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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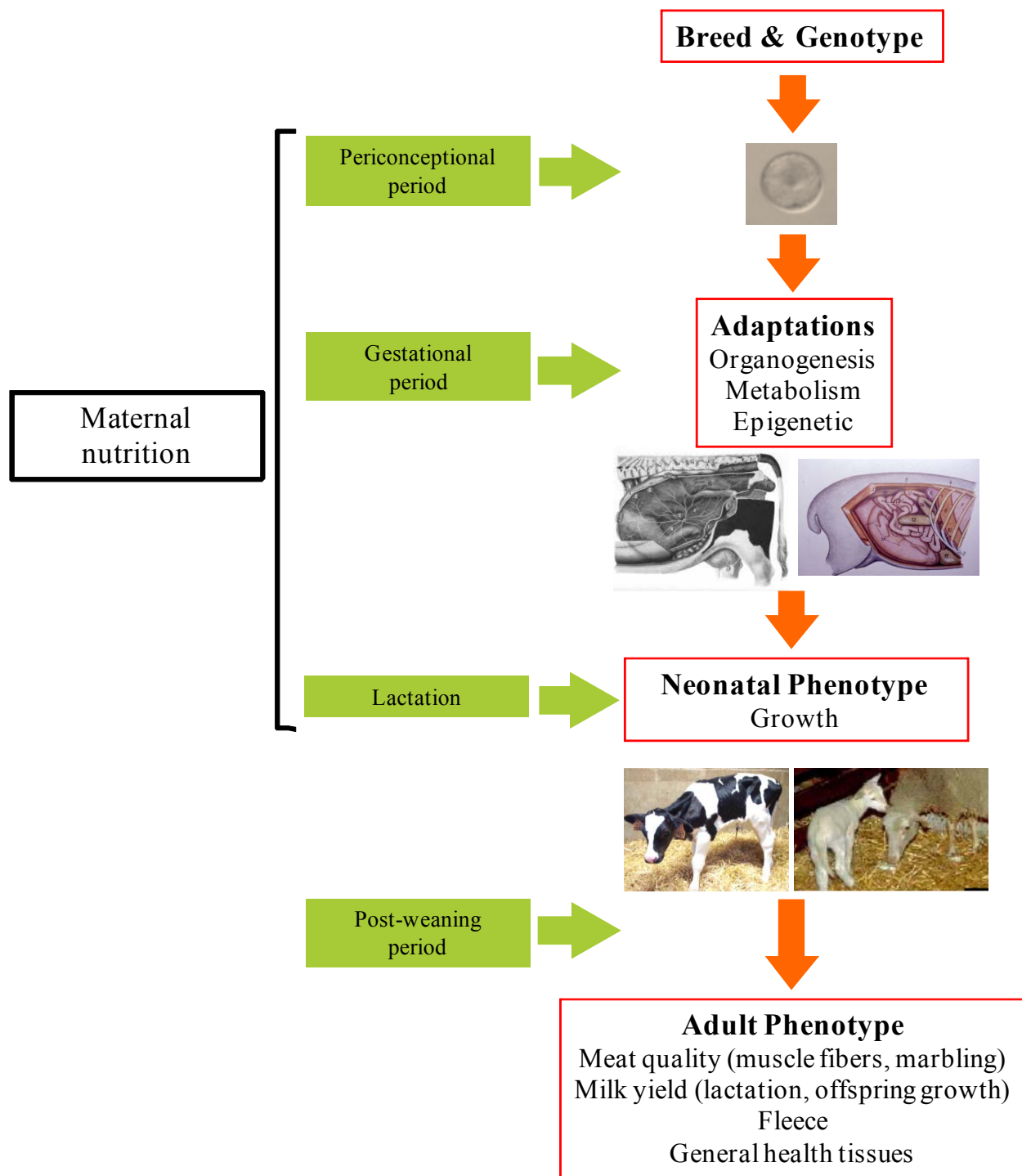Phone : +33(1)3465-2558

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.
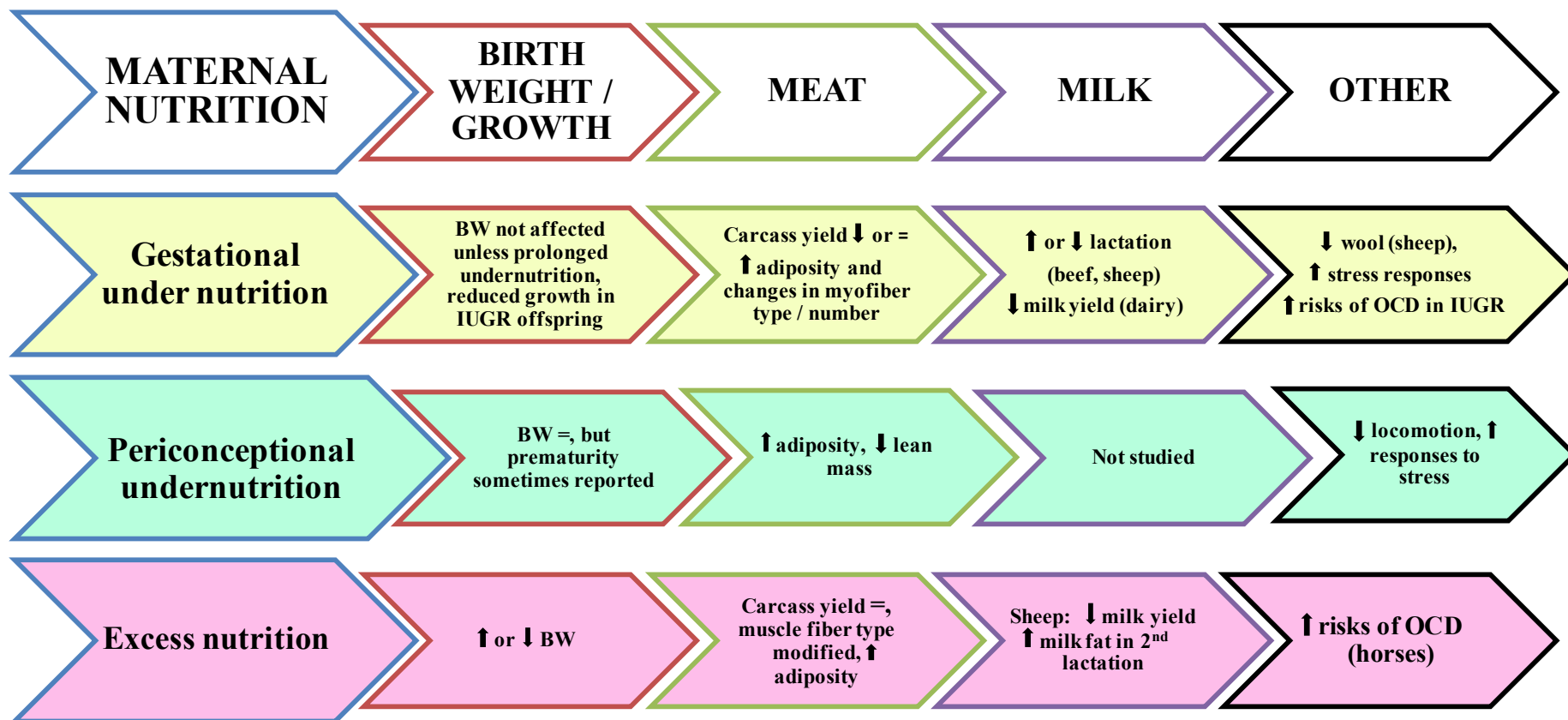
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MATERNAL NUTRITION	BIRTH WEIGHT / GROWTH	MEAT	MILK	OTHER
Gestational under nutrition	BW not affected unless prolonged undernutrition, reduced growth in IUGR offspring	Carcass yield ↓ or = ↑ adiposity and changes in myofiber type / number	↑ or ↓ lactation (beef, sheep) ↓ milk yield (dairy)	↓ wool (sheep), ↑ stress responses ↑ risks of OCD in IUGR
Periconceptional undernutrition	BW =, but prematurity sometimes reported	↑ adiposity, ↓ lean mass	Not studied	↓ locomotion, ↑ responses to stress
Excess nutrition	↑ or ↓ BW	Carcass yield =, muscle fiber type modified, ↑ adiposity	Sheep: ↓ milk yield ↑ milk fat in 2nd lactation	↑ risks of OCD (horses)

Figure 2. Main effects observed on production traits after maternal undernutrition or overnutrition during gestation, or after periconceptional 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 form 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 (Bossaert *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 form 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

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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 fators (IGFs; Micke *et al*., 2011), Growth hormone (Rehfeldt and Kuhn, 2006), transcription factors involved in adipogenesis such as the Peroxisome Proliferator-Activited receptor gamma (PPARγ; Tong *et al*., 2008, 2009) and nutrient sensors such as mTOR. Indeed, the main regulators of adipogenesis are the peroxisome proliferator activated receptor (PPARγ) 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.

Periconceptional programming

The developmental plasticity of embryos in the pre-implantation period leads to different embryo, feto-placental and post-natal responses to the environment (Laguna-Barraza *et al*., 2012). Specific targeting of the periconceptional 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 periconceptional 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 periconceptional 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). Periconceptional 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 periconceptional 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 periconceptional nutrition. Indeed, uterine blood flow is increased by 13% in ewes that were undernourished during the periconceptional period compared to controls (Rumball *et al*., 2008) with increased expression of growth factors (Zhu *et al*., 2007).

Effects of periconceptional (-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

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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 periconceptional undernutrition only in twin-bearing Welsh mountain ewes carrying fetuses of opposite sex (Cleal *et al*., 2007). In another study, maternal periconceptional 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-riched 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 periconceptional undernutrition, possibly reflecting decreased responses to stress (Hernandez *et al*., 2010; Abecia *et al*., 2014).

Conclusions

The pre- and periconceptional 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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