Developmental programming: Can nutrition of the mare influence the foal's health?

Programação de desenvolvimento embrionário: A nutrição da égua pode influenciar a saúde do potro?

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Abstract

As demonstrated in humans and animal models, prenatal developmental conditions can affect phenotype, through adaptive changes that induce persistent modifications in offspring gene expression. Although epigenetic modifications, shown in other species to be seminal to these effects, have not yet been demonstrated in horses, the Developmental Origins of Health and Disease (DOHaD) nevertheless apply to the equine species. The physiological, metabolic and nutritional status of the mare, such as her parity, her body condition or whether the dam is fed cereals during gestation or is obese, are key elements that may affect foal health and metabolism. The placenta, that orchestrates feto-maternal exchanges, adapts to maternal conditions and is considered as a major programming agent. Although so far, there are no reliable, easily applicable, biomarkers of adverse programming of the foal, the use of supplementary feeds, such as maternal arginine, is currently being explored to try and restore optimal placental function in adverse conditions.

Keywords: Horse, DOHaD, growth, metabolism**.**

Introduction

In domestic animals, genetic selection has been used for centuries to improve performances. Genetic selection is based on the prediction of the genetic value of upcoming offspring, whereas actual performance will depend both on genetic value and environment. Nevertheless, the transmission of information from the dam to the offspring is not based only on nuclear DNA, as epigenetic mechanisms have been shown in model and/or domestic species and/or humans to be able to transfer information at least from one generation to the next. The possibility to improve or modify offspring performance through the modification of the parental environment offers new perspectives in animal breeding.

Environment & Developmental programming: a multispecies perspective

The developmental origins of health and disease (DOHaD) and epigenetic mechanisms

In the 90’s, David Barker and Nick Hales performed a series of epidemiological studies that demonstrated a link between weight at birth and the subsequent onset of non-communicable disease (diabetes, cardiovascular disease) at adulthood (Barker et al., 1991; Fall et al., 1995; Hales, 1997). Low birthweight, considered as a proxy for in-utero development, was shown to increase risk of non-communicable diseases at adulthood and it was proposed that fetal adaptations to an adverse in-utero environment induced permanent changes in the fetus – referred to as programming – that were revealed as the individual aged or in the presence of an adverse post-natal environment. Initially overtly criticized by the scientific community, the phenomenon was confirmed over the following decades through a multitude of epidemiological studies in humans (Hanson and Gluckman, 2014) as well as in animal models (Chavatte-Palmer et al., 2016) and domestic animals (Wu et al., 2006), and is now referred to as the Developmental Origins of Health and Disease (DOHaD).

The epigenome, considered as the organism’s memory of past metabolic and environmental events, and the afferent epigenetic marks, are considered as the underlying mechanisms of programming (Crews et al., 2014), to the point that often the two concepts are merged in the public’s mind. Epigenetic mechanisms are defined as heritable, potentially reversible (Mazzio and Soliman, 2014), changes affecting gene expression that do not involve changes in the DNA sequence. These changes are essential during gametogenesis, early embryonic development and subsequent cellular differentiation. Epigenetic modifications are also induced by environmental factors (nutrition, exposure to drugs or pollutants, stress…) and can be considered as the memory of the cell. Mechanisms include DNA methylation, the most stable and most studied epigenetic modification, histone modifications and non-coding RNAs, as reviewed by Jammes et al., (2011) and Chavatte-Palmer et al., (2018a).

DNA methylation takes place on DNA cytosine residues of CpG dinucleotides. Methionine is transferred from S-adenosylmethionine (SAM, the universal methyl group donor) by DNA methyltransferases enzymes (DNMTs). The One–carbon cycle, enabling DNA methylation, depends on the availability of methyl donors such as methionine, mostly derived from dietary proteins, but also co-factors such as B vitamins (B12, B6 and B2) as well

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as folates, choline and betaine. Thus, any imbalance in these nutritional factors may possibly affect epigenetic marks. Methylation is most often associated with transcription repression as the chromatin is more compact, restricting access of transcription factors to DNA, but this is not always the case.

Histone modifications: Histones are proteins localized in the nucleus that compose chromosomes in association to DNA. Histones can be modified by many mechanisms located mainly on the N-terminal tails of core histones, of which histone acetylation is the most studied. Acetylation of histone tails reduces the accessibility of DNA to the transcription machinery whereas deacetylation loosens the interactions of histones with DNA, thus enabling the DNA access to transcription factors.

Non-coding RNAs: Only about 20% of gene transcription across the mammalian genome is associated with protein-coding genes, indicating that approximately 80% of transcripts are non-coding. MicroRNAs are the most studied family of non-coding RNAs that act at the post-transcriptional level by binding target complementary sequences of messenger RNAs (mRNAs) and thus modulate gene expression. One miRNA may have several targets. Extra-cellular or intra-cellular miRNAs vary depending on the individual's nutritional/pathological status and conversely, miRNAs are involved in nutritional control. They are thus obvious candidates to modulate phenotypes in domestic species.

Although there is now a large body of evidence on the role of parental nutrition and environmental conditions, from periods preceding conception and throughout gestation in domestic mammals, so far, direct substantiation that epigenetic marks are the causative link between maternal or even paternal nutrition and offspring phenotype are yet rare in these species (Feeney et al., 2014; Ibeagha-Awemu and Zhao, 2015; Sinclair et al., 2016; Chavatte-Palmer et al., 2018a).

Critical periods of development

Environmental changes are continuously inducing adaptations in living organisms and thus inducing changes in their epigenome. Nevertheless, some periods are particularly sensitive to environmental perturbations (whereas nutrition, exposure to pollutants or drugs, emotional or environmental stress…). As mentioned above, epigenetic mechanisms are essential for cell differentiation during gametogenesis, early embryo development and the establishment of cellular lineages as the conceptus develops. Pre-conceptional diet has thus been demonstrated, both in females and males, to be able to affect offspring phenotype and health as reviewed recently by Fleming et al., (2018) and Soubry (2018). Subsequently, intense environmental perturbations during the embryonic period may induce death of the embryo, whereas more subtle changes may permanently affect the offspring development and phenotype (McMillen et al., 2008; Watkins et al., 2010; Steegers-Theunissen et al., 2013). For example, maternal nutritional restriction, micro-nutrient deficiency (Sinclair et al., 2007), low protein nutrition (Watkins et al., 2008) or exposure to maternal diabetes (Rousseau-Ralliard et al., 2019) during the conceptional period have been associated with abnormal placental function, hypertensive disorders, excess adiposity or disturbed metabolism in offspring.

During subsequent development, the placenta ensures the exchanges between the dam and the fetus through a constant endocrine dialogue. The placenta adapts to the maternal environment in terms of cellular growth, blood flow, expression of nutrient transporters, endocrine function, etc., in order to allow optimal fetal growth. It is considered as a key programming agent (Tarrade et al., 2015) and modifications in placental function have been shown to affect fetal cardiovascular, pancreatic and kidney function, among others (Barker and Thornburg, 2013).

Fetal adaptations to an adverse maternal environment aim at ensuring immediate fetal survival (for example increased insulin resistance, alteration of blood flows to ensure the correct perfusion of the brain to the expense of less vital organs). As these adaptations persist after birth, the individual is "programmed" to be adapted to an environment resembling that of its prenatal life. In the event that the early post-natal environment is different (for example post-natal overfeeding following pre-natal undernutrition), the subsequent nutritional mismatch often reveals the adverse programming whereas careful management of the offspring in terms of nutritional management may help prevent or delay the negative consequences of fetal programming. The work of Ozanne and co-workers in 2004 is a good example. Maternal or neonatal protein undernutrition was applied to mice whose male offspring were subsequently challenged with a post-weaning high fat-high sugar diet or fed a control diet. Maternal protein undernutrition during pregnancy reduced offspring birthweight. Subsequent rapid post-natal catch-up growth during the suckling period considerably reduced offspring lifespan regardless of post-weaning diet (but with a more severe effect when offspring where fed the obesogenic diet) compared to controls. In contrast, adequate maternal nutrition during pregnancy and subsequent undernutrition during lactation had a protective effect and even increased offspring lifespan (Ozanne and Hales, 2004). These data also illustrate the fact that very early correction of environmental insults are essential to prevent or improve long term outcomes (Hanson et al., 2011).

Finally, puberty is accompanied by important physiological changes underlined by many epigenetic modifications and can also be considered as a critical period where modifications of the environment may induce epigenetic perturbations.

Programming of health and athletic capacities

As detailed above, programming may occur at several stages of development. So far, although the initial data focused on metabolic diseases, all physiological functions were shown to be potentially affected, albeit to various extent. Depending on the nature of the nutritional/environmental insults, the timing of these events and the genetic background of the individual, different functions and organs may be affected. In domestic animals, inasmuch as strong effects can be demonstrated in cases of extreme adverse conditions, these effects are subtler when overall breeding conditions are good. Nevertheless, conventional breeding and rearing practices may affect traits related to health and sports performance, as illustrated below, not aiming at an exhaustive review. We will not illustrate effects on metabolism as those are almost always described and observations in horses are detailed in the chapters below.

Fetal programming has been shown to affect bone function and the development of osteoporosis in humans (Dennison et al., 2013), which may be conveyed in part through the relationship between bone growth and energy metabolism (Chapurlat and Confavreux, 2016).

In terms of muscle function, research has been motivated by the impulse to improve meat quality and quantity in ruminants and pigs. Although rather limited alterations in muscle development have been described in cattle (Greenwood et al., 2017), aiming at targeting critical periods of fetal muscle fiber formation and growth may reveal promising to improve muscle development (Du et al., 2010; 2017). Indeed, marbling scores, intra-muscular lipid contents, gene expression and epigenetic marks (DNA methylation and miRNAs) could be modified by changing maternal nutrition in cattle and pigs, often in relation with altered glucose/insulin metabolism (Moisá et al., 2015).

Immune function can also be affected by in-utero environmental conditions, with heat stress being one of the factors involved as shown elegantly with periconceptional maternal hyperthermia induced by a LPS (lipopolysaccharide – present in the external membrane of Gram- bacteria) injection in mice immediately after fertilization (Williams et al., 2011). In cattle, maternal heat stress in late gestation has also been show to affect the methylation of genes in the mammary gland and liver of offspring (Skibiel et al., 2018).

Finally, reproductive function may also be affected as reviewed elsewhere (Chadio and Kotsampasi, 2014; Chavatte-Palmer et al., 2014). This is particularly important because the relationship between early developmental conditions and subsequent offspring fertility may often not be considered. Moreover, artificial reproduction procedures such as embryo transfer or *in vitro* production of embryos per se may also affect placental function and offspring metabolism and health (Duranthon and Chavatte-Palmer, 2018).

What are key factors to consider when formulating a feed for pregnant and lactating mares, stallions and growing foals?

As detailed above, the concept of DOHaD is well established in domestic animal species. It has been demonstrated to be valid in the horse (Rossdale and Ousey, 2003; Fowden et al., 2013; Peugnet et al., 2016a).

Nutritional developmental programming in the equine species (Fig. 1).

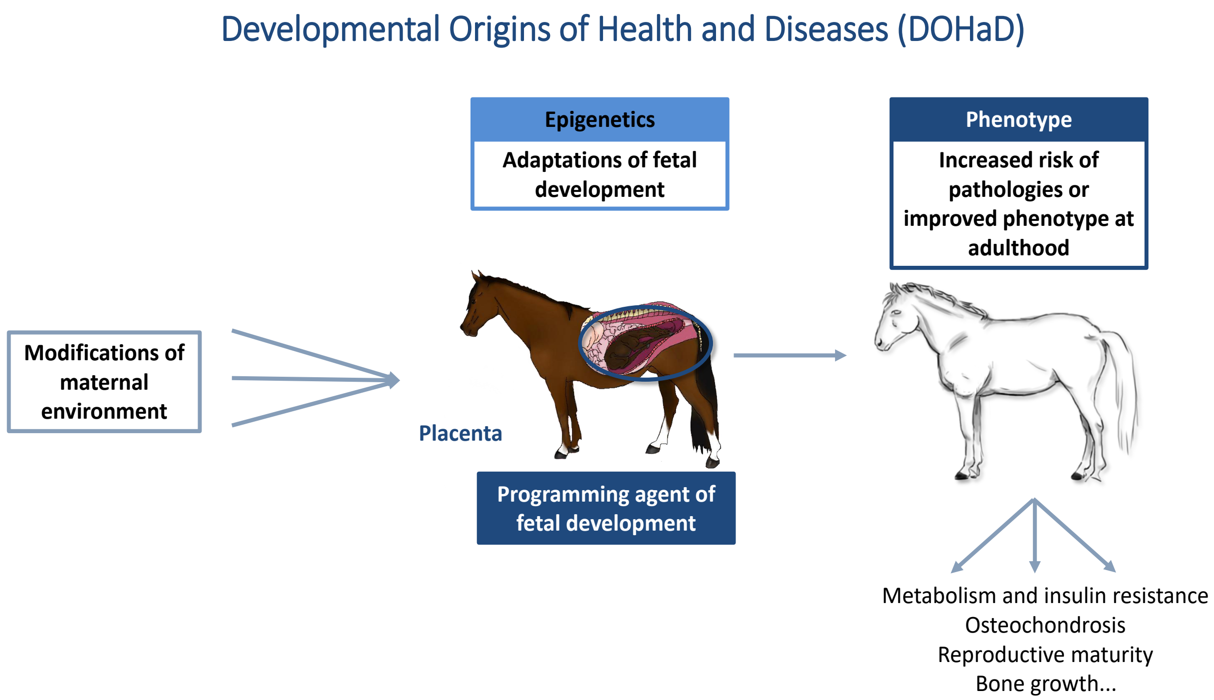

Figure 1. The principles of the Developmental Origins of Health and Disease in the horse.

Undernutrition

During pregnancy, feeding the broodmare with a diet insufficient in energy, but also affection by debilitating diseases, such as Streptococcus equi infection (strangles), can lead to undernutrition.

If moderate (at around 80% of the energy needs), maternal undernutrition does not appear to affect in utero, nor early post-natal growth of the foal (Sutton et al., 1977; Banach and Evans, 1981; Henneke et al., 1984; Hines et al., 1987; Peugnet et al., 2015; Robles et al., 2017). Placental adaptations, through an increased vascularisation and amino acids and vitamins transport and metabolism seemed to be sufficient to sustain the foetal growth during late gestation (Robles et al., 2018b).

If severe, however, undernutrition can affect the in-utero growth of the foal and its birthweight, despite placental adaptations that cannot overcome the effects of undernutrition on foetal growth (Wilsher and Allen, 2006).

Nevertheless, if effects of moderate undernutrition were not observed at birth, foals born to undernourished mares were shown to have delayed testicular maturation at 12 months of age (beginning of puberty), reduced insulin sensitivity at 19 months of age, and reduced cannon width between 19 and 24 months of age compared to foals born to mares fed with enough energy (Robles et al., 2017).

Overnutrition and obesity

Overnutrition can lead to obesity. But obesity can be a transient or long-term disease. These two categories will not affect the health of the foal in the same way.

Overnutrition during pregnancy, leading to obesity in late gestation, did not affect the birthweight of the foals (Henneke et al., 1984; Kubiak et al., 1988). In one study, overnutrition of the dam (between 137 and 147% of the 2007 NRC recommendations) from 2 months of gestation, decreased the weight and the thoracic perimeter of foals at 2 months of age, possibly because of a decreased production of milk in the overnourished group during the first 2 months of lactation (Kubiak et al., 1991). In another study, however, overnutrition of the dam from the 8th month of gestation did not affect the growth of the foals until at least 3 months of age (Henneke et al., 1984).

In early gestation, obesity has already strong effects on embryo development. In fact, it has been shown that obese mares had an altered uterine environment at 16 days post ovulation, that was reflected by an increased endometrial expression of genes involved in inflammatory cytokines, lipid homeostasis regulation and mitochondrial stress growth factors (Sessions-Bresnahan et al., 2018). Embryos produced by obese mares presented an altered expression of genes involved in inflammation, lipid homeostasis, endoplasmic reticulum, oxidative and mitochondrial stress and lipid fingerprints between 8 and 16 days after ovulation. These alterations may be detrimental for the development of the foetus.

Altogether, maternal obese status from the time of insemination, associated to a decreased insulin sensitivity and an increased concentration of blood inflammation markers in mares in late gestation, did not affect the birthweight, nor the growth of foals until at least 18 months of age (Robles et al., 2018a). Nevertheless, maternal obesity increased systemic inflammation in foals until 6 months of age, decreased their insulin sensitivity at 6 and 18 months and increased the development of osteochondrosis lesions

Effects of macro and micronutrient unbalances will be presented below.

The quality of energy sources is detrimental for the health of the foal

Use and effects of starch

It has been shown epidemiologically that feeding the pregnant mares with concentrated feeds increased the risks for the foals to develop osteochondrosis later in life, compared to forage only (Vander Heyden et al., 2012). Although highly interesting, this study did not consider the quality and quantity of concentrated feeds given to the mares. These factors, however, may have affected the results. In fact, experimental studies performed afterwards, validated this observation (Peugnet et al., 2015). Because often, the quality of forages does not offer enough energy for pregnant mares to maintain an optimal body condition during gestation, the distribution of a concentrated feed remains important.

Is it therefore possible to provide enough energy to broodmares without affecting the health of their future foals?

In experimental studies, quality of feeds used is known and can help to develop recommendations:

- In the study of Peugnet et al., (2015) the mares received 167g of starch/100kg of body weight (BW) per meal as barley in addition to forages, or forages only during the last 4.5 months of gestation. Mares fed with barley produced more foals affected with osteochondrosis lesions at six months of age (45%) compared to mares fed with hay only (17%).
- Another unpublished study, performed in our laboratory, also compared different nutrition planes during late pregnancy. The mares were fed with a maximum of 75g of starch/100kg BW per meal (range 40-75, n=5), or a

minimum of 110g of starch/100kg of BW per meal (range 110-160, n=5) during the last 2 months of gestation. The amount of forage distributed to the mares did not differ between groups. As a result, foals born to mares fed low-starch meals were fewer to present osteochondrosis lesions (20%) compared to foals born to mares fed high-starch meals (80%) (Fig. 2).

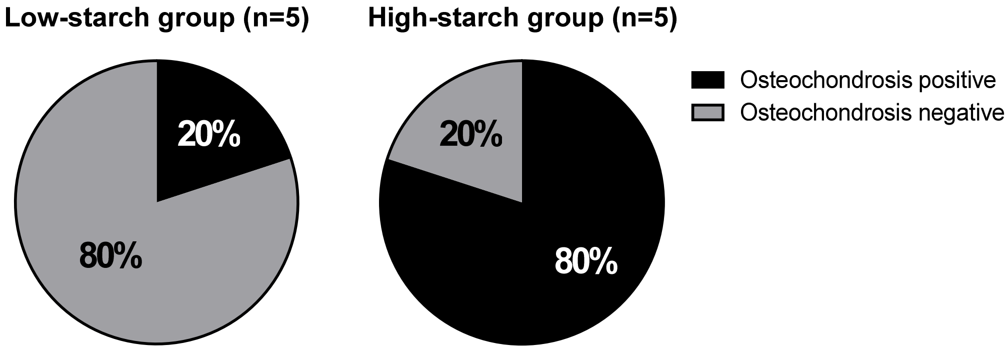

Figure 2. More foals born to mares fed with high-starch meals (>110g/100kg BW) presented osteochondrosis lesions at 12 months of age compared to foals born to mares fed with low-starch meals (<75g/100kg BW).

Clearly, these results indicate that the amount of starch distributed to mares per meal has an impact on the osteoarticular development of foals. It seems therefore that concentrated feed distributed to the mares should not exceed 100g of starch per 100kg of body weight per meal to prevent, at least, osteoarticular lesions in the foal. Further studies are needed, but this limit should be considered when balancing the feed for total energy, and when developing recommendations for customers. Long-term effects of starch amount during early pregnancy are currently unknown.

Besides an epidemiological study demonstrating that foals fed with concentrated feeds during post-natal growth had an increased risk of developing osteochondrosis lesions (Mendoza et al., 2016), no study focused on the effect of starch amount during post-natal growth in osteoarticular health of foals. The fact that the intensity of post-prandial glycaemic and insulinemic response in foals is correlated to the development of osteoarticular pathologies (Ralston, 1996; Pagan et al., 2001) indicates that starch amount in the feed of growing foals is also an important factor to consider. Until new studies are performed on the subject, it seems reasonable to set the maximum amount of starch to be distributed to foals, per meal, as 100g/100kg BW, as in pregnant mares. Effects of the choice of energy source in diet during post-natal growth on health at adulthood are however unknown in the horse.

The effect of starch amount given to stallions on sperm quality and long-term effects in the offspring are currently unknown.

Use and effects of fat

Because diets richer in starch were also richer in energy in the studies previously cited, it is not possible to discriminate between the effect of starch and the effect of energy contents in the diet on the foals' osteoarticular development. If studies performed to answer this question are still missing, feeding pregnant mares with a diet rich in starch (corn, >100g starch /100kg BW per meal) was shown to alter the glucose metabolism of foals during pre-weaning growth compared to a diet rich in lipids (corn oil, <15g starch /100kg BW per meal, 14% fat). These results indicate that fat may be a good way to increase the energetic density of the diet of pregnant mares, without increasing the starch content and without altering the post-natal metabolism of the foal.

Quality of the fat source is, however, crucial, as some fatty acids have immunomodulatory properties, are also involved in the foetal neuronal development, and can therefore affect pathways involved in fertility, but also in inflammation. They can therefore affect the quality of the maternal environment and subsequently the development of the embryo and the foetus.

Supplementing the diet with fat sources rich in omega-3 fatty acids in adult mares has been shown to:

- Increase the expression of genes involved in a hospitable uterine environment for the embryo, and in embryo and trophoblast (placental tissue) development in early gestation, at least in overweight mares. The authors supplemented the mares with algae flakes (0.06g/kg BW), rich in docosahexaenoic acid (DHA), from 60 days before, until 12.5 days after insemination.
- Increase the total omega-3 and DHA transfer from the dam to the foetus at birth (Adkin et al., 2013a), leading to an improved social behaviour before weaning (Adkin et al., 2013b) and memory and learning ability of foals at 2 years of age (Adkin et al., 2015). The authors supplemented the mares with an algae source of omega-3, from 90 days before foaling, until 74 days after, providing 18.6g of fat, 1.5g of total omega-3 and 2g of DHA per day.
- Mare supplementation with fish oil (0.11ml/kg BW) from 28 days before until 84 days after foaling (Hodge et al., 2017) increased the concentration of omega-3 fatty acid, and especially in eicosapentaenoic acid (EPA) in their

milk, compared to the use of an omega-6 riche oil (mixture of fish and soybean oil (0.33ml/kg BW), that increased the milk concentration of omega-6 fatty acids.

No effect of omega-3 fatty acid supplementation on colostrum immunoglobulin concentration (Adkin et al., 2013a; Hodge et al., 2017), gestation length (Adkin et al., 2013c), placental and foal weight at birth (Ferreira et al., 2012; Adkin et al., 2013c), nor interval to first postpartum ovulation (Adkin et al., 2013c) have been observed. Moreover, the effects of maternal supplementation with omega-3 fatty acid during gestation on maternal and foal metabolism are still unknown.

In breeding stallions, supplementation with omega-3 fat source, rich in DHA and EPA, has been shown to increase the quality of cooled and frozen semen, through the incorporation of omega-3 fatty acid in spermatozoa membranes and their role in membrane fluidity (Brinsko et al., 2005; Freitas et al., 2016). Nevertheless, effects on foal development and long-term health have not been studied.

A few sources of omega-3 fatty acid have been studied, but because of their richness in DHA and EPA, algae-rich and fish sources seem to be the most adapted to breeding.

Feed supplements: useful for improving the health of the future foal?

Proteins and amino acids

Protein needs are increased during pregnancy and lactation in mares, growth in foals, and breeding season in stallions. The quality of proteins, and especially the content of essential amino acids, such as lysine and threonine, is crucial for the development of foals. If the role of protein excess in the development of osteochondrosis lesions has been ruled out (Savage et al., 1993), no studies, however, have been performed on the effect of protein quality on the long-term health of the foals.

L-arginine is an essential amino acid during pregnancy and growth in the horse. The particular abundance of arginine in mare's milk indicates that L-arginine might be needed in much larger proportions in the foals than in other species (Davis et al., 1994). Moreover, this amino acid is the precursor of ornithine, urea, nitric oxide (NO), polyamines and creatine, which are involved in angiogenesis, cellular proliferation and differentiation, and glucose tolerance (Wu et al., 2009).

- Early gestation: Oral supplementation of pregnant mares with L-arginine (0.0125% of BW) in early gestation (from 15 to 45 days after ovulation) seemed to have very few effects on the embryo and foetus size (Köhne et al., 2018). Long term effects, however, have not been investigated.
- Late gestation: Supplementation with L-arginine (100g/day) during le last 4 months of gestation improved the glucose metabolism of primiparous mares and increased the birthweight of foals born to primiparous dams (Chavatte-Palmer et al., 2018). When the parity of the dam is not described, however, supplementation with 100g of L-arginine per day from 21 days before foaling to 7 days after, increased the non-pregnant horn arterial blood flow and shortened the gestational length (-12 days), but without affecting the placental and foal weight at birth (Mortensen et al., 2011). Effects on gestational length were however not observed in another study supplementing 50g of L-arginine/day in pregnant mares from 90 days before foaling until 14 days after (Mesa et al., 2015). Finally, L-arginine supplementation (50g/day) during lactation did not seem to affect the milk composition, nor the foal's growth and adiposity (Hunka et al., 2016).

Further studies are needed to determine the effect of protein deficiency or excess, as well as the effect of protein quality during pregnancy, lactation, growth and stallion breeding season on the long-term health of foals. As a matter of fact, alteration of protein intake in other species has been shown to affect the behaviour, health and lifespan of the offspring (Chen et al., 2009; Jahan-Mihan et al., 2015). Because some amino acids can influence the absorption and cell use of other amino acids, amino acid content of the diet should be developed in accordance to the known optimal ratios that may change between the different physiological states.

Vitamins

Studies on the effects of vitamin excess and deficiency on the health of the offspring are lacking. In other species, it has been shown that maternal imbalance in D and B-group vitamins could affect in-utero growth, but also long-term growth, metabolism diseases and behaviour of the offspring (Pannia et al., 2016).

In the horse, oral supplementation with natural vitamin E (RRR-α-tocopherol, 1678mg/day) during the last 3 months of gestation increased the quantity of vitamin E in the colostrum, the milk and the plasma of neonatal foals (Bondo and Jensen, 2011). This supplementation also increased the colostrum concentration of IgG and IgM, as well as the IgM concentration in the plasma of foals at 3 days of age (Hoffman *et al.*, 1999; Bondo and Jensen, 2011). Moreover, oral supplementation with β-carotene (1000mg/day) from 2 weeks before foaling until 6 weeks after, increased the concentration of β-carotene in colostrum and plasma of foals at 1 day of age (Kuhl et al., 2012). Long-term effects of these supplementations have not been studied but the fact that β-carotene supplementation increases insemination success may imply an effect on the uterine environment, and then, on embryo and foetal development (Kuhl et al., 2012).

Moreover, colostrum is important for the foal immunity, by bringing him immunoglobulins, native immune cells and cytokines (Burton et al., 2009; Secor et al., 2012; Perkins et al., 2014), but also for his intestinal microbiota development, because of its effects on immunity as well as its richness in oligosaccharides (Difilippo et al., 2015). Because in other species, alteration of the intestinal microbiota at birth has been linked with metabolic diseases later in life (Stiemsma and Michels, 2018), colostrum quality could also affect the long-term health of the foal through its effects on intestinal microbiota. As explained below, colostrum quality may also be correlated to the osteoarticular development of foals.

Minerals and microminerals

Calcium and phosphorus are strongly involved in bone and cartilage development. Between 4 and 8 months, foals fed with a diet imbalanced for the phospho-calcic ratio (Ca/P: 0.4) had osteoarticular lesions that were more numerous and more severe compared to foals fed with a diet balanced for the phospho-calcic ratio (Ca/P: 1.7) or enriched in calcium (Ca/P: 5.7). Effect of phospho-calcic ratio during pregnancy and lactation have not been studied but may also negatively impact the bone and articular development of the foals.

Copper is a micromineral essential for the development of cartilage and bone. Foals that develop osteochondrosis present a plasma copper concentration below normal, occasionally associated to zinc toxicosis, but also low copper storages in liver (Carbery, 1978; Bridges et al., 1984; Van Weeren et al., 2003; Coskun et al., 2016). Moreover, a diet impoverished in copper (8ppm) distributed to foals between 3 and 9 months of age was associated with development of osteochondrosis lesions compared to a diet containing 25ppm of copper (Hurtig et al., 1993). Supplementation with copper above the recommendations, however, did not seem to improve the osteoarticular health of foals, while not altering it (Pearce et al., 1998a). Nevertheless, copper supplementation to pregnant mares (0.5mg/kg BW) decreased the prevalence of articular cartilage lesions in growing foals (Knight et al., 1990; Pearce et al., 1998a), possibly through the increased copper storage in the liver of new-born foals (Pearce et al., 1998b).

Selenium deficiencies during pregnancy have been associated to white muscle disease in foals, a myodegenerative pathology, affecting skeletal and cardiac muscles, which leads to the death of the foal in most cases (Löfstedt, 1997).

The form of selenium distributed to pregnant mares is important. In fact:

- Supplementation with selenium yeast (+0.35ppm, 0.65ppm Se in total diet) during the last 4 months of gestation increased the selenium concentration in the plasma and muscle of foals (Karren et al., 2010) and decreased their plasma leptin concentration during the first 36 hours after birth (Cavinder et al., 2012). This form of selenium, however, did not affect the glutathione peroxidase activity in the plasma of foals.
- Mares supplemented with selenomethionine during the last 3 months of gestation and the 1st month of lactation had an increased concentration of selenium in milk at 7 and 30 days after birth compared to mares supplemented with sodium selenite. Moreover, foals born to mares supplemented with selenomethionine had an increased plasma selenium and bone specific alkaline phosphatase concentrations as well as an increased blood glutathione peroxidase activity at 30 days of age compared to foals born to mares supplemented with sodium selenite (Leleu *et al.*, 2017).

Special caution must be paid to selenium excess, as optimal range is very narrow, and level of toxicity close to the recommended amounts.

Other minerals and microminerals are also involved in metabolism regulation (chromium), inflammation and oxidation (iron), bone and teeth development (fluorine) and their imbalances may impact the long-term health of the offspring. As for amino acid, mineral supplementation should be developed in accordance to the balance between minerals and microminerals, as it can affect their absorption and cell use.

Pre-pro-post biotics

The quality of the intestinal microbiota in early life can impact the metabolic health, the growth and the behaviour of the individual (Stiemsma and Michels, 2018). In the horse, the composition of the microbiota has been linked to resistance to parasites (Clark et al., 2018), colic (Costa et al., 2012; Weese et al., 2015), metabolic syndrome (Elzinga et al., 2016) and behaviour (Bulmer et al., 2018; Destrez et al, 2019), but very few studies focused on the effect of the composition of the gut microbiota in early life in the development of foals.

Nevertheless, it has been shown that supplementing the pregnant mares with live yeasts (S. cerevisiae CNCM-I1079, 7.10^{10}CFU/day) from 8 days before foaling to 4 days after decreased the quantity of E. coli and enterobacteria in the faeces of foals at 10 days of age, increased the proportion of normal-looking dung and tended to increase the average daily gain of foals from birth until 20 days of age (Betsch *et al.*, 2014). These results were also observed in foals supplemented with live yeasts (from 2 to 4.10^{10} CFU/day) between the 1 and 7 days of age (Betsch *et al.*, 2014). In another study, the supplementation of pregnant mares with fermented feed products from 45 days before foaling until 60 days after did not affect the faecal pH of mares, nor the faecal concentration of culturable bacteria, but increased the maternal faecal proportion of acetate. Moreover, foals born to supplemented mares had an earlier development of the gut microbiota (anaerobic) and the gut function, leading to an increased weight between 19 and 60 days of age (Faubladier et al., 2013).

Finally, it has been shown that physiological response of foals to weaning was correlated with gut microbiota. Foals with the best responses, i.e. decreased salivary cortisol level, faecal egg count, load of commensal fungi, and increased telomere length, N-butyrate production, and average daily gain presented the highest level of Eubacterium, Coprococcus, Clostidium XI and Blautia spp. (community type 2) (Mach et al., 2017). Bacteria involved in type 2 community have been also associated to increased resistance to strongyle infection in adult horses in another study (Clark et al., 2018). These results highlight the fact that the early gut microbiota may have long-term effects on the health of the horses.

In conclusion, effects of early nutrition on other factors, such as muscular and cardio-vascular development, as well as bone strength and resistance remain to be studied in the horse. These recommendations will therefore evolve when new research will bring new information. Finally, studies on the long-term effect of quality of the intestinal microbiota, through the use of pre-pro-post biotics, but also on use of chondroprotectors during pregnancy and/or growth will help to develop recommendation use of these supplements in breeding horses.

Early markers to predict the development of the foal

Monitoring the health of the mare during pregnancy

Monitoring the body condition

Because both obesity and undernutrition during pregnancy can lead to metabolic and osteoarticular alterations in growing foals, the body condition of the pregnant mare has to be monitored regularly to adapt the diet accordingly to the mares' needs.

The body condition can be measured using:

- The body condition score, a semi-quantitative method based on palpation and visualisation of the horse. Two main different systems have been developed: on a 0-5 scale (Carrol and Huntington, 1988; Arnaud et al., 1997; Martin-Rosset et al., 2008) or on a 1-9 scale (Henneke et al., 1983). This method is easy to apply and requires no equipment, but has a low sensitivity (Dugdale et al., 2010; El-Maaty and Gabr, 2010) and reproducibility (Suagee et al., 2008). During late gestation, Henneke et al., 1983 noticed that conformation changes occur and that the weight of the foal stretch the musculature of the back, ribs and tailhead of the mare. They recommend therefore to measure the body condition score of late pregnant mares behind the shoulder and along the withers (Henneke et al., 1983). In early pregnancy, the body condition score of the mare should be below 4/5 or 7/9. At foaling, the mare should have a body condition score of 2.5-3/5 or 5-6/9.
- Because it has been shown that metabolic alterations are correlated to abnormal deposition of fat tissues in the neck crest, a cresty neck score system has also been developed and can help to identify animals with strong metabolic alterations (Carter et al., 2009).
- The measurement of subcutaneous fat using ultrasonography is precise and reproducible (Kearns et al., 2002) and may be a useful tool to assess the body condition of the mares. Nevertheless, more studies have to be performed to correlate measurements in different sites with metabolic disorders during pregnancy and health of the offspring.
- Quantification of body water through deuterium oxide and bioelectric impedance has not been tested in the pregnant mare.

Unpublished data from our laboratory suggest that subcutaneous fat measured at the rump at foaling may help to predict metabolic alteration in growing foals as this measurement is negatively correlated to insulin sensitivity in foals at 6 months (r^2=0.28) but not at 12 and 18 months of age. Body condition score at foaling, however, was negatively correlated with the insulin sensitivity of foals at 6 (r^2=0.15) and 18 (r^2=0.28) months of age. Between birth and 6 months of age and between 12 and 18 months of age foals were housed in pasture and received no cereals. Between 6 and 12 months of age, they were housed in open barns and fed cereals that affected their glucose homeostasis.

Monitoring the metabolic health

The maternal glucose metabolism has been shown to be correlated to the foal metabolism and osteoarticular development until at least 18 months of age. Insulin resistant mares, or mares that had an abnormally high insulin response to glucose injection in late gestation, produced more foals that were affected with osteochondrosis lesions (Caure and Lebreton, 2004; Peugnet et al., 2015; Robles et al., 2018a). Moreover, mares that were insulin resistant in late gestation produced foals that were more insulin resistant at 6 and 18 months of age (Robles et al., 2018a). The use of fasting/basal glucose and insulin concentrations, as well as proxies derived from these two measures did not correlate with the post-natal development of the foals (Peugnet et al., 2015; Robles et al., 2017, 2018a). Maternal metabolism needs therefore to be measured using more complex, but also more complete methods.

Insulin resistance can be measured using glucose tolerance tests, like oral or intravenous glucose tolerance tests, or euglycemic hyperinsulinemic clamps. In practice, oral and intravenous glucose tolerance tests are easier to set up than clamps. Here we will present intravenous glucose tolerance tests, because these tests were used in scientific literature.

- IVGTT: An intravenous injection of a bolus of glucose (traditionally 0.25g of glucose/kg of BW) is followed by blood sampling during 3 hours. The calculation of the area under the curve of glucose and insulin plasma/serum concentration allows the estimation of glucose tolerance.

- FSIVGTT: This test allows the simultaneous estimation of insulin sensitivity and glucose tolerance through the calculation of quantitative indexes. An intravenous injection of a bolus of glucose (Toth et al., 2009 recommend to use 0.1g of glucose/kg of BW to avoid urinary glucose spilling (Toth et al., 2009)), is followed 20 min later by an injection of insulin (traditionally 20mUI/kg of BW) and by blood sampling during 3 hours. The use of a mathematical black box model (Bergman, 1989; Boston et al., 2003) allows the calculation of insulin sensitivity (SI), pancreatic production of insulin (AIRg), glucose mediated glucose transport (Sg) and whole body insulin sensitivity (DI = SI*AIRg).

Pregnant mares in late gestation are more insulin resistant than barren mares and pregnant mares in early gestation (Fowden et al., 1984; Hoffman et al., 2003; Peugnet et al., 2015; Beythien et al., 2017a). Moreover, metabolic regulation can differ between breeds (Bamford et al., 2014; Peugnet et al., 2014). Currently, reference data, are still lacking to be able to conclude if the mare is insulin resistant or not. In French Anglo-Arabian mares, we observed that mares with an insulin resistance below 1 (as measured with an FSIVGTT, using 0.3g of glucose/kg of BW) at 300 days of gestation produced more foals that were affected with osteochondrosis lesions (Robles et al., 2018a). More work is needed to develop reference charts (quintile charts (Treiber et al., 2005)), according to breed and gestational age, that can help diagnose insulin resistance in pregnant mares.

In the young foals, however, glucose tolerance tests are not predictive of their glucose metabolism at adulthood, because glucose homeostasis is evolutive during growth and can be altered by nutrition, body condition score, exercise… (George et al., 2009; Peugnet et al., 2015; Robles et al., 2017, 2018a). It has been shown that feeding the foals with cereals during winter, compared to grass only during summer decreased the insulin sensitivity of foals born to mares with an optimal body condition during pregnancy but did not affect the insulin sensitivity of foals born to obese mares (Robles et al., 2018a). Moreover, overnutrition between 20 and 24 months of age decreased the insulin sensitivity of foals born to mares fed with enough energy, but did not alter the insulin sensitivity of foals born to undernourished mares that were already insulin resistant at 20 months of age (Robles et al., 2017).

Insulin resistance is often correlated to systemic inflammation (Robles et al., 2018a). Moreover, systemic inflammation can lead to placental inflammation. It has been shown that mares that were insulin resistant in late gestation had increased placental inflammation, as observed using RNA-sequencing and microscopy methods (Robles et al., 2018b). Furthermore, obese and insulin resistant mares, had increased plasma concentrations of serum amyloid A (SAA), a marker of inflammation, as well as their foals until 6 months of age (Robles et al., 2018a). In both studies, mares with systemic of placenta inflammation produced more foals that were affected with osteochondrosis lesions than mares that did not present these alterations. As for glucose metabolism, charts, as well as placental and blood markers, have to be developed, according to breed and gestational age.

The placenta, a marker of pregnancy disorders

Because the placenta is a transient organ delivered at birth and considered as the programming agent of foetal development, this organ is a useful marker of pregnancy disorders.

Placental measurements, such as weight, volume, surface, and placental efficiency (birthweight of foal/placental weight or birthweight of foal/placental surface) are not good markers of the future foal's development (Peugnet et al., 2014; Robles et al., 2018a,c). Moreover, these measurement are strongly correlated to maternal wither's height (Robles *et al.*, 2018d) and thus differ between breeds, but are also naturally decreased in primiparous pregnancies (Wilsher and Allen, 2003; Elliott et al., 2009; Meirelles et al., 2017; Robles et al., 2018e). Placental adaptability seem to be important in the equine species and even strong alterations of maternal environment, such as embryo transfer between breed, do not affect placental efficiency (Robles et al., 2018c).

It remains important, however, to carefully examine the placenta at birth, and particularly to search for missing parts, and white patches or abnormal coloration on the villous side.

Monitoring the quality of colostrum

As presented in part II, the colostrum is essential for the short-term health of the foal. Nutrition of the mare during pregnancy has been shown to impact the quality of the colostrum. Indeed, pregnant mares fed with a concentrated feed composed of sorghum, wheat middlings, soybean meal and hulls (starch amount unknown) or with flattened barley (167g of starch/100kg BW per meal) produce a colostrum that is less concentrated in IgG, compared to mares fed with forages only, at birth or between 12 and 18h after birth (Thorson et al., 2010; Robles et al., unpublished data).

Low quality colostrum is detrimental for the health of the neonate, but has also been correlated to onset of osteochondrosis lesions. In an epidemiological study, mares that produced foals with osteochondrosis lesions had a colostrum poorer in IgG at birth compared to mares that produced foals that remained healthy (Caure and Lebreton, 2004). Colostrum quality may be a cofounding factor with maternal energy intake and metabolism, but not with starch intake, as we did not observe any difference in colostrum quality between high-starch (>110g of starch/100kg BW per meal) and low-starch (<75g of starch/100kg BW per meal) mares at birth (Robles et al., unpublished data).

Monitoring the foal at birth and during early growth, useful to predict its health at adulthood?

As for placental measurements, foal measurements at birth are not good predictive markers for the long-term development of the foal (Peugnet et al., 2015; Robles et al., 2017, 2018a). Moreover, these measurement are also strongly correlated to maternal wither's height (Robles et al., 2018d) and thus differ between breeds, and are naturally reduced in primiparous pregnancies (Elliott et al., 2009; Meirelles et al., 2017; Robles et al., 2018d, e). They also differ depending on maternal age (Wilsher and Allen, 2003; Elliott et al., 2009; Meirelles et al., 2017) and season of birth (Hintz et al., 1979; Beythien et al., 2017b). On average, a foal born to a primiparous dam will weigh 7kg less than foal born to a multiparous dam at birth (Doreau et al., 1991 ; Lawrence *et al.*, 1992 ; Wilsher and Allen, 2003; Elliott et al., 2009; Meirelles et al., 2017; Robles et al., 2018e). When it strongly differs from expectations (considering the breed, the wither's height of the mare, and the placental measurements), however, the foal birthweight may indicate increased susceptibility to diseases in adulthood (Giussani et al., 2003; Forhead et al., 2004; Peugnet et al., 2014, 2016b). Foals born very heavy or very light for their breed (above the 90th or below the 10th percentile) should therefore be particularly monitored.

Growth rate has been linked to alterations of osteoarticular development, especially in fast growing foals, due to genetics and breed (Makvandi-Nejad et al., 2012; Teyssedre et al., 2012; Orr et al., 2013; Naccache et al., 2018), or to overnutrition (Donabédian et al., 2006; Lepeule et al., 2009). Normal growth rate, however, is not a marker of proper cartilage development, as foals with the same average daily gain have been shown to be more or less affected with osteochondrosis lesions, depending on the metabolism of the dam (Peugnet et al., 2015; Robles et al., 2017, 2018c). If fast growing foals are more susceptible to developing osteoarticular diseases, osteoarticular development can be altered by other factors in normal growing foals.

Finally, so far, no blood marker in the growing foal has been linked to the development of osteochondrosis lesions (Donabédian et al., 2008; Serteyn et al., 2010; Peugnet et al., 2016b), other than glycaemic response to feeding (Pagan et al., 2001).

Conclusion

Animal selection based on the use of phenotypic records and pedigrees is the founding principle for improvement in animal production, increasingly assisted by the analysis of genomic information. Genetics, however, are not sufficient to account for all of an individual's phenotype as its environment plays a major role for defining how genetic traits are expressed. Taking into consideration the early environment may help improve offspring health and performance. More research is needed to further understand mechanisms involved and their relevance for the equine industry, to develop biomarkers of adverse programming and propose mitigation strategies. Finally, the gut microbiota are also involved in modulating the adult phenotype and their role in transgenerational transmission of phenotype in the horse need to be explored.

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