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Metabolic Programming: Origin of Non-Communicable Diseases in Early Life Nutrition

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ABSTRACT

Metabolic programming (MP) is defined the induction, deletion, or impaired development of a somatic structure or "setting" of a physiological system by an early life stimulus. Epidemiological and animal studies support the theory that suboptimal intrauterine conditions are associated with non-communicable disease (NCD) in adulthood. Using ovine models, we investigated the long-term consequences of late gestation undernutrition on glucose–insulin axis function and energy metabolism. We found that early life undernutrition had life-lasting consequences on insulin-secretory and adipose lipolytic capacity as well as intermediary metabolism later in life. Furthermore, we showed that suboptimal intrauterine nutrition impairs energy expenditure (EE) in gestation, apparently via an increase in the energy cost of conceptus development. Our findings, and those of other studies, support the hypothesis that energy balance is, to a certain extent, programmed early in life, presumably through appetite, EE, physical activity, and/or disproportional postnatal growth programming.

Implication for health policy/practice/research/medical education:
Metabolic programming is an emerging area of science dealing with the origins of non-communicable diseases. Impaired development due to suboptimal intrauterine conditions may cause short term as well as long term effects on the function of the organisms subsequently determining the health and disease in later life. Reading this review article is recommended to all family physicians, epidemiologists, nutritionists, animal scientist, endocrinologists and health policy makers.

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1. Metabolic Programming

Metabolic programming (MP), or developmental plasticity, is a term used to describe the induction, deletion, or impaired development of a somatic structure or "setting" of a physiological system by an early life stimulus operated at a "critical" or "sensitive" period during development (1). Impaired development may cause short-term, as well as long-term or permanent, effects on the structure or function of the organism (2). MP has been of great interest among epidemiologists and animal scientists since epidemiological observations have revealed that the manifestation of non-communicable disease (NCD; obesity, type-2 diabetes, cardiovascular disease, stroke, cancer, chronic respiratory disease, and renal disease) in adulthood can have their origin in suboptimal intrauterine conditions. The Developmental Origin of Health and Disease Society (DOHaD Society), an international, rapidly expanding society, is dealing with multidisciplinary research in the area of MP (www.dohadsoc.org). One of the aims of the DOHaD Society is to promote co-ordination of a global research strategy for scientific exploration of the link between early life conditions and NCDs in later life.

Twenty years ago, Hales and Barker, in an attempt to explain the association between poor fetal and infant growth and risk of impaired glucose tolerance and the

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metabolic syndrome in adult life, proposed the "thrifty phenotype hypothesis." According to their hypothesis, if, during intrauterine development, the supply of nutrients is scarce, the fetus is programmed to spare nutrients and become thrifty, even if nutrient availability becomes abundant later in life (3, 4). These alterations could be valuable for survival in a poor nutritional environment, but may lead to disease if the postnatal nutritional environment does not match the prenatal life conditions. In short, in their hypothesis they suggested that poor fetal and infant nutrition, mainly via maternal malnutrition, can act as the stress that triggers the metabolic programming process and suppresses the fetal growth. They also proposed that the key element linking poor early nutrition to later type-2 diabetes was poor development of pancreatic β-cell mass during fetal life. In an updated version of the thrifty phenotype hypothesis, presented in 2001, Hales and Barker included the intergenerational effects of poor maternal nutrition. The poorly nourished mother forecasts the nutritional environment into which the fetus will be born.

The metabolic processes in the fetus are set in motion, such that postnatal metabolism is adapted to survival under conditions of poor nutrition. These alterations could be valuable for survival in a poor nutritional environment, but may lead to diseases if the postnatal nutritional environment does not match the prenatal life conditions (5). They proposed that the growth, metabolism, and vasculature of the fetus may be affected by impairment in the mother's development and growth, maternal malnutrition, maternal hyperglycemia, and other maternal/placental influences. In summary, they proposed that poor fetal and infant growth leads to subsequent development of type 2-diabetes and the metabolic syndrome (5).

Developmental plasticity theory is a modification which attempts to clarify the original observed association between suboptimal conditions early in life and metabolic disorders in adulthood. According to developmental plasticity theory, permanent characteristics of an individual are founded based on environmental conditions early in life, which modify the developmental trajectory of that individual. Individuals developmentally adapted to one environment may therefore be at risk when exposed to another later in life. (6).

2. NCDs Are a Worldwide Challenge

The increased prevalence of NCD has become a major health issue in both developed and developing countries. According to the World Health Organization (WHO), nearly 80% of the 36 million global deaths were due to NCD in 2008 (63% of all deaths), and these occurred in low- and middle-income countries (7). The WHO predicts that NCD will show a significant increase, of about 15% globally from 2010, to reach 44 million deaths by 2020. Currently, 346 million people are suffering from diabetes in developed and underdeveloped nations (8). Overweight and obesity is increasing among both men and women (7, 9) in developed (10, 11) as well as in developing countries (12-16), and the shift towards earlier onset and the development of childhood obesity is particularly alarming.

In Iran, a nutritional transition toward a western lifestyle has occurred in recent decades. Along with the recent nutritional transition, the prevalence of diet-related NCD has increased in the Iranian population. Cardiovascular diseases are the leading cause of deaths in Iran, accounting for 50% of all deaths per year. More than 3.5 million people (about 5% of the Iranian population) suffer from diabetes (17). Prevalence of overweight among urban regions was higher, compared with corresponding values for rural areas (16). Prevalence of obesity, especially among Iranian women, is even higher than their counterparts in western countries (18). High prevalence of the metabolic syndrome (19), particularly among overweight adolescents (20), has also been reported.

3. Early Life Undernutrition as a Programming Stimulus

The first evidence supporting early nutrition as a stimulus for MP comes directly from epidemiological studies in human populations, particularly from the Dutch Winter Famine during World War II. During the Dutch famine, women exposed to undernutrition during late gestation gave birth to offspring with reduced birth size and these infants were found to have an increased risk of developing glucose intolerance (21) and obesity (22) in adult life. Many other studies have confirmed a clear adverse relationship between low birth weight and risk of type-2 diabetes (23-27), obesity (28), insulin resistance (29, 30), cardiovascular disease (31-34), elevated blood pressure (35-38), and elevated fat-free body mass in adults (39).

The second line of evidence is based on current knowledge of the regulation of mammalian fetal growth. In mammals, 2 major determinants of the size of the baby are uterus size and food supply from the mother. The size of the baby is regulated according to the size of the mother. A convincing study about influence of maternal size on fetal and postnatal growth has been conducted with the horses, where Shetland ponies were crossed with Shire horses. At birth, the foals were approximately proportional in weight to the weights of their mothers. Maternal regulation of fetal growth was very marked and obscured any genetic differences. (39). Nutritional animal studies provide the third line of evidence supporting nutrition as the programming stimulus (40-43). There are different kinds of animal model that have been used to study the underlying mechanisms of MP, which for ethical reasons cannot be studied in controlled human experiments. Later on in this report, we review these animal studies briefly.

What are the early life causative factors inducing de-

velopmental programming? Hormones such as glucocorticoids, insulin, and leptin are, thus far, the main candidates for the underlying mechanism of MP. Increased exposure to glucocorticoids (cortisol) can be one of the direct causative mechanisms linking adverse exposure to fetal adaptation. The fetus is normally protected against corticocorticoids due to maternal and placental corticosteroid binding globulin and placental type 1 and type 2 11β-hydroxysteroid dehydrogenase (11βHSD1 and 11βHSD2). However, under maternal stress or exogenous corticosterone administration, these protective mechanisms become deficient or fail (44, 45). Thus, excessive glucocorticoid exposure during gestation may result in long-term effects in different organs. Leptin and insulin can cross the placental/fetal barrier and affect development of the neural system important in energy metabolism. For example, leptin controls the development of the hypothalamic appetite regulatory system (46).

It has been postulated that MP can be associated with epigenetic changes, resulting in altered phenotypic expression of the genome (47, 48). Recently it is has been shown that epigenetic mechanisms are involved in different pathophysiological conditions, including the metabolic syndrome (49, 50). Epigenetic modifications fit well with the fact that the phenotype is altered in programmed individuals. However, it is puzzling that, in programmed individuals, metabolic and endocrine phenotypes are virtually absent at birth (except for changes in birth weight) and in early life, and only become increasingly manifested with age.

4. Nutritional Animal Models in MP

Possibilities such as manipulating the diet, controlling food intake and environmental conditions, establishing challenge–response data, performing frequent non-invasive measurements and invasive procedures (e.g. sampling by biopsy), and providing multiple data points within the same animal are some of the advantages of experimental animal models. Studies in rodent models, the most common animal models used in the field of MP, have been extensively reviewed previously (43, 51-53). Ovine models and their contribution to our understanding of the mechanisms underlying MP have been discussed recently (54-56). Thus, in this review, we do not intend to discuss animal models in great detail (for further discussion about animal models, see (57)). Sheep are comparable to humans in terms of birth weight (2.5–5.5 kg), litter size (singletons or twins), gestation period (term = 147 days), body size, developmental trajectory, and timing of organ development. For instance, a full complement of cardiomyocytes and nephrons occurs at birth in both sheep and humans (58). Sheep are relatively easy to manipulate surgically, and this permits studies on the effects of suboptimal intrauterine environments directly on the fetus. Biomedical research using a pregnant ovine model showed that maternal undernutrition during the periconceptional period results in altered fetal hypothalamic–pituitary–adrenal (HPA) axis development, an increased rate of premature birth, and altered fetal pancreatic function, insulin signaling, and amino acid metabolism (59). Restricted nutrition in the early part of pregnancy altered postnatal muscle development, fat deposition, cardiovascular regulation, and HPA axis function in the offspring. Maternal undernutrition during mid-gestation resulted in altered growth, adiposity, and glucose tolerance in male offspring (60). Undernutrition from day 0 to 95 during gestation programmed aspects of cardiovascular control and adipocyte function in adult sheep (61). Undernutrition during late gestation (from day 110 until term) affected intermediary metabolism and, in particular, glucose–insulin homeostasis in offspring (62). In our ovine model we investigate the long-term consequences of late gestation undernutrition (from day 100 until term) on glucose–insulin axis function, growth hormone–insulin-like growth factor-1 (GH-IGF-1) axis function, HPA axis function, and energy metabolism. Pregnant ewes were fed either adequate (100%) or restricted (60%) intake during late gestation. Postnatally, lambs were kept and reared under the same environmental conditions. We showed that offspring (about 6 months of age) born to undernourished mothers had lower insulin-secretory capacity, an increased adipose lipolytic capacity (63), and signs of perturbations in ketone body metabolism during fasting (64). After 3 years, in spite of significant reduction in body weight (16% lighter), early life undernutrition did not affect pregnancy outcome in ewes born to mothers with restricted dietary intake (total lamb birth weight). This was somewhat surprising, since litter weight is normally considered to be related to the size of the dam (65). Furthermore our studies showed that nutritional restriction during early life impaired the metabolic rate of a adult pregnant ewes later in life (discussed later in this article) (66).

With the aim of overcoming adverse phenotypic outcomes driven by early life pre- and postnatal exposure to dietary interventions, a special ovine protocol (Danish ovine model) was designed by Nielsen and her research team at Copenhagen University. In this model, ewes are fed adequately or restrictedly during the last trimester of pregnancy, and lambs born to these ewes receive either a normal milk replacer (19% fat and 24% protein) or a high-fat (38% fat and 2.1% protein) diet for the first 6 months of life. Thereafter, the animals are fed conventionally. The model has shown that skeletal muscle mitochondria of offspring are affected by both undernutrition during late gestation, and a high-fat diet in early postnatal life. Late gestational undernutrition programmed a reduction in the mitochondrial maximal oxygen uptake (VO_2max) in adult, 24-month-old sheep, but not in adolescent animals (6-month-old). The postnatal high-fat diet, on the other hand, induced a pronounced increase in the respiratory coupling ratio and VO_2max, effects, which were reversible by exposure to a normal diet from 6 months

to 2 years (67).

5. Energy Metabolism and MP

The balance between energy intake and energy expenditure (EE) is controlled through the appetite regulatory networks in the hypothalamus. There are a range of appetite regulatory neuropeptides, which either stimulate or inhibit appetite (68). In humans as well as in sheep, the neural network of the appetite regulatory system develops during late gestation (69, 70), a critical period during which the appetite regulatory network in the fetal hypothalamus is susceptible to change in fetal nutrient supply (71, 72). Since experimental studies in animals support the concept that prenatal and postnatal dietary interactions may give rise to later obesity (73-75), susceptibility of energy balance through early life programming has also received much interest in the scientific community (42, 50, 76, 77). Possible pathways of energy balance programming include permanent alteration in appetite regulation, EE, and physical activity, and disproportional postnatal growth (*Figure 1*). Different nutritional inputs can influence an immature hypothalamic appetite network (78). Interestingly, an enhanced nutritional plane during late gestation in sheep influenced early appetite behavior (72). A key mediator of this effect is leptin and its effects on hypothalamic reorganization. It has been shown that neonatal exposure to leptin can simply reverse both the genetically predetermined hyperphagic and obese ob/ob mouse phenotype and the dietary-induced obese and lethargic rat phenotype (79, 80). Recently, it has been shown in sheep that fetal hypothalamic leptin signaling is altered by increased adiposity and leptinemia (81).These prenatal changes in appetite regulating networks in the hypothalamus could impact the regulation of postnatal energy balance.

There is evidence both in humans (82) and in animals (83) that cost of pregnancy in terms of energy is closely related to the maternal energy status. The fact that mothers in different countries have enormously different energy intakes (82) proves that drastic metabolic adaptations in both the pregnant mother and/or her fetus must take place (84). In pregnant women, energy-sparing adaptive mechanisms have been observed (82), and similarly, in sheep we have shown that intake restriction during

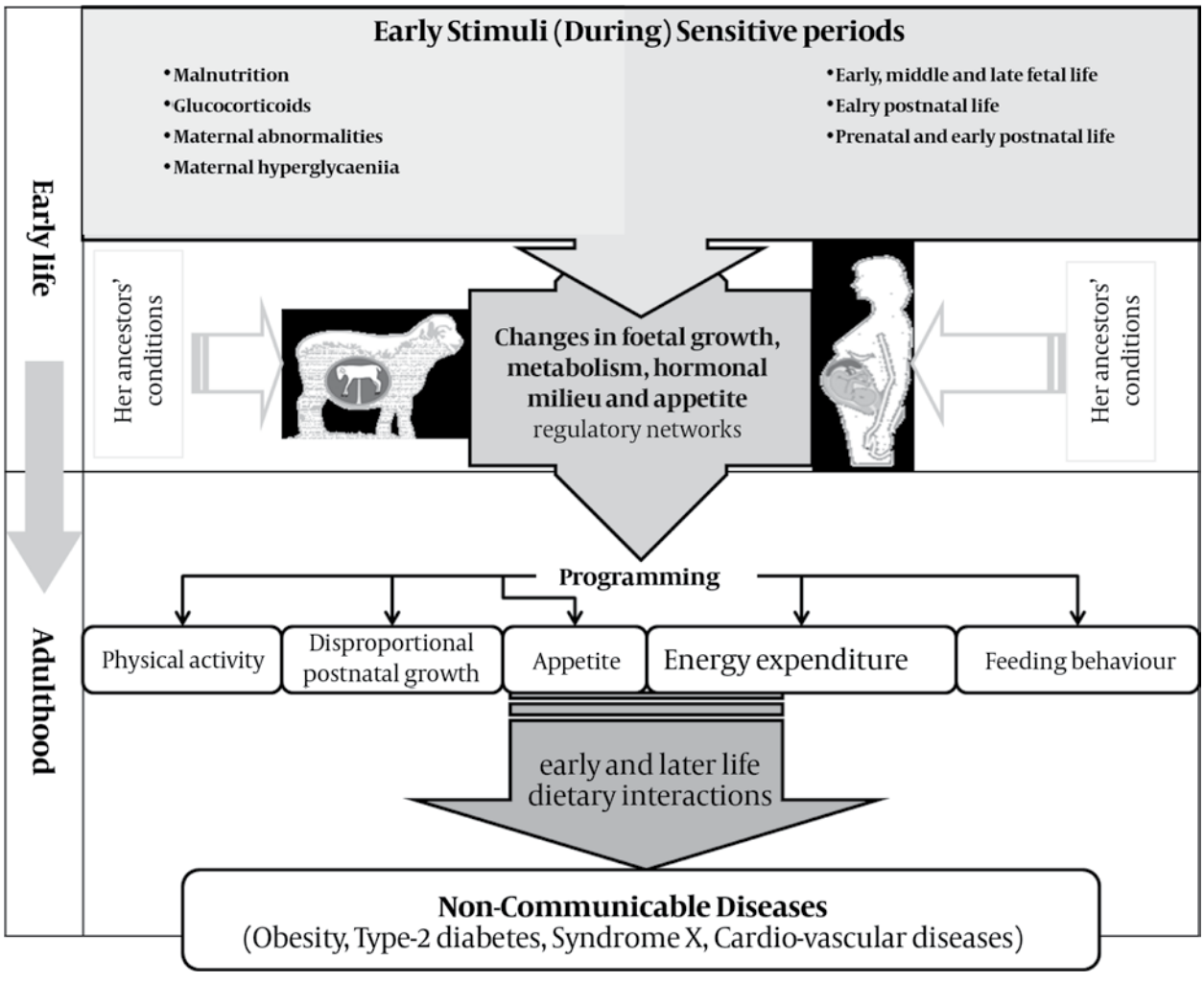

Figure 1. Schematic representation of Metabolic Programming of Energy Metabolism and Related NCDs

late gestation reduces EE of gestation (83). On the other hand, a developing fetus is capable of adapting cellular and body functions upon exposure to suboptimal conditions. One clear example of fetal adaptation is the reaction of the fetus to hypoxemia. When a fetus becomes hypoxic, the fetal blood flow is redistributed towards the brain and away from other organs. The weight of the fetal liver and thymus decreases due to late gestation maternal undernutrition in sheep (85). Even though functional metabolic adaptation in maternal and fetal energy metabolism may presumably support fetal growth, fetal compensations that either deprive organs or alter functions may impact energy balance later in life. Basically, during gestation, the fetus is growing and meanwhile EE increases in humans (86, 87) and in animals (88). The increase in EE during gestation has 3 different origins: 1) EE required for body maintenance; 2) EE required for conceptus growth; and 3) EE from increased metabolism in the non-gravid tissues (88). Metabolic features and endocrine systems involved in regulation of energy intake and expenditure are indeed altered in undernourished dams and fetuses. However, it is as yet unknown whether adaptations in gestational energy balance can induce permanent alterations in energy balance, in terms of intake and expenditure in later life.

We conducted a long-term study in order to investigate whether late gestational undernutrition programs the EE of gestation during adulthood in the offspring. Offspring were maintained for 3 years. When the female offspring became pregnant adult ewes, they were fed adequately or restrictedly during late gestation of their second parity. Accordingly, offspring were categorized into 3 groups: Adequate–Adequate (AA), Adequate–Restricted (AR), and Restricted–Restricted (RR), based on their early life and current nutrition status. At 2 weeks prepartum, the EE of gestation was measured. Surprisingly, RR ewes did not reduce the EE of gestation in response to late gestational feed restriction, in contrast to the AR ewes. This finding indicates that nutritional restriction during early life may impair the ability of adult pregnant ewes to adapt to changes in metabolic rate. Furthermore, the failure of RR ewes to reduce the EE of gestation in response to late gestation nutrient restriction was apparently related to the higher EE for conceptus development. Even though the underlying mechanism for the apparent loss of metabolic adaptive response in adult ewes subjected to early life undernourishment is at present unknown, it might be interpreted as a thrifty way by which nutritional challenges are handled by ewes who were nutritionally-restricted in early life. Unfortunately, feed intake and physical activity of animals were not recorded. Studies in rats showed that prenatal high protein exposure increases adiposity and decreases EE in young rats (89, 90). Increased food intake and reduced physical activity has also been reported to be induced by maternal undernourishment or protein restriction during pregnancy in rats (91, 92). These studies are not yet conclusive, and thus more clinical and epidemiological studies are needed to elucidate whether suboptimal conditions in early life can program energy metabolism (intake, expenditure, physical activity, feeding behavior, and appetite) in humans.

6. Challenges and Future Research

A dramatic global increase in the prevalence of NCD has occurred in recent decades. Taking into consideration that the cost of hospitalization and healthcare expenditure is higher for NCD, urgent preventive strategies and multidisciplinary research approaches are needed to tackle the increasing prevalence of NCD amongst the Iranian population. More attention to the research into MP may help us to slow down the increase in NCD, and particularly, the manifestation of NCD in adulthood, which may originate in suboptimal intrauterine conditions. Both epidemiological and animal studies are required to understand the pathophysiological underlying mechanisms. Because energy balance has an obvious relation to NCD, more focused research in MP will also help us to challenge the increasing rate of NCD in our community.

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