MATERNAL NUTRITIONAL STATUS AND IMPACT ON THE OFFSPRING

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Stella Chadio
Department of Anatomy and Physiology of Farm Animals, Faculty of Animal Science and Aquaculture, Agricultural University of Athens, Greece.
shad@aua.gr

Abstract

The concept of developmental programming implies that a stimulus or insult acting during critical periods of growth and development may result in developmental adaptations that permanently change the structure, physiology and metabolism of the offspring. Maternal nutritional status has been recognized as a prominent cause of programming. To date such nutritional programming effects have been largely characterized in terms of susceptibility to cardiovascular or metabolic disease, but accumulating evidence also suggest that the concept of programming can be applied to reproductive and immunity function, as well. Specific outcomes depend on the severity, duration and stage of development when nutritional perturbations are imposed, while sex-specific effects are also manifested. Apart from undernutrition, effects of overnutrition and the complex interactions between pre- and postnatal nutrition is of high importance, especially in the context of our days obesity epidemic.Mechanisms underlying programming might include altered cell proliferation/apoptosis, changes in hormone levels or receptor abundance. The periconceptional period, during which major epigenetic changes take place, is of critical importance. Maternal malnutrition can disturb the apposition of epigenetic marks throughout this period, leading to detrimental outcomes in later life. Evidence also exists that adverse outcomes extend beyond first generation to induce transgenerational effects, through epigenetic mechanisms. Early nutritional effects on offspring phenotype also apply to domestic animals and their production traits.Delineating the mechanisms responsible for long-lasting effects of early nutritional programming will help in developing useful interventions during periconceptional and fetal life to ensure health and productivity in later life.

Keywords: *maternal nutrition, fetus, programming, offspring, periconceptional, epigenetics*

Introduction

It has become increasingly evident in recent years that the phenotype of an individual can be driven by *in utero* and early life environmental conditions. The underlying mechanism has been termed ‘‘developmental programming of health and disease hypothesis, (DOHaD), which proposes that the conditions presented during a critical window of development may result in permanent changes to the structure, physiology and metabolism in offspring (Wadhwa et al., 2009). This concept evolved from the pioneering studies of David Barker and colleagues in the late 1980s who suggested an association between birthweight and rates of adult death from ischemic heart disease (Barker & Osmond, 1986; Barker et al., 1993). Further studies were to establish inverse relationships between birthweight, a proxy of *in utero* development and the incidence of non-communicable diseases, such as cardiovascular disease and metabolic syndrome, leading to the “fetal origins of adult disease hypothesis”

(Barker, 1995). This first hypothesis turned later to "developmental origins of adult health and disease" (DOHaD) hypothesis in order toencompasses all molecular, cellular, structural and functional responses that occur after exposure to different environmental stimuli during critical periods of development, resulting to long term health consequences (Gluckman & Hanson, 2004a).

Variation in the nutrient supply during fetal life and especially maternal undernutrition has been highlighted as a dominant cause of programming, since maternal nutritional status is implicated in programming nutrient partitioning and ultimately growth, development and function of the major fetal organ systems (Lutheret al., 2005).

In an attempt to explain the observed association between early development and later disease, Hales and Baker (2001) proposed the thrifty phenotype hypothesis, according to which maternal undernutrition induces a series of adaptive processes in the fetus, trying to maximize the chances of survival in the given nutrient-poor environment, but this adaptation may become detrimental in the case of a mismatch between pre- and postnatal nutrient supply, increasing the risk for diseases later in life. Another similar approach, the "predictive adaptive response hypothesis" (PAR) was later introduced by Gluckman and Hanson (2004b), which implies that the fetus makes adaptive metabolic adjustments based on its *in utero* environment that predicts the environment into which it is likely to be born and that a mismatch between prediction and subsequent conditions leads to later health problems.

Developmental programming of disease has been tested in both human populations and experimental animal models, providing evidence of its veracity. Although the initial epidemiological studies focused on individuals with low birth weight, used as a proxy for maternal nutritional status, it is now well acknowledged that birth weight *per se* is only a reflection of an insult or multiple insults to the fetus during development and that developmental programming can occur independently of birth weight (Chadio et al., 2007; Reynolds & Caton., 2012). Evidence for epigenetic differences among individuals, who were exposed to famine early in gestation, but exhibiting a normal birth weight, strengthens this aspect further (Heijmans et al., 2008). Finally, whilst maternal undernutrition has been implicated as a key factor of developmental programming, a number of other gestational insults, such as maternal stress, metabolic conditions, obesity/overnutrition, and endocrine disrupting factors etc. have been implicated as important developmental programming factors (Vaiserman, 2015).

Metabolic programming

Effects of undernutrition

The most widely studied outcomes in both human and animals models are those related to metabolic health. In particular, the relationship between poor early growth and the development of type 2 diabetes and the metabolic syndrome is robust, as it has been observed in a wide range of studies in both human and animal models (McMillen & Robinson, 2005; Fernandez-Twinn & Ozanne, 2010). In humans, evidence linking maternal undernutrition and subsequent adult health risks have emerged from well-researched historical famines, particularly the Dutch Hunger Winter famine. From October 1944 until May 1945 cities in the western Netherlands, including Amsterdam, suffered extreme famine resulting from an embargo of food supplies imposed by the Nazi régime (Lumey et al., 1993). Numerous studies on this cohort have clearly shown that prenatal exposure to famine is associated with the later development of non-communicable diseases, such as cardiovascular disease and metabolic syndrome (Lumey et al., 2007). Direct evidence supporting the developmental

origin of health and disease hypothesis has been derived from experimental animal studies, using controlled maternal food supply during key developmental windows and precisely defining the specific outcomes related to different nutritional regimens. Animal models, most widely used in developmental programming studies have been rodents and sheep. Rodents offer significant advantages due to their short gestation period, while studies in sheep provide power for translation to human pregnancy, as sheep have a long gestation period, enabling targeting of specific developmental windows during pregnancy and produces a fetus comparable in size to humans. The pregnant sheep also serves as a valuable model for itself and other ruminants for meat and milk production throughout the world. In rats, maternal caloric restriction leads to insulin resistance and hypertension in the adult offspring (Kwong et al., 2000), while sheep offspring derived from undernourished mothers are characterized by glucose intolerance and hyperinsulinemia (Todd et al., 2009).

Effects of overnutrition

It has recently been realized that apart from fetal undernutrition, excessive energy supply during gestation as well as maternal obesity may also lead to adverse consequences, especially in our days obesity epidemic (Armitage et al., 2005). Epidemiological evidence in humans have demonstrated that maternal overnutrition result in large for gestational age babies (Catalano & Ehrenberg, 2006) and that high birth weights are also associated with increased risk for the offspring to develop obesity and metabolic alterations during adult life (Alfaradhi & Ozanne, 2011). Thus, the relation between prenatal nutrition and later metabolic disease is likely to be U-shaped, with increased risk at both ends of the birth-weight curve (Vickers & Sloboda, 2012). In later life, offspring of obese or high-fat fed mothers are mor esusceptible to developing insulin resistance, glucose intolerance and obesity (Hartil et al., 2009). More recent studies also indicate that obesity and insulin sensitivity appear not only in first generation offspring but in subsequent generations as well (Jimenez-Chillaron et al., 2016), suggesting transgenerational effects.

Reproductive programming

Reproductive axis represents a target for developmental programming, since it is largely established in fetal life. Thus, apart from metabolic programming, in the last years the DOHaD approach has been extended to encompass programming of reproductive axis and function (Chadio & Kotsampasi, 2014a). A number of data from our studies in sheep showed a sex and window of exposure effect of undernutrition *in utero* on subsequent gonadal development and function in adult animals. In particular, disturbances in follicular development reflected by increased accumulation of antral follicles of small size and reduced number of corpora lutea, consistent with anovulation were found in ten months old female lambs , born to mothers undernourished from day 1-30 or day 30-90 of gestation, respectively (Kotsampasi et al., 2009a). In males, maternal undernutrition during early to mid- gestation resulted in a reduction in the number of Sertoli cells, accompanied by an increased apoptotic rate, indicating a direct gonadal effect (Kotsampasi et al., 2009b). Effects on gonadal development have also been reported for other animal models. For instance, maternal nutrient restriction during the first third of pregnancy in cows resulted in diminished ovarian reserve, as measured by *anti-Mullerian* (AMH) and follicle stimulating hormone (FSH) levels and antral counts up to 86 weeks of age (Mossa et al., 2013).

In human studies, given the difficulty to retrospectively assess nutrition *in utero*, birth weight is usually used as a proxy for fetal nutritional status. In particular, small weight at birth

may be the result of either maternal undernutrition or reduced nutrient delivery to the fetus due to different placental insufficiency. Prospective studies with girls born small for gestational age (SGA), followed by catch-up growth, showed reduced uterine and ovarian volume and a marked low ovulation rate during their adolescence (Ibáñez et al., 2002), suggesting poor ovarian reserve. In SGA males, a number of studies have shown reduced gonadal function, as compared with those born of adequate for gestational age (AGA) weight (Cicognani et al., 2002), while others failed to detect any significant relationship between body weight and gonadal function (Jensen et al., 2007).

Overall, despite the methodological inadequacies of individual study results, accumulating evidence from animal and human studies points towards an impairment of gonadal function caused by perinatal growth restriction, probably associated with increased risk of reproductive health.

Mechanisms of developmental programming and the role of epigenetics

The mechanisms underlying programming effects may include tissue remodeling by alterations in cell proliferation or differentiation, resulting to altered organ structure and function (Hoppe et al., 2007). Endocrine programming is also considered a possible mechanism, since hormones, influenced by maternal undernutrition, can directly or through changes in placenta phenotype act on the fetal tissues to alter cell growth and differentiation, consequently affecting their function later in life (Harding et al., 2010). Particularly, glucocorticoid exposure has been implicated as a mediator of developmental programming effects (Seckl, 2004) and in this regard maternal undernutrition has been shown to alter Hypothalamo-Pituitary Adrenal (HPA) axis function in young and adult offspring (Chadio et al., 2007).

An important question arising from developmental programming hypothesis is how a transient stimulus occurring early in life can result in long-lasting phenotypic consequences later in life. Epigenetic modulation of gene transcription provides the most plausible mechanism through which fetal nutrient supply can alter gene expression in the developing fetus, leading to later permanent effects. Epigenetic regulation of gene expression include DNA methylation, chromatin and histone modifications and non-coding RNAs, which can initiate and regulate epigenetic changes in both DNA and histones (Canani et al., 2011)

Epigenetic underlying mechanisms have been implicated in a number of metabolic programming paradigms (Laker et al., 2013; Elolimy et al., 2019). For example, in the rat model of maternal dietary restriction, altered promoter methylation and gene expression have been reported for the hepatic glucocorticoid receptor (GR) and the peroxisome proliferator-activated receptor α (PPAR-α), (Lillycrop et al., 2007, 2008), influencing carbohydrate and lipid metabolism (Lillycrop et al., 2005). More interestingly, maternal overnutrition has been shown to elicit epigenetic modifications of key genes involved in insulin signaling leading to development of insulin resistance (Liu et al., 2013).

Our data in sheep also showed an increased hepatic expression,of the gluconeogenic gene PEPCK, accompanied by decreased methylation of the Glucocorticoid receptor (GR) promoter, in offspring derived from undernourished mothers (Chadio et al., 2017). Finally, in humans, data from the Dutch famine research has shown epigenetic dysregulation of genes involved in growth and metabolism, such as conserved hypomethylation of the imprinted *IGF2* gene into adulthood (Tobi et al., 2014).

The importance of periconceptional period

Another crucial issue relating to DOHad hypothesis is the timing, when environmental factors, interact with reproduction to induce a change in the development that could lead to later detrimental outcomes.

In this context, periconceptional period, which encompasses gametogenesis, fertilization, conceptus formation, implantation and placentation, represent particular time window during which epigenetic changes can have long-lasting consequences on offspring phenotype (Fleminget al., 2004). In particular, gametogenesis and conceptus development as being the main periods of major chromatin remodeling represent the most important periods during which a perturbation of the erasure and resetting of the epigenetic patterns can have long-lasting consequences on the development and function of the tissues and therefore long-term effects on offspring phenotype (Vickers, 2014; Velazquez et al., 2019).

Sex specific effects and the father's side

Sexual dimorphism is an important component of the DOHaD concept. Most developmental programming studies have shown that the same stimulus can elicit different long term effects, depending on the sex of the offspring. In particular, the phenotypic outcomes of adverse *in utero* conditions are often more prominent in male than female offspring (Chadio et al., 2007, 2014a), but the underlying mechanism is not yet well understood. The sex-specific effects observed for several programming outcomes, as a result to early nutritional perturbations, could also be explained in the light of the well-documented sexual dimorphism in environmental epigenetic programming. Male and female embryonic genomes may react quite differently to environmental stress, as has been suggested by Bermejo-Alvarez et al. (2011). As dimorphic genes' expression might be under the control of sex-specific epigenetic marks, environmental factors, including nutrition, can influence, in a sex-specific manner these flexible epigenetic marks, mainly during critical windows of development (Gabory et al., 2009).

Most epidemiological and experimental studies have focused on the maternal influence on offspring's health. However, recent studies provide evidence that paternal health conditions and in particular obesity or diabetes can induce epigenetic alterations in sperm that can be inherited, altering epigenetic marks in offspring somatic tissues (Portha et al., 2019).

The impact of DOHaD in livestock

In livestock, there is increasing evidence for the effects of prenatal conditions and especially nutrition on later development affecting tissues and organs, direly related to traits of economic importance and existed evidence is summarized in a number excellent reviews (Chavatte-Palmer et al., 2016; Sinclair et al., 2016, Murdoch et al., 2016). In animals, muscle fibers and the number of adipocytes are primarly determines during fetal and early postnatal period, thus representing possible targets of developmental programming (Spalding et al., 2008; Du et al., 2015). In particular, data on sheep suggest relatively small long-term effects of maternal nutrition on muscle fibre number, but evidence exists for increased measures of adiposity, particularly in male offspring (Jaquiery et al., 2012). Cattle studies (Micke et al., 2011) showed that the maternal diet during the first and second trimesters alters growth and carcass development, including fat deposition, from weaning through to slaughter at 22 months of age in a sex-specific manner. Therefore, improving maternal nutrition during gestation, especially during the periods corresponding to major muscle and intramuscular fat

development, may improve fetal muscle and adipose tissue development, which has long-term impacts on the production efficiency in offspring animals.

On the other hand, successful reproduction and fertility are central to the financial success of livestock enterprises and have their origins in fetal life. Accumulating evidence points towards an impairment of gonadal function caused by perinatal growth restriction, but it is of significant importance to determine if this prenatal compromise translates into any significant functional deficit in subsequent fertility, under practical conditions of breeding management (Gardner et al., 2009; Chadio et al., 2014a)

Another trait of significant importance that could be influenced by fetal development is offspring health and disease susceptibility. To this respect, it is of interest to note that the immune system is also a potential target for fetal programming (Palmer, 2011), not only during fetal life but also through colostrum transfer of maternal factors with immunomodulatory functions (Chadio, 2014b).

However, the magnitude and transgenerational persistence of prenatal effects, including those mediated by epigenetic modifications of the genome, need to be better quantified in livestock species.

Conclusions

The impact of early nutritional environment on postnatal health outcomes has been a target of an ongoing research activity and there is now ample evidence to support the developmental programming concept. The way through which environmental insults, such as nutrition contribute to the onset of later detrimental outcomes likely involves a complex interaction between the maternal environment, placental changes, and epigenetic programming of the embryo. Evidence also exists that adverse outcomes extend beyond first generation to induce transgenerational effects, through epigenetic mechanisms.

Epigenetic modulation of critical genes involved in the control of metabolic and reproductive function as well as potential intergenerational effects represent an exciting area of interdisciplinary research towards development of new nutritional approaches during pre- and postnatal periods to ensure offspring health in later life.

Nevertheless, the contribution of paternal lineage to the intergenerational transmission of detrimental outcome needs to be further elucidated. Delineating the mechanisms responsible for long lasting effects of early nutritional programming may lead to develop useful interventions during periconceptional and fetal life to ensure health in later life.

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