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The developmental origins of health and disease: importance for animal production

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Abstract

The importance of management of pregnant animals during pregnancy has been long known to have effects on the quality of their offspring products. In this review, after defining and setting up the current understanding of the Developmental Origins of Health and Disease (DOHaD), effects on traits relevant to animal production, such as meat quality and lactation as well as general health are discussed, with a special interest for effects of periconceptional nutrition.

Keywords: animal production, DOHaD, fetal programming, lactation, meat.

Introduction

Animal management during pregnancy has been long known to have effects on the quality of offspring products. In this review, after explaining the current understanding of the Developmental Origins of Health and Disease (DOHaD), effects on traits relevant to animal production, such as meat quality and lactation as well as general health are discussed, with a particular interest for the effects of periconceptional nutrition. Since effects on reproductive function have been recently widely reviewed (Gardner *et al.*, 2009; Chadio and Kotsampasi, 2014; Chavatte-Palmer *et al.*, 2014; Kenyon and Blair, 2014), effects on offspring reproductive function have not been developed as the reader can refer to these reviews. Post-natal management will not be discussed thoroughly as this goes beyond the objectives of this review, but maternal environment impact on offspring's phenotype at adulthood will be.

Principles of the developmental origins of health and disease

In the 90's, Barker and co-workers' epidemiological studies underlined an increased risk of non-communicable metabolic diseases in people born Small-for-Gestational Age (SGA) and/or with a poor growth rate in infancy (Barker and Osmond, 1986; Hales *et al.*, 1991; Barker, 1992). These observations, referred to as "Fetal programming", suggested that fetal

and neonatal adaptations to a nutritionally poor environment induced permanent adaptations leading to a "thrifty phenotype", where the restricted individual favors energy storage and insulin resistance throughout his life. Such early and long-lasting adaptations increase the risk of developing metabolic pathologies at adulthood in the presence of excess food intake, often described as an "energy mismatch" between early life and adulthood (Hales and Barker, 1992, 2001). Subsequently, the concept of the "Predictive Adaptive Response" stated that cues about environment delivered during pregnancy to the developing organism could also induce adaptive responses that would favor long term survival in a similar environment but may be less favorable for survival in a different environment (Bateson *et al.*, 2004). This plasticity could provide an evolutionary advantage in the case of environments that change over a few generations but be deleterious in case of even faster changes, when the environment is very different between fetal and post-natal life (Gluckman *et al.*, 2009). Moreover, more recent focus on obesity has shown that excess maternal body weight and adiposity also induced fetal adaptations leading to adverse outcomes at adulthood that are curiously close to that observed with growth retardation.

It is now generally admitted that components of human obesity, type-2 diabetes (T2D) and hypertension, but also bone health (Goodfellow *et al.*, 2010), psychiatric health (Khandaker *et al.*, 2012) and fertility (Faure *et al.*, 2015) take root during early development, throughout gestation and lactation, as stated in the "Developmental Origins of Health and Disease" (DOHaD) hypothesis (<http://www.mrc.soton.ac.uk/dohad/>). Indeed, many studies in humans and animals have demonstrated that an individual's nutritional and hormonal status during fetal development and early life plays an important role for his long-term control of energy metabolism (Barker, 1995; McMillen *et al.*, 2008). Epidemiological and experimental reports indicate that epigenetic mechanisms are the link between early life events and health later in life, with epigenetic marks being considered as long-lasting environmental cues (Gabory *et al.*, 2011). Animals are affected by this process, which can also affect traits related to production, such as lactation, meat quality and other production traits (Wu *et al.*, 2006; Kenyon and Blair, 2014; Fig. 1).

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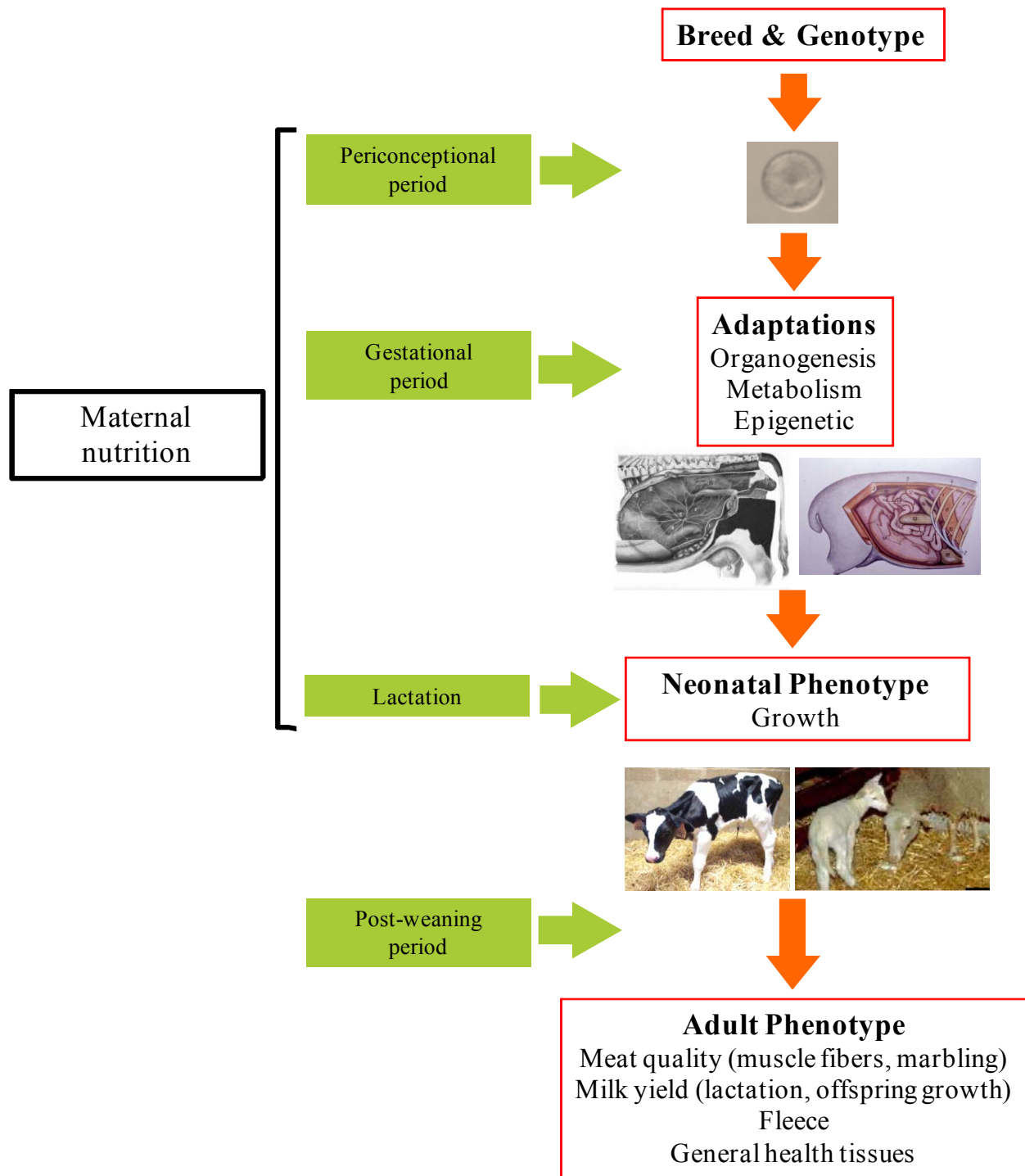


Figure 1. Principles of the developmental origins of health and disease.

DOHaD and the quality of products

It is only recently that studies have started to explore the effects of maternal nutrition during pregnancy on livestock performance in mammals. Although considerable effort has been directed towards defining nutrient requirements of animals over the past

30 years, suboptimal nutrition during gestation remains a significant problem for many farm animal species as well worldwide (including cattle, pigs, and sheep; Wu *et al.*, 2004). Ruminants have been the main focus of research, but data in pigs, rabbits and horses also exist. Major observed effects, as detailed below, are summarized in Fig. 2.

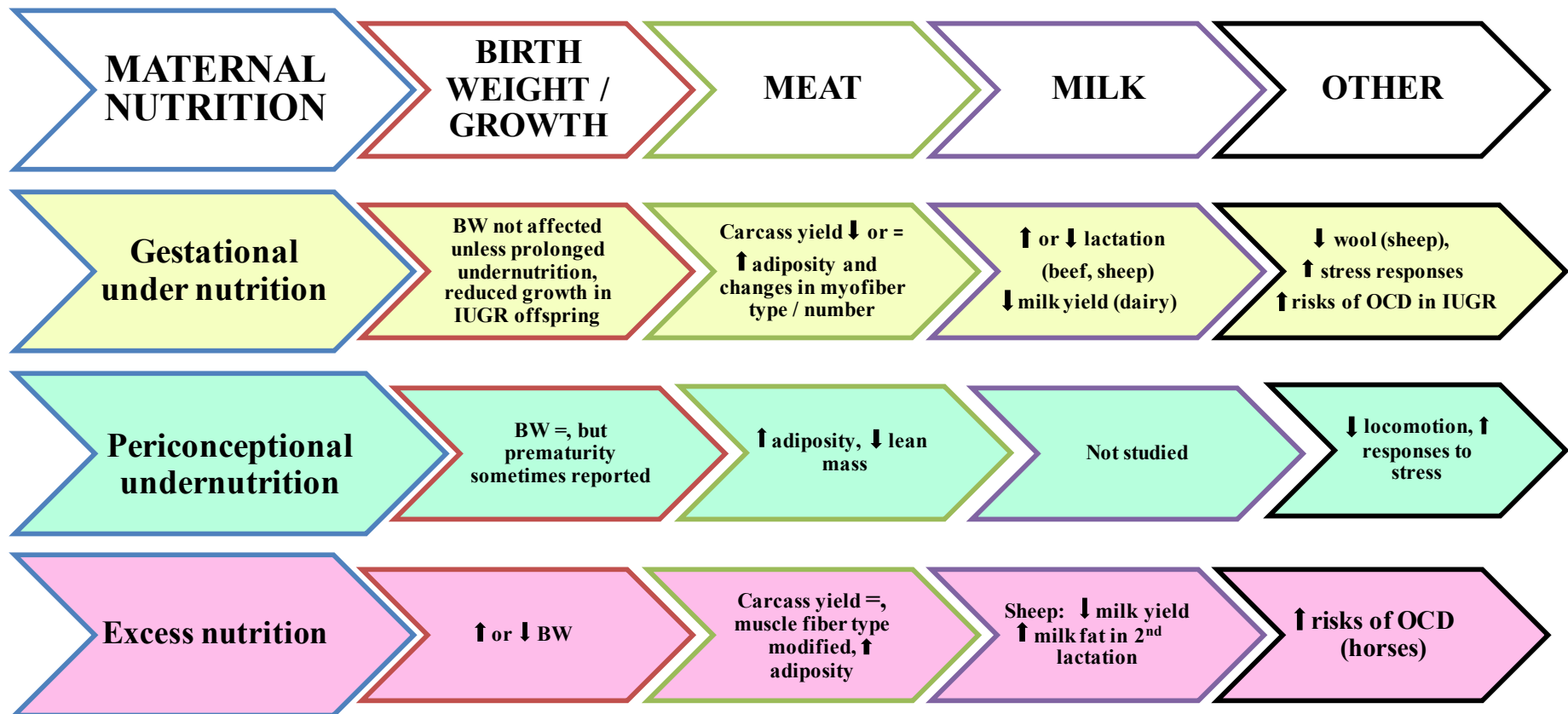


Figure 2. Main effects observed on production traits after maternal undernutrition or overnutrition during gestation, or after periconceptual undernutrition. BW = birthweight; IUGR = intra-uterine growth retardation; OCD = osteochondrosis.



Growth

Growth and attainment of adult size is essential for production. Adult size is dependent on the genetics of the individual, but will be modulated by nutrition and environmental parameters at large. Already in the 1970's, McCance and Widdowson demonstrated that "critical periods" of undernutrition in the prenatal or immediate post-natal period can lead to growth retardation that cannot be recovered by subsequent catch-up growth (McCance, 1976). More studies using animal models have shown how intra-uterine growth restriction and post-natal under-nutrition can restrict offspring size as adults (Desai *et al.*, 2005; Bieswal *et al.*, 2006). In ruminants, undernutrition during the first half of gestation, although birth weight was usually not affected, was shown to impact metabolic function of sheep and cattle offspring, resulting in altered production and body composition later in life (Ford *et al.*, 2007; Long *et al.*, 2010, 2012). Undernutrition of ~75% of recommended allowance during early stages of pregnancy compromises placental angiogenesis, cotyledon weight, and thus, fetal development (Zhu *et al.*, 2007), with significant impact on development and function of liver and pancreas (Symonds *et al.*, 2010). Overnutrition can also restrict placental and fetal development, resulting in decreased birth weights, post-natal growth, and altered body composition (Caton *et al.*, 2007). Protein imbalance, with dams either nutrient restricted or supplemented with proteins, affects the development of the fetus through gestation, driving to born-too-thin or overweight neonates, respectively, both in bovine and ovine models (Funston *et al.*, 2010).

Beef cattle - In order to reduce fetal growth, severe maternal undernutrition is required for at least a third or half of pregnancy in beef cattle (Greenwood and Cafe, 2007; Martin *et al.*, 2007). Fetal growth restriction, however, may also result from twinning, excess heat and is observed in heifers as opposed to multiparous animals (Greenwood and Cafe, 2007). Intra-uterine growth retardation (IUGR) due to maternal food restriction throughout gestation (difference of 10 kg at birth) was shown to lead to reduced post-natal growth (Greenwood and Cafe, 2007). Moreover, undernutrition during the last third of pregnancy will decrease birth weights with a potential negative impact on long-term growth and body composition of the progeny (Underwood *et al.*, 2010).

Dairy cattle - While growth (2 years old cows) and milk production of the dam have clear implications for development of the fetus (Banos *et al.*, 2007), diet during pregnancy is the primary modifiable factor that has a substantial influence on body condition and energy status of the dairy cattle as well as viability and body composition of newborn calves. Like in beef cattle, reduced post-natal growth was observed in naturally occurring low birth weight Holstein calves (Swali and Wathes, 2006).

Sheep - Effects of maternal dietary level and timing in sheep have been recently very thoroughly reviewed (Kenyon and Blair, 2014). Like in cattle, maternal undernutrition generally does not reduce birth weight, although offspring may be lighter at weaning, in particular when undernutrition has been prolonged until term (Kelly *et al.*, 1996, 2006; Field *et al.*, 2015). Variation in the effects of undernutrition may also depend on the breed, or genetic / epigenetic background. Indeed, maternal undernutrition from 28 et 78 days of pregnancy did not reduce fetal weight in "Baggs" ewes which originated from a nomadic herd living in harsh conditions, whereas reduced fetal weight was observed in ewes bred for several generations in good conditions at the University of Wyoming (Vonnahme *et al.*, 2006). These differences were accompanied with different placental responses to undernutrition, with earlier placental maturation in the "Baggs" ewes (Vonnahme *et al.*, 2006). Heat stress during pregnancy also induces IUGR in sheep (Barry *et al.*, 2008). In the field, the combination of maternal heat stress and undernutrition during pregnancy reduces lamb birth weight in ewes, which seem to better adapt to restricted feeding than to thermal stress (Sejian *et al.*, 2011).

Overfeeding may also be harmful. As a result of dietary induced obesity in ewes, fetuses at mid-gestation were macrosomic, hyperglycemic, hyperinsulinemic with markedly increased pancreatic weight and β -cell numbers compared with fetuses of ewes fed to requirements (MacLaughlin *et al.*, 2005; George *et al.*, 2010; Zhang *et al.*, 2011a). Although they were still hyperglycemic at birth, the insulin secretion was blunted with decreased pancreatic growth and β -cell numbers by the end of gestation (Zhang *et al.*, 2011a).

Horse - In the horse, fetal growth is limited mainly by the uterine size of the dam, as shown by experiments using artificial insemination or embryo transfer in horses of different size (Walton and Hammond, 1938; Tischner, 2000; Allen *et al.*, 2002, 2004; Peugnet *et al.*, 2014, 2015b). These works have demonstrated the importance of fetal growth for the achievement of the expected adult size, with growth retarded foals being permanently affected in terms of growth, at least for some bone segments. This is of particular importance in these species, where reduced adult size will limit access to studbooks and to some sporting events, and may affect performance. Similar experiments in sheep indicate that these effects on birth weight are not driven by changes in maternal insulin sensitivity during pregnancy (Oliver *et al.*, 2015).

In the horse, similar to what was described in sheep, maternal overnutrition is reported to reduce glucose uptake and reduce growth rate of two thirds of pregnancy (Satterfield *et al.*, 2010). In equidae, however, maternal undernutrition does not seem to affect birthweight nor subsequent growth, at least until



weaning (Wilsher and Allen, 2006; Ousey *et al.*, 2008; Peugnet *et al.*, 2015a), which does not preclude effects on performance (Rossdale and Ousey, 2003).

Meat quality

Meat quantity depends on the muscle mass whereas meat quality will depend on muscle fibers, which play an important role for tenderness (Guillemin *et al.*, 2009) and the intramuscular fat, which is a major component of flavor. Different levels of intramuscular fat will be looked for according to cultures and cooking traditions.

The fetal period is crucial for skeletal muscle development, because no net increase in the number of muscle fibers occurs after birth in farm animals (Greenwood *et al.*, 2000; Nissen *et al.*, 2003). Myogenesis takes place during several chronologically distinct phases occurring in fetal life: proliferation of precursor cells (myoblasts), fusion of myoblasts into differentiated multinuclear cells (myotubes), and differentiation of these cells into muscle fibers. Myotube formation gives rise to primary and secondary muscle fibers, respectively. Muscle fiber generations are set up around the last third of gestation in larger species - day 180 in cattle (term = 280-284 days), around 90 days in pigs (term = 115 days) and in the early post-natal period in less mature species such as rabbits (first month after birth) and there is no increase in muscle fibers thereafter (Stickland, 1978; Picard *et al.*, 2002; Oksbjerg *et al.*, 2004). Therefore, a reduction in the number of muscle fibers during fetal development will lead to reduced muscle mass in the adult. Fiber type is also important for production: slow oxidative fibers (Type I) originate from primary muscle fibers, and fast, type II myofibers, which mostly develop from secondary fibers, mature into type IIA (fast-oxidative glycolytic) or IIB (fast-glycolytic) fibers. Type II fibers are more efficient in terms of growth (Du *et al.*, 2010), but oxidative, and more so, slow oxidative fibers, are generally more likely to produce more tender meat, although there are clear discrepancies between different muscles (Guillemin *et al.*, 2009).

Intramuscular fat (marbling) is dependent on the presence of intramuscular adipocytes. Adipocytes originate primarily from mesenchymal cells in fetal life around mid-gestation at the same time when secondary muscle fibers are produced (Du *et al.*, 2010), but ontogenesis still needs to be completely elucidated (Boone *et al.*, 2000; Hocquette *et al.*, 2010), although intramuscular adipogenesis can be modified through maternal nutrition during pregnancy in sheep (Tong *et al.*, 2008). Triglycerides are initially stored within the muscle fibers and then, in the immediate postnatal period, intramuscular adipocytes will increase in size and volume (Hocquette *et al.*, 2010). The hyperplasia of adipocytes is an important factor for marbling during growth (Hocquette *et al.*, 2010).

Maternal undernutrition

Beef cattle - Severe maternal undernutrition leading to fetal growth restriction in beef cattle significantly reduces postnatal growth compared to controls but was not shown to affect muscle fiber characteristics, carcass composition and retail yield at similar carcass weight (Greenwood and Cafe, 2007). In regions where droughts are common, however, cows may experience periods of undernutrition during pregnancy, which may affect meat quality. Traditionally, they are supplemented in late gestation but not earlier (Du *et al.*, 2010). In these harsh conditions, protein supplementation of pregnant cows in mid-gestation (day 60 to 180), or improvement of the pastures through irrigation, however, was shown to increase lean growth and reduce fat in offspring (Du *et al.*, 2010). In a study using Angus x Gelbvieh cattle, Long *et al.* (2012) found no effect of maternal global undernutrition with or without protein supplementation during the first half of pregnancy on body weight or organ weight at slaughter (around 1.5 years of age). The ratio of semitendinosus muscle to carcass weight, however, tended to be reduced in the offspring from non-supplemented undernourished dams, with average adipocyte size increased in several anatomical locations (Long *et al.*, 2012). The effect of increased or reduced maternal protein intake on offspring skeletal muscle development, however, is dependent on the timing of the supplementation during pregnancy as well as the sex of the offspring, as demonstrated in beef heifer offspring (Micke *et al.*, 2011): as adults, males born to heifers fed a low protein diet during the first trimester of pregnancy and subsequently a high protein diet had greater *longissimus dorsi* muscle cross-sectional area compared to those whose dams were exposed to continuous high protein diet, whereas there was no effect of maternal protein intake on the female offspring. In contrast, maternal protein restriction in the second trimester was associated with higher *longissimus dorsi* muscle cross-sectional area in male and female offspring (Micke *et al.*, 2011) although there was no effect on the *longissimus dorsi* weight/carcass weight ratio (Micke *et al.*, 2010). These changes were associated with changes in the muscle expression of insuline-like growth factors IGF1 and IGF2 and their receptors (Micke *et al.*, 2010, 2011).

Dairy cattle - In dairy cattle, conception usually takes place during early lactation, and thus lactating dams are in relative energy deficit compared to non-lactating dams (Funston and Summers, 2013). In a retrospective study of more than 1500 dairy calves, the size of the dam and its milk yield were shown to be the two most important factors influencing birth weight, with lower birth weights of calves born to high yielding cows with similar body size (Kamal *et al.*, 2014). When heifers and cows were compared in a small number of Holstein females, maternal parity did not affect girth,



birthweight nor glucose metabolism in the first month post-partum, although the birthweight and withers height of first born calves were reduced (Bossart *et al.*, 2014).

Sheep - In sheep, several studies indicate that maternal undernutrition in the early stages of pregnancy can affect meat quality, although birth weight is not always affected (Kenyon and Blair, 2014). Indeed, an extended period of maternal nutrient restriction during the first half of gestation results in relatively normal birth weights, but leads to increases in the length and thinness of the neonates, increased adiposity, and suppressed glucose tolerance (Whorwood *et al.*, 2001; Ford *et al.*, 2007). Moreover, carcass weight quality appears to be affected more by genetic background and litter size at birth than by maternal nutrition, except when undernutrition lasts most of the gestation (Kenyon and Blair, 2014). Indeed, the placenta adapts to the nutritional environment to minimize nutritional consequences to the fetus, although the extent of its adaptive capacities depend on the timing and intensity of the nutritional insult (Fowden *et al.*, 2008; Symonds *et al.*, 2012).

Restricted fetal nutrition throughout gestation as experienced by ewes during twin pregnancies leads to increased fetal adiposity (Edwards *et al.*, 2005). Undernutrition of twin-bearing ewes throughout pregnancy led to low-birthweight lambs that remained smaller until adolescence and had poor energetic efficiency (Husted *et al.*, 2007). Moreover, offspring were shown to have disturbed responses to fasting at 6 months of age in terms of leptin (reduced), IGF1 and cortisol (increased; Kongsted *et al.*, 2013). When low (mean 2.29 kg) and high (mean 4.84 kg) birthweight lambs were compared, although the weight of the *semitendinosus* muscle was very significantly decreased in low birthweight lambs, the number of myofibers was similar but the fact that low birthweight lambs did not catch up in muscle growth may be due to the reduced myonuclei number (Greenwood *et al.*, 1998, 2000).

Like in cattle, however, the timing of undernutrition matters and numerous nutritional planes have been studied, using animals of different breeds, making comparisons rather difficult (Kenyon and Blair, 2014). If most undernutrition studies do not indicate a strong effect on post-weaning liveweight, higher adiposity has been sometimes observed (Kenyon and Blair, 2014). In ewes undernourished in early gestation, term fetuses had more adipose tissue compared to controls that were fed *ad libitum* (Bispham *et al.*, 2003), which is associated with increased glucocorticoid sensitivity (Gnanalingham *et al.*, 2005; Mostyn and Symonds, 2009). In another study, castrated males at 8 months of age born to white face dams that were nutritionally restricted to 50% of requirements from day 28 to 78 of pregnancy had heavier carcass weight than controls, but intra-abdominal fat deposits were also heavier and intramuscular triglyceride contents were

increased as a result of the reduction of the activity of carnitine palmitoyltransferase-1, which is involved in fatty-acid oxidation (Zhu *et al.*, 2006; Ford *et al.*, 2007). Moreover, the total number of muscle myofibers was decreased with an increased ratio of IIB fibers (fast-glycolytic fibers) in muscle (Zhu *et al.*, 2006). Similar findings were observed in another study where only twin animals were selected, with males and females analyzed separately (Daniel *et al.*, 2007). This is an important point, as clear differences have been shown according to sex and litter size for many physiological parameters (MacLaughlin *et al.*, 2010; Tarrade *et al.*, 2015).

Pigs - In pigs, moderate IUGR is not always associated with a modification in carcass composition but very small piglets have slower growth and fatter carcasses than controls (Powell and Aberle, 1980; Mostyn and Symonds, 2009; Morise *et al.*, 2011). Low birthweight piglets are also characterized by a reduced number of enlarged myofibers (Rehfeldt and Kuhn, 2006). Maternal undernutrition of Large White sows from mating to 50 days of pregnancy did not affect carcass weight, lean tissue and adipose tissue yield in offspring, whereas the composition of muscle in terms of myofiber types was slightly affected, with a reduced percentage of type IIB fibers (Bee, 2004). Maternal protein restriction, however, was shown to reduce the lean and increase the fat contents of offspring at 6 months of age with a tendency for reduced number of muscle myofibers associated with reduced expression of IGF2 mRNA (Rehfeldt *et al.*, 2012).

Iberian pigs, which are genetically different from modern commercial pigs, deposit more intramuscular fat and are naturally leptin resistant (Ovilo *et al.*, 2005; Munoz *et al.*, 2009), presenting what resembles a "thrifty phenotype", which has been attributed to centuries of adaptation to low quality nutrition in semi-feral conditions (Lopez-Bote, 1998). In this breed that is prone to obesity, maternal undernutrition during pregnancy reduces birthweight and increases the incidence of IUGR piglets in the litter (Gonzalez-Bulnes *et al.*, 2012). Female offspring appear to catch-up growth to controls at weaning whereas males are still growth-retarded at weaning (Gonzalez-Bulnes *et al.*, 2012).

Excess maternal nutrition and obesity

Sheep - Extensive studies have shown that excess maternal nutrition retards placental and fetal growth, and increases fetal and neonatal mortality in sheep (Wallace *et al.*, 2003). Excess maternal nutrition increases mid-gestation fetal weight (Ford *et al.*, 2009). Lamb birth weight is similar to controls (Wallace *et al.*, 2005; Zhu *et al.*, 2009) or increased (Kenyon *et al.*, 2011) according to the extent of the overfeeding and breed, but subsequent growth is similar (Kenyon *et al.*, 2011). Maternal obesity, however, down-regulates



myogenesis through the Wnt/ β -catenin signaling pathway (Tong *et al.*, 2009).

Pigs - In pigs, excess maternal nutrition from mating to 50 days of pregnancy increased the adipose tissue yield in the offspring carcasses, without affecting overall carcass weight and lean yield, although muscle fiber type was modified (Bee, 2004). In another study, both reduced (50%) and excess (250%) maternal protein intake during pregnancy reduced piglet birthweight and birthweight/crown-rump length, reflecting adiposity (Rehfeldt *et al.*, 2011). These effects, however, were not observed in fetuses at mid-pregnancy, indicating that placental insufficiency leading to IUGR had occurred in the second half of pregnancy (Rehfeldt *et al.*, 2011). Offspring of dams fed a protein excess, however, did not differ from controls for muscle myofiber numbers and adipose tissue at 6 months of age (Rehfeldt *et al.*, 2012).

In conclusion to this chapter, the favored fat development and reduced number in muscle myofibers mostly observed in maternal undernutrition experiments have been associated with changes in expression of insulin-like growth factors (IGFs; Mücke *et al.*, 2011), Growth hormone (Rehfeldt and Kuhn, 2006), transcription factors involved in adipogenesis such as the Peroxisome Proliferator-Activated receptor gamma (PPAR γ ; Tong *et al.*, 2008, 2009) and nutrient sensors such as mTOR. Indeed, the main regulators of adipogenesis are the peroxisome proliferator activated receptor (PPAR α) and CCAAT -enhancer binding protein (C/EBP; Hausman *et al.*, 2009). Moreover, fetal fat development may be favored by disturbed maternal plasma cortisol (reduced in undernourished pregnant sheep (Debus *et al.*, 2012) or increased in pregnant sows fed a low protein diet (Otten *et al.*, 2013)) observed during nutritional restrictions (Symonds *et al.*, 2012).

Lactation

So far, the amount of data on the fetal programming of offspring lactation through the manipulation of maternal nutrition in domestic animals remains limited. Hence, in this part, the effects of under and over-nutrition are treated together. The organogenesis of the mammary gland begins early in pregnancy (Hovey *et al.*, 2002; Houdebine, 2003) and may therefore be affected by maternal nutrition like other organs.

Beef cattle - In beef cattle, slower growing female calves whose dams have poor lactations tend to produce better lactation when they are adults and have offspring with faster growth, which in turn have reduced quality lactation as adults (Koch, 1972; Pala and McCraw, 2005).

Dairy cattle - In dairy cattle, the analysis of data available on the UK national fertility database and from Irish dairy cows showed that offspring from dams producing more milk before and during conception had

reduced milk yields, increased somatic cell count and were culled earlier compared to those born to dams with lower milk yields (Banos *et al.*, 2007; Berry *et al.*, 2008). Similar observations were made in Spain, which showed that females born to dams that were lactating during early pregnancy produced significantly less milk compared to those born to dams that were not lactating and that this reduction in milk production was correlated to maternal production (Gonzalez-Recio *et al.*, 2012).

Sheep - Kenyon and Blair (2014) have reviewed the effects of maternal nutrition on milk production in sheep. Maternal undernutrition from day 21 to 50 was shown to reduce the mammary gland weight in fetuses near term (Martín *et al.*, 2012) and reduce milk production at first lactation (Paten *et al.*, 2013). In contrast, fetal mammary duct density and fat production in milk in the second lactation was increased in female sheep born to dams that were fed *ad libitum* during pregnancy (1.5 times maintenance) compared to those born to control dams fed to maintenance (Blair *et al.*, 2010). Nevertheless, the mammary mass was increased in the offspring of the maintenance group, and these offspring produced more protein and lactose, only in the first lactation at 2 years of age (Blair *et al.*, 2010). The authors suggest that these effects limited to the first lactation may be the result of an "Adaptive Predictive Response", as defined above, where the "restricted" offspring would favor the survival of their own first offspring, with no investment in further lactations when the survival of the individual would be more hazardous. As a consequence, second generation effects were hence observed in two studies where grand-daughters of ewes fed a moderate diet during pregnancy were heavier at birth compared to the grand-daughters of dams that were fed *ad libitum* during pregnancy (van der Linden *et al.*, 2009; Blair *et al.*, 2010). Interestingly, this effect was confirmed in farmed minks bred for fur, when grand-mothers were protein restricted (Matthiesen *et al.*, 2010).

Fleece

Fleece weight in sheep is affected by body size, which induces confounding factors for the analysis of maternal effects of this parameter and may explain why a reduction in fleece has been reported in response to maternal undernutrition (Schinckel and Short, 1961; Kenyon and Blair, 2014). One study reported a change in hair follicle number, however, which could persist throughout the life of the animal (Schinckel and Short, 1961).

General health issues

Thermogenesis - In the newborn sheep, brown adipose tissue (BAT, representing 1-2% of birthweight; Symonds and Lomax, 1992) is essential for ensuring effective adaptation to the extrauterine environment, in



particular thermogenesis. Neonatal pigs and horses, although they possess BAT (Ousey, 1997; Mostyn *et al.*, 2014), are much more dependent on shivering thermogenesis to maintain heat production during cold exposure. Gestational BAT development depends on transplacental glucose supply to the fetus (Symonds *et al.*, 2012). In contrast to rodents, brown fat, although present at birth, is very reduced in adult large animals as most BAT is progressively replaced by white fat (Symonds *et al.*, 2012). Moreover, it may not have the same myoblastic origin as white fat (Budge *et al.*, 2009).

Behavior – Few studies have focused on the impact of maternal nutrition on offspring behavior in large animals, although alterations in food intake and response to stress may be important to the breeding industry.

Food restriction in late gestation in sheep was shown to decrease voluntary milk intake in lambs from 3 to 60 days of age (Geraseev *et al.*, 2006) whereas, in another study, feed intake was not affected after weaning (Sibbald and Davidson, 1998). In dairy goats, no effects were observed in feeding behavior and stress responses in male kids before weaning (Laporte-Broux *et al.*, 2011). Although no effects on feeding behavior in females at one year of age, at 2 years of age, the cortisol response to ACTH injection was increased in offspring from restricted dams, suggesting a higher susceptibility to stress (Laporte-Broux *et al.*, 2012). Similarly, in pigs born to dams fed a low protein diet during pregnancy, cortisol response to weaning was increased and the medulla area within the adrenal was increased (Otten *et al.*, 2013).

Osteoarticular pathology - In horses, although maternal undernutrition does not affect birth weight, epidemiological and experimental data indicate that IUGR due to transfer of saddle embryos into ponies (Peugnet *et al.*, 2014), but also feeding mares with concentrates during gestation (Van der Heyden *et al.*, 2013; Peugnet *et al.*, 2015a), may be associated with an increased risk of developing lesions of osteochondrosis in their foal, which is of strong economical importance for the horse industry. Since osteochondrosis is related to glucose/insulin metabolism, the effects may be linked to the observed trend for a reduced insulin sensitivity at 5 days of age in offspring of mares fed a high starch diet (George *et al.*, 2009). More work is currently on-going in the authors' laboratory to explore this phenomenon.

Periconceptual programming

The developmental plasticity of embryos in the pre-implantation period leads to different embryo, fetoplacental and post-natal responses to the environment (Laguna-Barraza *et al.*, 2012). Specific targeting of the periconceptual period for experiments on maternal nutrition in large animals use different timing for the nutritional challenge, making it difficult to draw

comparisons, although there are a lot of data available in model species and humans, which have been reviewed elsewhere (Watkins *et al.*, 2010; Zhang *et al.*, 2011b; Fleming *et al.*, 2012; van Montfoort *et al.*, 2012; Steegers-Theunissen *et al.*, 2013; Lane *et al.*, 2015). Experiments using embryo transfer between a nutritionally challenged oocyte or embryo donor have also provided valuable insight into periconceptual effects. So far, most data on farm animals have been generated in sheep.

Using embryo transfer, it was shown that B12 vitamin and folate deficiency in embryo donor ewes and transfer of these embryos in control females induces excess weight and adiposity in sheep offspring, insulin resistance, increased blood pressure and altered response to immunological challenges, as well as differences in liver methylation (Sinclair *et al.*, 2007). The transfer of embryos, collected from restricted or obese ewes maintained in the same nutritional plane or induced to loose or gain weight in the last month before mating and for the pre-implantation period, into control recipients, showed that maternal restriction in the periconceptual period, regardless of previous nutritional status, resulted in adrenocortical hypertrophy (Zhang *et al.*, 2013b) together with changes in the renin-angiotensin system regulation within the adrenal (Zhang *et al.*, 2013a). Periconceptual undernutrition was shown to induce an increment in the body weight and the oocyte population of the offspring, as well as an alteration of their locomotor activity (Abecia *et al.*, 2014).

Like for general nutrition, the effects of maternal undernutrition around conception vary depending on the number of implanted embryos. First, maternal weight loss as a result of periconceptual undernutrition in sheep has been shown to reduce twinning rate (MacLaughlin *et al.*, 2005; Debus *et al.*, 2012; Abecia *et al.*, 2014). In general, birth weight is not directly affected by periconceptual nutrition. Indeed, uterine blood flow is increased by 13% in ewes that were undernourished during the periconceptual period compared to controls (Rumball *et al.*, 2008) with increased expression of growth factors (Zhu *et al.*, 2007).

Effects of periconceptual (-60 days before to 7 days after conception) or pre-implantation (0-7 days after conception) nutrition were observed on fetal skeletal muscle insulin signaling, lipogenesis, adipose tissue and liver metabolism as well as miRNA expression, depending on twin or singletons pregnancy (Lie *et al.*, 2012, 2013, 2014). The timing and importance of fetal pre-partum ACTH and cortisol increases as well as gestational length were shown to differ depending on embryo number, with reduced gestation duration only in singletons (Edwards *et al.*, 2002, 2004; Edwards and McMillen, 2002; Bloomfield *et al.*, 2003). These effects may be related to the increased weight and disturbed function in the adrenal



observed in singletons in these and other studies (Connor *et al.*, 2009; Williams-Wyss *et al.*, 2014). Responses to glucocorticoids are also affected: hypothalamic glucocorticoid receptor promoter methylation, as well as gene and protein expression, were still observed in 5 year old male and female offspring, which could explain the increased obesity observed in these animals (Begum *et al.*, 2013). Regardless of singleton or twin status, the cardiovascular function was impaired in adult sheep (Gardner *et al.*, 2004; Torrens *et al.*, 2009).

Twins are generally smaller than singletons. Using an elegant approach of fetal reduction during pregnancy, Hancock *et al.* (2012) have shown that twins had lower lean mass and higher fat mass until 2 years of age compared to their contemporary singletons. Twin reduction to singleton pregnancy at 42-43 days of gestation did not recover the programmed twin fat and lean mass phenotype, indicating the early origin of these traits (Hancock *et al.*, 2012).

As mentioned earlier, the genetic background of the animals induces large differences in the response to undernutrition. For example, gestational length was increased by periconceptual undernutrition only in twin-bearing Welsh mountain ewes carrying fetuses of opposite sex (Cleal *et al.*, 2007). In another study, maternal periconceptual undernutrition did not reduce birth weight nor gestational length in the hardy Mediterranean breed Merinos d'Arles (Debus *et al.*, 2012). Nevertheless, increased post-natal adiposity was observed in males but not in females, underlining the importance of offspring sex as well as litter size and breed (Debus *et al.*, 2012).

In terms of response to post-natal nutritional treatment, it is interesting to observe that maternal nutrition at the time of conception was shown to directly affect lamb responses to nutritional supplementation with n-3 polyunsaturated fatty acid (PUFA)-enriched diets: offspring of dams fed a high n-6 fatty acid-rich diet for 6 weeks before mating had lower responses to algae supplementation (n-3 PUFA-enriched diet) compared to those born to control dams (Clayton *et al.*, 2014).

In terms of behavior, maternal restriction from 60 days before to 30 days after the beginning of pregnancy was reported to be associated with decreased locomotion in 18 month old offspring (Donovan *et al.*, 2013) whereas locomotion and attempts to escape were decreased during isolation after maternal periconceptual undernutrition, possibly reflecting decreased responses to stress (Hernandez *et al.*, 2010; Abecia *et al.*, 2014).

Conclusions

The pre- and periconceptual periods are critical in the context of the Developmental Origins of Health and Disease (DOHaD). Maternal *in vivo*

environment, in particular nutrition, can disturb the apposition of epigenetic marks throughout gametogenesis, fertilization and the first steps of embryonic development, which are times during which major epigenetic changes take place (Jammes *et al.*, 2011). These marks will subsequently affect organ function during development, resulting in alterations in the post-natal phenotype (Watkins *et al.*, 2008; Watkins *et al.*, 2010). The *in vitro* environment, in the case of assisted reproduction techniques, also affects epigenetic marks. Whilst the embryo is a target of these changes, female and male gametes are both target and vector of these epigenetic changes, thus leading to multigenerational effects, so that long-term consequences on the phenotype of offspring vary according to the sex of the vector parent, the sex of the individual and the generation (Aiken and Ozanne, 2014).

More work is needed to understand how the environment modulates the genomic inheritance in order to induce a phenotype and how this may be used in agriculture to lead to more robust animals able to tackle the climatic challenges that we will be facing in the future.

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References

- Abecia JA, Casao A, Pascual-Alonso M, Lobón S, Aguayo-Ulloa LA, Meikle A, Forcada F, Sosa C, Marín RH, Silva MA, Maria GA. 2014. The effect of periconceptual undernutrition of sheep on the cognitive/emotional response and oocyte quality of offspring at 30 days of age. *J DOHaD*, 5:79-87.
- Aiken CE, Ozanne SE. 2014. Transgenerational developmental programming. *Hum Reprod Update*, 20:63-75.
- Allen WR, Wilsher S, Turnbull C, Stewart F, Ousey J, Rossdale PD, Fowden AL. 2002. Influence of maternal size on placental, fetal and postnatal growth in the horse. I. Development in utero. *Reproduction*, 123:445-453.
- Allen WR, Wilsher S, Tiplady C, Butterfield RM. 2004. The influence of maternal size on pre- and postnatal growth in the horse. III. Postnatal growth.



Reproduction, 127:67-77.

Banos G, Brotherstone S, Coffey MP. 2007. Prenatal maternal effects on body condition score, female fertility, and milk yield of dairy cows. *J Dairy Sci*, 90:3490-3499.

Barker DJP, Osmond C. 1986. Infant mortality, childhood nutrition and ischaemic heart disease in England and Wales. *Lancet*, 327:1077-1081.

Barker DJ. 1992. The fetal origins of diseases of old age. *Eur J Clin Nutr*, 46(suppl. 3):S3-9.

Barker DJP. 1995. Intrauterine programming of adult disease. *Mol Med Today*, 1:418-423.

Barry JS, Rozance PJ, Anthony RV. 2008. An animal model of placental insufficiency-induced intrauterine growth restriction. *Semin Perinatol*, 32:225-230.

Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, Gluckman P, Godfrey K, Kirkwood T, Lahr MM, McNamara J, Metcalfe NB, Monaghan P, Spencer HG, Sultan SE. 2004. Developmental plasticity and human health. *Nature*, 430(6998):419-421.

Bee G. 2004. Effect of early gestation feeding, birth weight, and gender of progeny on muscle fiber characteristics of pigs at slaughter. *J Anim Sci*, 82:826-836.

Begum G, Davies A, Stevens A, Oliver M, Jaquiere A, Challis J, Harding J, Bloomfield F, White A. 2013. Maternal undernutrition programs tissue-specific epigenetic changes in the glucocorticoid receptor in adult offspring. *Endocrinology*, 154:4560-4569.

Berry DP, Lonergan P, Butler ST, Cromie AR, Fair T, Mossa F, ad Evans ACO. 2008. Negative influence of high maternal milk production before and after conception on offspring survival and milk production in dairy cattle. *J Dairy Sci*, 91:329-337.

Bieswal F, Ahn MT, Reusens B, Holvoet P, Raes M, Rees WD, Remacle C. 2006. The importance of catch-up growth after early malnutrition for the programming of obesity in male rat. *Obesity (Silver Spring)*, 14:1330-1343.

Bispham J, Gopalakrishnan GS, Dandrea J, Wilson V, Budge H, Keisler DH, Pipkin FB, Stephenson T, Symonds ME. 2003. Maternal endocrine adaptation throughout pregnancy to nutritional manipulation: consequences for maternal plasma leptin and cortisol and the programming of fetal adipose tissue development. *Endocrinology*, 144:3575-3585.

Blair HT, Jenkinson CMC, Peterson SW, Kenyon PR, van der Linden DS, Davenport LC, Mackenzie DDS, Morris ST, Firth EC. 2010. Dam and granddam feeding during pregnancy in sheep affects milk supply in offspring and reproductive performance in grand-offspring. *J Anim Sci*, 88:E40-E50.

Bloomfield FH, Oliver MH, Hawkins P, Campbell M, Phillips DJ, Gluckman PD, Challis JRG, Harding JE. 2003. A periconceptional nutritional origin for noninfectious preterm birth. *Science*, 300(5619):606.

Boone C, Mourou J, Grégoire F, Remacle C. 2000.

The adipose conversion process: regulation by extracellular and intracellular factors. *Reprod Nutr Dev*, 40:325-358.

Bossaert P, Franssen E, Langbein A, Stalpaert M, Vandebroek I, Bols PE, Leroy JL. 2014. Effects of parity and periconceptional metabolic state of Holstein-Friesian dams on the glucose metabolism and conformation in their newborn calves. *Animal*, 8:975-981.

Budge H, Sebert S, Sharkey D, Symonds ME. 2009. Session on 'Obesity'. Adipose tissue development, nutrition in early life and its impact on later obesity. *Proc Nutr Soc*, 68:321-326.

Caton JS, Grazul-Bilska AT, Vonnahme KA, Luther JS, Lardy GP, Hammer DA, Redmer D, Reynolds LP. 2007. Nutritional management during gestation: impacts on lifelong performance? In: 18th Annual Florida Ruminant Nutrition Symposium, 2007, Gainesville, FL. Gainesville, FL: UFL/IFAS. 20 pp.

Chadio S, Kotsampasi B. 2014. The role of early life nutrition in programming of reproductive function. *J Dev Orig Health Dis*, 5:2-15.

Chavatte-Palmer P, Debus N, Dupont C, Camous S. 2014. Nutritional programming and the reproductive function of the offspring. *Anim Prod Sci*, 54:1166-1176.

Clayton EH, Lamb TA, Refshauge G, Kerr MJ, Bailes KL, Ponnampalam EN, Friend MA, Hopkins DL. 2014. Differential response to an algae supplement high in DHA mediated by maternal periconceptional diet: intergenerational effects of n-6 fatty acids. *Lipids*, 49:767-775.

Cleal JK, Poore KR, Newman JP, Noakes DE, Hanson MA, Green LR. 2007. The effect of maternal undernutrition in early gestation on gestation length and fetal and postnatal growth in sheep. *Pediatr Res*, 62:422-427.

Connor KL, Bloomfield FH, Oliver MH, Harding JE and Challis JRG. 2009. Effect of periconceptional undernutrition in sheep on late gestation expression of mRNA and protein from genes involved in fetal adrenal steroidogenesis and placental prostaglandin production. *Reprod Sci*, 16:573-583.

Daniel ZC, Brameld JM, Craigon J, Scollan ND, Buttery PJ. 2007. Effect of maternal dietary restriction during pregnancy on lamb carcass characteristics and muscle fiber composition. *J Anim Sci*, 85:1565-1576.

Debus N, Chavatte-Palmer P, Viudes G, Camous S, Roséfort A, Hassoun P. 2012. Maternal periconceptional undernutrition in Merinos d'Arles sheep: 1. Effects on pregnancy and reproduction results of mothers and offspring growth performances. *Theriogenology*, 77:1453-1465.

Desai M, Gayle D, Babu J, Ross MG. 2005. Programmed obesity in intrauterine growth-restricted newborns: modulation by newborn nutrition. *Am J Physiol Regul Integr Comp Physiol*, 288:91-96.

Donovan EL, Hernandez CE, Matthews LR, Oliver MH, Jaquiere AL, Bloomfield FH, Harding JE



2013. Periconceptional undernutrition in sheep leads to decreased locomotor activity in a natural environment. *J Dev Orig Health Dis*, 4:296-299.
- Du M, Tong J, Zhao J, Underwood KR, Zhu M, Ford SP, Nathanielsz PW.** 2010. Fetal programming of skeletal muscle development in ruminant animals. *J Anim Sci*, 88:E51-60.
- Edwards LJ, Bryce AE, Coulter CL, McMillen IC.** 2002. Maternal undernutrition throughout pregnancy increases adrenocorticotrophin receptor and steroidogenic acute regulatory protein gene expression in the adrenal gland of twin fetal sheep during late gestation. *Mol Cell Endocrinol*, 196:1-10.
- Edwards LJ, McMillen IC.** 2002. Impact of maternal undernutrition during the periconceptional period, fetal number, and fetal sex on the development of the hypothalamo-pituitary adrenal axis in sheep during late gestation. *Biol Reprod*, 66:1562-1569.
- Edwards LJ, McFarlane JR, Kauter KG, McMillen IC.** 2004. Impact of maternal undernutrition before and during pregnancy on maternal and fetal leptin and fetal adiposity in singleton and twin pregnancies. *Am J Physiol Regul Integr Comp Physiol*. doi: 10.1152/ajpregu.00127.2004.
- Edwards LJ, McFarlane JR, Kauter KG, McMillen IC.** 2005. Impact of periconceptional nutrition on maternal and fetal leptin and fetal adiposity in singleton and twin pregnancies. *Am J Physiol*, 288:R39-R45.
- Faure C, Dupont C, Chavatte-Palmer P, Gautier B, Levy R, Group AC.** 2015. Are semen parameters related to birth weight? *Fertil Steril*, 103:6-10.
- Field ME, Anthony RV, Engle TE, Archibeque SL, Keisler DH, Han H.** 2015. Duration of maternal undernutrition differentially alters fetal growth and hormone concentrations. *Domest Anim Endocrinol*, 51:1-7.
- Fleming TP, Velazquez MA, Eckert JJ, Lucas ES, Watkins AJ.** 2012. Nutrition of females during the periconceptional period and effects on foetal programming and health of offspring. *Anim Reprod Sci*, 130:193-197.
- Ford SP, Hess BW, Schwobe MM, Nijland MJ, Gilbert JS, Vonnahme KA, Means WJ, Han H, Nathanielsz PW.** 2007. Maternal undernutrition during early to mid-gestation in the ewe results in altered growth, adiposity, and glucose tolerance in male offspring. *J Anim Sci*, 85:1285-1294.
- Ford SP, Zhang LR, Zhu MJ, Miller MM, Smith DT, Hess BW, Moss GE, Nathanielsz PW, Nijland MJ.** 2009. Maternal obesity accelerates fetal pancreatic beta-cell but not alpha-cell development in sheep: prenatal consequences. *Am J Physiol Regul Integr Comp Physiol*, 297:R835-R843.
- Fowden AL, Forhead AJ, Coan PM, Burton GJ.** 2008. The placenta and intrauterine programming. *J Neuroendocrinol*, 20:439-450.
- Funston RN, Larson DM, Vonnahme KA.** 2010. Effects of maternal nutrition on conceptus growth and offspring performance: implications for beef cattle production. *J Anim Sci*, 88:E205-215.
- Funston RN, Summers AF.** 2013. Effect of prenatal programming on heifer development. *Vet Clin North Am Food Anim Pract*, 29:517-536.
- Gabory A, Attig L, Junien C.** 2011. Developmental programming and epigenetics. *Am J Clin Nutr*, 94:1943S-1952S.
- Gardner DS, Pearce S, Dandrea J, Walker R, Ramsay MM, Stephenson T, Symonds ME.** 2004. Peri-implantation undernutrition programs blunted angiotensin II evoked baroreflex responses in young adult sheep. *Hypertension*, 43:1290-1296.
- Gardner DS, Ozanne S, Sinclair AJ.** 2009. Effect of the early-life nutritional environment on fecundity and fertility of mammals. *Phil Trans R Soc B*, 364:3419-3427.
- George LA, Staniar WB, Treiber KH, Harris PA, Geor RJ.** 2009. Insulin sensitivity and glucose dynamics during pre-weaning foal development and in response to maternal diet composition. *Domest Anim Endocrinol*, 37:23-29.
- George LA, Uthlaut AB, Long NM, Zhang L, Ma Y, Smith DT, Nathanielsz PW, Ford SP.** 2010. Different levels of overnutrition and weight gain during pregnancy have differential effects on fetal growth and organ development. *Reprod Biol Endocrinol*, 8:75.
- Geraseev LC, Perez JRO, Carvalho PA, Oliveira RPd, Quintão FA, Lima AL.** 2006. Efeitos das restrições pré e pós-natal sobre o crescimento e o desempenho de cordeiros Santa Inês do nascimento ao desmame. *Rev Bras Zootec*, 35:245-251.
- Gluckman PD, Hanson MA, Bateson P, Beedle AS, Law CM, Bhutta ZA, Anokhin KV, BounĒres P, Chandak GR, Dasgupta P, Smith GD, Ellison PT, Forrester TE, Gilbert SF, Jablonka E, Kaplan H, Prentice AM, Simpson SJ, Uauy R, West-Eberhard MJ.** 2009. Towards a new developmental synthesis: adaptive developmental plasticity and human disease. *Lancet*, 373:1654-1657.
- Gnanalingham MG, Mostyn A, Symonds ME, Stephenson T.** 2005. Ontogeny and nutritional programming of adiposity in sheep: potential role of glucocorticoid action and uncoupling protein-2. *Am J Physiol Regul Integr Comp Physiol*, 289:R1407-R1415.
- Gonzalez-Bulnes A, Ovilo C, Lopez-Bote CJ, Astiz S, Ayuso M, Perez-Solana ML, Sanchez-Sanchez R, Torres-Rovira L.** 2012. Gender-specific early postnatal catch-up growth after intrauterine growth retardation by food restriction in swine with obesity/leptin resistance. *Reproduction*, 144:269-278.
- Gonzalez-Recio O, Ugarte E, Bach A.** 2012. Trans-generational effect of maternal lactation during pregnancy: a Holstein cow model. *Plos One*, 7:e51816.
- Goodfellow LR, Earl S, Cooper C, Harvey NC.** 2010. Maternal diet, behaviour and offspring skeletal health. *Int J Environ Res Public Health*, 7:1760-1772.
- Greenwood PL, Hunt AS, Hermanson JW, Bell AW.** 1998. Effects of birth weight and postnatal nutrition on



- neonatal sheep. I. Body growth and composition, and some aspects of energetic efficiency. *J Anim Sci*, 76:2354-2367.
- Greenwood PL, Hunt AS, Hermanson JW, Bell AW.** 2000. Effects of birth weight and postnatal nutrition on neonatal sheep. II. Skeletal muscle growth and development. *J Anim Sci*, 78:50-61.
- Greenwood PL, Cafe LM.** 2007. Prenatal and pre-weaning growth and nutrition of cattle: Longterm consequences for beef production. *Animal*, 1:1283-1296.
- Guillemin N, Cassar-Malek I, Hocquette JF, Jurie C, Micol D, Listrat A, Leveziel H, Renand G, Picard B.** 2009. La maîtrise de la tendreté de la viande bovine: identification de marqueurs biologiques. *INRA Prod Anim*, 22:331-344.
- Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD.** 1991. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ*, 303:1019-1022.
- Hales CN, Barker DJ.** 1992. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*, 35:595-601.
- Hales CN, Barker DJ.** 2001. The thrifty phenotype hypothesis. *Br Med Bull*, 60:5-20.
- Hancock SN, Oliver MH, McLean C, Jaquiery AL, Bloomfield FH.** 2012. Size at birth and adult fat mass in twin sheep are determined in early gestation. *J Physiol (London)*, 590:1273-1285.
- Hausman GJ, Dodson MV, Ajuwon K, Azain M, Barnes KM, Guan LL, Jiang Z, Poulos SP, Sainz RD, Smith S, Spurlock M, Novakofski J, Fernyhough ME, Bergen WG.** 2009. The biology and regulation of preadipocytes and adipocytes in meat animals. *J Anim Sci*, 87:1218-1246.
- Hernandez CE, Matthews LR, Oliver MH, Bloomfield FH, Harding JE.** 2010. Effects of sex, litter size and periconceptional ewe nutrition on offspring behavioural and physiological response to isolation. *Physiol Behav*, 101:588-594.
- Hocquette JF, Gondret F, Baeza E, Medale F, Jurie C, Pethick DW.** 2010. Intramuscular fat content in meat-producing animals: development, genetic and nutritional control, and identification of putative markers. *Animal*, 4:303-319.
- Houdebine LM.** 2003. Physiologie de la lactation. In: Cabrol D, Pons JC, Goffinet F. *Traité d'Obstétrique*. Paris: Médecine-Sciences Flammarion. pp. 66-76.
- Hovey R, Trott J, Vonderhaar B.** 2002. Establishing a framework for the functional mammary gland: from endocrinology to morphology. *J Mammary Gland Biol Neoplasia*, 7:17-38.
- Husted SM, Nielsen MO, Tygesen MP, Kiani A, Blache D, Ingvarthsen KL.** 2007. Programming of intermediate metabolism in young lambs affected by late gestational maternal undernourishment. *Am J Physiol Endocrinol Metab*, 293:548-557.
- Jammes H, Junien C, Chavatte-Palmer P.** 2011. Epigenetic control of development and expression of quantitative traits. *Reprod Fertil Dev*, 23:64-74.
- Kamal MM, Van Eetvelde M, Depreester E, Hostens M, Vandaele L, Opsomer G.** 2014. Age at calving in heifers and level of milk production during gestation in cows are associated with the birth size of Holstein calves. *J Dairy Sci*, 97:5448-5458.
- Kelly RW, Macleod I, Hynd P, Greeff JC.** 1996. Nutrition during fetal life alters annual wool production and quality in young Merino sheep. *Aust J Exp Agric*, 36:259-267.
- Kelly RW, Greeff JC, Macleod I.** 2006. Lifetime changes in wool production of Merino sheep following differential feeding in fetal and early life. *Aust J Agric Res*, 57:867-876.
- Kenyon PR, van der Linden DS, Blair HT, Morris ST, Jenkinson CMC, Peterson SW, Mackenzie DDS, Firth EC.** 2011. Effects of dam size and nutritional plane during pregnancy on lamb performance to weaning. *Small Rumin Res*, 97:21-27.
- Kenyon PR, Blair HT.** 2014. Foetal programming in sheep: effects on production. *Small Rumin Res*, 118:16-30.
- Khandaker GM, Dibben CRM, Jones PB.** 2012. Does maternal body mass index during pregnancy influence risk of schizophrenia in the adult offspring? *Obes Rev*, 13:518-527.
- Koch RM.** 1972. The role of maternal effects in animal breeding. VI. Maternal effects in beef cattle. *J Anim Sci*, 35:1316-1323.
- Kongsted AH, Husted SV, Thygesen MP, Christensen VG, Blache D, Tolver A, Larsen T, Quistorff B, Nielsen MO.** 2013. Pre- and postnatal nutrition in sheep affects beta-cell secretion and hypothalamic control. *J Endocrinol*, 219:159-171.
- Laguna-Barraza R, Bermejo-Alvarez P, Ramos-Ibanez P, de Frutos C, Lopez-Cardona AP, Calle A, Fernandez-Gonzalez R, Pericuesta E, Ramirez MA, Gutierrez-Adan A.** 2012. Sex-specific embryonic origin of postnatal phenotypic variability. *Reprod Fertil Dev*, 25:38-47.
- Lane M, Zander-Fox DL, Robker RL, McPherson NO.** 2015. Peri-conception parental obesity, reproductive health, and transgenerational impacts. *Trends Endocrinol Metab*, 26:84-90.
- Laporte-Broux B, Roussel-Huchette S, Ponter AA, Perault J, Chavatte-Palmer P, Duvaux-Ponter C.** 2011. Short term effects of maternal feed restriction during pregnancy on goat kid morphology, metabolism and behavior. *J Anim Sci*, 89:2154-2163.
- Laporte-Broux B, Roussel S, Ponter AA, Giger-Reverdin S, Camous S, Chavatte-Palmer P, Duvaux-Ponter C.** 2012. Long-term consequences of feed restriction during late pregnancy in goats on feeding behavior and emotional reactivity of female offspring. *Physiol Behav*, 106:178-184.
- Lie S, Morrison JL, Wyss O, Zhang S, Ozanne SE, McMillen IC.** 2012. Periconceptional undernutrition



- differentially alters insulin signalling in skeletal muscle in singleton and twin fetal sheep in late gestation. *Reprod Sci*, 19:263A-263A.
- Lie S, Morrison JL, Williams-Wyss O, Ozanne SE, Zhang S, Walker SK, Kleemann DO, MacLaughlin SM, Roberts CT, McMillen IC.** 2013. Impact of embryo number and periconceptional undernutrition on factors regulating adipogenesis, lipogenesis, and metabolism in adipose tissue in the sheep fetus. *Am J Physiol Endocrinol Metab*, 305:E931-E941.
- Lie S, Morrison JL, Williams-Wyss O, Suter CM, Humphreys DT, Ozanne SE, Zhang S, MacLaughlin SM, Kleemann DO, Walker SK, Roberts CT, McMillen IC.** 2014. Impact of embryo number and maternal undernutrition around the time of conception on insulin signaling and gluconeogenic factors and microRNAs in the liver of fetal sheep. *Am J Physiol Endocrinol Metab*, 306:E1013-1024.
- Long NM, Prado-Cooper MJ, Krehbiel CR, DeSilva U, Wettemann RP.** 2010. Effects of nutrient restriction of bovine dams during early gestation on postnatal growth, carcass and organ characteristics, and gene expression in adipose tissue and muscle. *J Anim Sci*, 88:3251-3261.
- Long NM, Tousley CB, Underwood KR, Paisley SI, Means WJ, Hess BW, Du M, Ford SP.** 2012. Effects of early- to mid-gestational undernutrition with or without protein supplementation on offspring growth, carcass characteristics, and adipocyte size in beef cattle. *J Anim Sci*, 90:197-206.
- Lopez-Bote CJ.** 1998. Sustained utilization of the Iberian pig breed. *Meat Sci*, 49(S1):S17-27.
- MacLaughlin SM, Walker SK, Roberts CT, Kleemann DO, McMillen IC.** 2005. Periconceptional nutrition and the relationship between maternal body weight changes in the periconceptional period and fetoplacental growth in the sheep. *J Physiol*, 565.
- MacLaughlin SM, Walker SK, Kleemann DO, Tosh DN, McMillen IC.** 2010. Periconceptional undernutrition and being a twin each alter kidney development in the sheep fetus during early gestation. *Am J Physiol Regul Integr Comp Physiol*, 298:R692-R699.
- Martin JL, Vonnahme KA, Adams DC, Lardy GP, Funston RN.** 2007. Effects of dam nutrition on growth and reproductive performance of heifer calves. *J Anim Sci*, 85:841-847.
- Martin NP, Kenyon PR, Morel PCH, Pain SJ, Jenkinson CMC, Hutton PG, Morris ST, Peterson SW, Firth EC, Blair HT.** 2012. Ewe nutrition in early and mid- to late pregnancy has few effects on fetal development. *Anim Prod Sci*, 52:533-539.
- Matthiesen CF, Blache D, Thomsen PD, Tauson AH.** 2010. Feeding mink (*Neovison vison*) a protein-restricted diet during pregnancy induces higher birth weight and altered hepatic gene expression in the F(2) offspring. *Br J Nutr*, 104:544-553.
- McCance RA.** 1976. Critical periods of growth. *Proc Nutr Soc*, 35:309-313.
- McMillen IC, MacLaughlin SM, Muhlhauser BS, Gentili S, Duffield JL, Morrison JL.** 2008. Developmental origins of adult health and disease: the role of periconceptional and foetal nutrition. *Basic Clin Pharmacol Toxicol*, 102:82-89.
- Micke GC, Sullivan TM, Gatford KL, Owens JA, Perry VEA.** 2010. Nutrient intake in the bovine during early and mid-gestation causes sex-specific changes in progeny plasma IGF-I, liveweight, height and carcass traits. *Anim Reprod Sci*, 121:208-217.
- Micke GC, Sullivan TM, McMillen IC, Gentili S, Perry VEA.** 2011. Protein intake during gestation affects postnatal bovine skeletal muscle growth and relative expression of IGF1, IGF1R, IGF2 and IGF2R. *Mol Cell Endocrinol*, 332:234-241.
- Morise A, Seve B, Mace K, Magliola C, Le Huerou-Luron I, Louveau I.** 2011. Growth, body composition and hormonal status of growing pigs exhibiting a normal or small weight at birth and exposed to a neonatal diet enriched in proteins. *Br J Nutr*, 105:1471-1479.
- Mostyn A, Symonds ME.** 2009. Early programming of adipose tissue function: a large-animal perspective. *Proc Nutr Soc*, 68:393-400.
- Mostyn A, Attig L, Larcher T, Dou S, Chavatte-Palmer P, Boukthir M, Gertler A, Djiane J, M ES, Abdennebi-Najar L.** 2014. UCP1 is present in porcine adipose tissue and is responsive to postnatal leptin. *J Endocrinol*, 223:M31-M38.
- Munoz G, Ovilo C, Silio L, Tomas A, Noguera JL, Rodriguez MC.** 2009. Single- and joint-population analyses of two experimental pig crosses to confirm quantitative trait loci on Sus scrofa chromosome 6 and leptin receptor effects on fatness and growth traits. *J Anim Sci*, 87:459-468.
- Nissen PM, Danielsen VO, Jorgensen PF, Oksbjerg N.** 2003. Increased maternal nutrition of sows has no beneficial effects on muscle fiber number or postnatal growth and has no impact on the meat quality of the offspring. *J Anim Sci*, 81:3018-3027.
- Oksbjerg N, Gondret F, Vestergaard M.** 2004. Basic principles of muscle development and growth in meat-producing mammals as affected by the insulin-like growth factor (IGF) system. *Domest Anim Endocrinol*, 27:219-240.
- Oliver MH, Jaquier AL, Kenyon PR, Pain SJ, Jenkinson CM, Blair HT, Derraik JGB, Bloomfield FH.** 2015. Maternal insulin sensitivity in midpregnancy does not determine birth weight after embryo transfer between large and small breed sheep. *Domest Anim Endocrinol*, 50:50-54.
- Otten W, Kanitz E, Tuchscherer M, Gräbner M, Nürnberg G, Bellmann O, Hennig U, Rehfeldt C, Metzges CC.** 2013. Effects of low and high protein:carbohydrate ratios in the diet of pregnant gilts on maternal cortisol concentrations and the adrenocortical and sympathoadrenal reactivity in their



- offspring. *J Anim Sci*, 91:2680-2692.
- Ousey JC.** 1997. Thermoregulation and the energy requirement of the newborn foal with reference to prematurity. *Equine Vet*, 29(S24):104-108.
- Ousey JC, Fowden AL, Wilsher S, Allen WR.** 2008. The effects of maternal health and body condition on the endocrine responses of neonatal foals. *Equine Vet J*, 40:673-679.
- Ovilo C, Fernandez A, Noguera JL, Barragan C, Leton R, Rodriguez C, Mercade A, Alves E, Folch JM, Varona L, Toro M.** 2005. Fine mapping of porcine chromosome 6 QTL and LEPR effects on body composition in multiple generations of an Iberian by Landrace intercross. *Genet Res*, 85:57-67.
- Pala A, McCraw R.** 2005. Replacement heifer selection in a beef cattle herd. *Am J Appl Sci*, 2:542-544.
- Paten AM, Kenyon PR, Lopez-Villalobos N, Peterson SW, Jenkinson CMC, Pain SJ, Blair HT.** 2013. Lactation Biology Symposium: maternal nutrition during early and mid-to-late pregnancy: comparative effects on milk production of twin-born ewe progeny during their first lactation. *J Anim Sci*, 91:676-684.
- Peugnet P, Wimel L, Duchamp G, Sandersen C, Camous S, Guillaume D, Dahirel M, Dubois C, Jouneau A, Reigner F, Berthelot V, Chaffaux S, Tarrade A, Serteyn D, Chavatte-Palmer P.** 2014. Enhanced or reduced fetal growth induced by embryo transfer into smaller or larger breeds alters post-natal growth and metabolism in pre-weaning horses. *Plos One*, 9:e102044.
- Peugnet P, Robles M, Mendoza L, Wimel L, Dubois C, Dahirel M, Guillaume D, Camous S, Berthelot V, Toquet M-P, Richard E, Sandersen C, Chaffaux S, Lejeune J-P, Tarrade A, Serteyn D, Chavatte-Palmer P.** 2015a. Effects of moderate amounts of barley in late pregnancy on growth, glucose metabolism and osteoarticular status of pre-weaning horses. *Plos One*, 10:e0122596.
- Peugnet P, Wimel L, Tarrade A, Robles M, Dubois C, Serteyn D, Chavatte-Palmer P.** 2015b. La santé du futur poulain se prépare dès la gestation. In: 41ème Journée de la Recherche Equine, Paris, France. Le Pin au Haras: Institut Français du Cheval et de l'Equitation/INRA. pp. 84-92.
- Picard B, Lefaucheur L, Berri C, Duclos MJ.** 2002. Muscle fibre ontogenesis in farm animal species. *Reprod Nutr Dev*, 42:415-431.
- Powell SE, Aberle ED.** 1980. Effects of birth weight on growth and carcass composition of swine. *J Anim Sci*, 50:860-868.
- Rehfeldt C, Kuhn G.** 2006. Consequences of birth weight for postnatal growth performance and carcass quality in pigs as related to myogenesis. *J Anim Sci*, 84:E113-E123.
- Rehfeldt C, Lang IS, Görs S, Hennig U, Kalbe C, Stabenow B, Brüssow KP, Pfuhl R, Bellmann O, Nürnberg G, Otten W, Metges CC.** 2011. Limited and excess dietary protein during gestation affects growth and compositional traits in gilts and impairs offspring fetal growth. *J Anim Sci*, 89:329-341.
- Rehfeldt C, Stabenow B, Pfuhl R, Block J, Nürnberg G, Otten W, Metges CC, Kalbe C.** 2012. Effects of limited and excess protein intakes of pregnant gilts on carcass quality and cellular properties of skeletal muscle and subcutaneous adipose tissue in fattening pigs. *J Anim Sci*, 90:184-196.
- Rosdale PD, Ousey JC.** 2003. Fetal programming for athletic performance in the horse: potential effects of IUGR. *Equine Vet Educ*, 15(S6):24-37..
- Rumball CW, Bloomfield FH, Harding JE.** 2008. Cardiovascular adaptations to pregnancy in sheep and effects of periconceptional undernutrition. *Placenta*, 29:89-94.
- Satterfield MC, Coverdale JA, Wu GY.** 2010. Review of fetal programming: implications to horse health. In: Proceedings of the Annual Convention of the AAEP, 2010, Baltimore, MD. Baltimore: AAEP. pp. 207-214.
- Schinckel P, Short B.** 1961. Influence of nutritional level during pre-natal and early post-natal life on adult fleece and body characters. *Aust J Agric Res*, 12:176-202.
- Sejian V, Maurya VP, Naqvi SMK.** 2011. Effect of thermal stress, restricted feeding and combined stresses (thermal stress and restricted feeding) on growth and plasma reproductive hormone levels of Malpura ewes under semi-arid tropical environment. *J Anim Physiol Anim Nutr*, 95:252-258.
- Sibbald AM, Davidson GC.** 1998. The effect of nutrition during early life on voluntary food intake by lambs between weaning and 2 years of age. *Anim Sci*, 66:697-703.
- Sinclair KD, Allegrucci C, Singh R, Gardner DS, Sebastian S, Bispham J, Thurston A, Huntley JF, Rees WD, Maloney CA, Lea RG, Craigon J, McEvoy TG, Young LE.** 2007. DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status. *Proc Nat Acad Sci USA*, 104:19351-19356.
- Steegers-Theunissen RP, Twigt J, Pestinger V, Sinclair KD.** 2013. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. *Hum Reprod Update*, 19:640-655.
- Stickland NC.** 1978. A quantitative study of muscle development in the bovine foetus (*Bos indicus*). *Anat Histol Embryol*, 7:193-205.
- Swali A, Wathes DC.** 2006. Influence of the dam and sire on size at birth and subsequent growth, milk production and fertility in dairy heifers. *Theriogenology*, 66:1173-1184.
- Symonds ME, Lomax MA.** 1992. Maternal and environmental influences on thermoregulation in the neonate. *Proc Nutr Soc*, 51:165-172.
- Symonds ME, Seibert SP, Budge H.** 2010. Nutritional regulation of fetal growth and implications for



- productive life in ruminants. *Animal*, 4:1075-1083.
- Symonds ME, Pope M, Sharkey D, Budge H.** 2012. Adipose tissue and fetal programming. *Diabetologia*, 55:1597-1606.
- Tarrade A, Panchenko P, Junien C, Gabory A.** 2015. Placental contribution to nutritional programming of health and diseases: epigenetics and sexual dimorphism. *J Exp Biol*, 218:50-58.
- Tischner M.** 2000. Maternal influence on pre- and postnatal growth of foals born after embryo transfer. *J Reprod Fertil Suppl*, 56:705-708.
- Tong JF, Zhu MJ, Underwood KR, Hess BW, Ford SP, Du M.** 2008. AMP-activated protein kinase and adipogenesis in sheep fetal skeletal muscle and 3T3-L1 cells. *J Anim Sci*, 86:1296-1305.
- Tong JF, Yan X, Zhu MJ, Ford SP, Nathanielsz PW, Du M.** 2009. Maternal obesity downregulates myogenesis and β -catenin signaling in fetal skeletal muscle. *Am J Physiol Endocrinol Metab*, 296:E917-E924.
- Torrens C, Snelling TH, Chau R, Shanmuganathan M, Cleal JK, Poore KR, Noakes DE, Poston L, Hanson MA, Green LR.** 2009. Effects of pre- and periconceptual undernutrition on arterial function in adult female sheep are vascular bed dependent. *Exp Physiol*, 94:1024-1033.
- Underwood KR, Tong JF, Price PL, Roberts AJ, Grings EE, Hess BW, Means WJ, Du M.** 2010. Nutrition during mid to late gestation affects growth, adipose tissue deposition, and tenderness in cross-bred beef steers. *Meat Sci*, 86:588-593.
- Van der Heyden L, Lejeune JP, Caudron I, Detilleux J, Sandersen C, Chavatte P, Paris J, Deliege B, Serteyn D.** 2013. Association of breeding conditions with prevalence of osteochondrosis in foals. *Vet Rec*, 172:68.
- van der Linden DS, Kenyon PR, Blair HT, Lopez-Villalobos N, Jenkinson CM, Peterson SW, Mackenzie DD.** 2009. Effects of ewe size and nutrition on fetal mammary gland development and lactational performance of offspring at their first lactation. *J Anim Sci*, 87:3944-3954.
- van Montfoort AP, Hanssen LL, de Sutter P, Viville S, Geraedts JP, de Boer P.** 2012. Assisted reproduction treatment and epigenetic inheritance. *Hum Reprod Update*, 18:171-197.
- Vonnahme KA, Hess BW, Nijland MJ, Nathanielsz PW, Ford SP.** 2006. Placentomal differentiation may compensate for maternal nutrient restriction in ewes adapted to harsh range conditions. *J Anim Sci*, 84:3451-3459.
- Wallace JM, Bourke DA, Aitken RP, Milne JS, Hay WW.** 2003. Placental glucose transport in growth-restricted pregnancies induced by overnourishing adolescent sheep. *J Physiol (London)*, 547:85-94.
- Wallace JM, Milne JS, Aitken RP.** 2005. The effect of overnourishing singleton-bearing adult ewes on nutrient partitioning to the gravid uterus. *Br J Nutr*, 94:533-539.
- Walton A, Hammond J.** 1938. The maternal effects on growth and conformation in shire horse-shetland pony crosses. *Proc R Soc Lond B*, 125:311-335.
- Watkins AJ, Papenbrock T, Fleming TP.** 2008. The preimplantation embryo: handle with care. *Semin Reprod Med*, 26:175-185.
- Watkins AJ, Lucas ES, Fleming T.** 2010. Impact of the periconceptual environment on the programming of adult disease. *J Dev Origins Health Dis*, 1:1-9.
- Whorwood CB, Firth KM, Budge H, Symonds ME.** 2001. Maternal undernutrition during early to midgestation programs tissue-specific alterations in the expression of the glucocorticoid receptor, 11 β -hydroxysteroid dehydrogenase isoforms, and type 1 angiotensin ii receptor in neonatal sheep. *Endocrinology*, 142:2854-2864.
- Williams-Wyss O, Zhang S, MacLaughlin SM, Kleemann D, Walker SK, Suter CM, Cropley JE, Morrison JL, Roberts CT, McMillen IC.** 2014. Embryo number and periconceptual undernutrition in the sheep have differential effects on adrenal epigenotype, growth, and development. *Am J Physiol Endocrinol Metab*, 307:E141-E150.
- Wilsher S, Allen WR.** 2006. Effects of a *Streptococcus equi* infection--mediated nutritional insult during mid-gestation in primiparous Thoroughbred fillies. Part 1: placental and fetal development. *Equine Vet J*, 38:549-557.
- Wu G, Bazer FW, Cudd TA, Meininger CJ, Spencer TE.** 2004. Maternal nutrition and fetal development. *J Nutr*, 134:2169-2172.
- Wu G, Bazer FW, Wallace JM, Spencer TE.** 2006. Intrauterine growth retardation: Implications for the animal sciences. *J Anim Sci*, 84:2316-2337.
- Zhang L, Long NM, Hein SM, Ma Y, Nathanielsz PW, Ford SP.** 2011a. Maternal obesity in ewes results in reduced fetal pancreatic beta-cell numbers in late gestation and decreased circulating insulin concentration at term. *Domest Anim Endocrinol*, 40:30-39.
- Zhang S, Rattanatray L, McMillen IC, Suter CM, Morrison JL.** 2011b. Periconceptual nutrition and the early programming of a life of obesity or adversity. *Prog Biophys Mol Biol*, 106:307-314.
- Zhang S, Morrison JL, Gill A, Rattanatray L, MacLaughlin SM, Kleemann D, Walker SK, McMillen IC.** 2013a. Dietary restriction in the periconceptual period in normal-weight or obese ewes results in increased abundance of angiotensin-converting enzyme (ACE) and angiotensin type 1 receptor (AT1R) in the absence of changes in ACE or AT1R methylation in the adrenal of the offspring. *Reproduction*, 146:443-454.
- Zhang S, Morrison JL, Gill A, Rattanatray L, MacLaughlin SM, Kleemann D, Walker SK, McMillen IC.** 2013b. Maternal dietary restriction during the periconceptual period in normal-weight or obese ewes results in adrenocortical hypertrophy, an up-regulation of the JAK/STAT and down-regulation of the



IGF1R signaling pathways in the adrenal of the postnatal lamb. *Endocrinology*, 154:4650-4662.

Zhu MJ, Ford SP, Means WJ, Hess BW, Nathanielsz PW, Du M. 2006. Maternal nutrient restriction affects properties of skeletal muscle in offspring. *J Physiol (London)*, 575:241-250.

Zhu MJ, Du M, Hess BW, Nathanielsz PW, Ford SP. 2007. Periconceptional nutrient restriction in the ewe

alters MAPK/ERK1/2 and PI3K/Akt growth signaling pathways and vascularity in the placentome. *Placenta*, 28:1192-1199.

Zhu MJ, Du M, Nijland MJ, Nathanielsz PW, Hess BW, Moss GE, Ford SP. 2009. Down-regulation of growth signaling pathways linked to a reduced cotyledonary vascularity in placentomes of over-nourished, obese pregnant ewes. *Placenta*, 30:405-410.
