ospina-Prieto, A. Schmidt, W. Chaiwangyen, U.R. Markert, Elsevier trophoblast research award lecture: origin, evolution and future of placenta miRNAs, Placenta 35 (2014) S39–45.
[72] A.C. Staff, S.J. Benton, P. von Dadelszen, J.M. Roberts, R.N. Taylor, R.W. Powers, C. W. Redman, Redefining preeclampsia using placenta-derived biomarkers, Hypertension 61 (5) (2013) 932–942.
[73] A. Nanaev, K. Chwalisz, H.G. Frank, G. Kohnen, C. Hegele-Hartung, P. Kaufmann, Physiological dilation of uteroplacental arteries in the guinea pig depends on nitric oxide synthase activity of extravillous trophoblast, Cell Tissue Res. 282 (3) (1995) 407–421.
[74] R.C. Gouge, P. Marshburn, B.E. Gordon, W. Nunley, Y.M. Huet-Hudson, Nitricoxide as a regulator of embryonic development, Biol. Reprod. 58 (4) (1998) 875–879.
[75] S. Gagioti, C. Scavone, E. Bevilacqua, Participation of the mouse implanting trophoblast in nitric oxide production during pregnancy, Biol. Reprod. 62 (2000) 260–268.
[76] T.L. Purcell, R. Given, K. Chwalisz, R.E. Garfield, Nitric oxide synthase distribution during implantation in the mouse, Mol. Hum. Reprod. 5 (5) (1999) 467–475.
[77] N.C. Serrano, J.P. Casas, L.A. Díaz, C. Páez, C.M. Mesa, R. Cifuentes, P. López-Jaramillo, N.O. Endothelial, Synthase genotype and risk of preeclampsia a multicenter case-control study, Hypertension 44 (5) (2004) 702–707.
[78] D. Schneider, C. Hernández, M. Farías, R. Uauy, B.J. Krause, P. Casanello, Oxidative stress as common trait of endothelial dysfunction in chorionic arteries from fetuses with IUGR and LGA, Placenta 36 (5) (2015) 552–558.
[79] R.H. Böger, Asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, explains the "L-arginine paradox" and acts as a novel cardiovascular risk factor, J. Nutr. 134 (2004) 2842S–2847S.
[80] V. Chiavaroli, L. Diesse, T. de Giorgis, C. Giannini, M.L. Marcovecchio, F. Chiarelli, A. Mohn, Is asymmetric dimethylarginine associated with being born small and large for gestational age? Antioxid. Redox Signal. 20 (15) (2014) 2317–2322.
[81] R.D. Mateo, G. Wu, F.W. Bazer, J.C. Park, I. Shinzato, S.W. Kim, Dietary L-arginine supplementation enhances the reproductive performance of gilts, J. Nutr. 137 (3) (2007) 652–656.
[82] G. Wu, Functional amino acids in growth, reproduction and health, Adv. Nutr. 1 (1) (2010) 31–37.
[83] K. Gao, Z. Jiang, Y. Lin, C. Zheng, G. Zhou, F. Chen, G. Wu, Dietary L-arginine supplementation enhances placental growth and reproductive performance in sows, Amino Acids 42 (6) (2012) 2207–2214.
[84] X. Li, F.W. Bazer, G.A. Johnson, R.C. Burghardt, J.W. Frank, Z. Dai, G. Wu, Dietary supplementation with L-arginine between days 14 and 25 of gestation enhances embryonic development and survival in gilts, Amino Acids 46 (2) (2014) 375–384.
[85] E.B. Marliss, S. Chevalier, R. Gougeon, J.A. Morais, M. Lamarche, O.A.J. Adegoke, G. Wu, Elevations of plasma methylarginines in obesity and ageing are related to insulin sensitivity and rates of protein turnover, Diabetologia 49 (2) (2006) 351–359.
[86] I.M. Bird, L. Zhang, R.R. Magness, Possible mechanisms underlying pregnancy-induced changes in uterine artery endothelial function, Am. J. Physiol. Regul. Integr. Comp. Physiol. 284 (2) (2003) R245–R258.
[87] X. Zhong, W. Li, X. Huang, L. Zhang, M. Yimamu, N. Raiput, T. Wang, Impairment of cellular immunity is associated with overexpression of heat shock protein 70 in neonatal pigs with intrauterine growth retardation, Cell Stress Chaperones 17 (4) (2012) 495–505.
[88] S. Visentin, A. Lapolla, A.P. Londero, C. Cosma, M. Dalfrà, M. Camerin, D. Faggian, M. Plebani, E. Cosmi, Adiponectin levels are reduced while markers of systemic inflammation and aortic remodelling are increased in intrauterine growth restricted mother–child couple, BioMed Res. Int. 2014 (2014) 401595.