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Intrauterine programming

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ABSTRACT

In mammals, the intrauterine condition has an important role in the development of fetal physiological systems in later life. Suboptimal maternal environment can alter the regulatory pathways that determine the normal development of the fetus in utero, which in post-natal life may render the individual more susceptible to cardiovascular or metabolic adult-life diseases. Changes in the intrauterine availability of nutrients, oxygen and hormones can change the fetal tissue developmental regulatory planning, which occurs genomically and non-genomically and can cause permanent structural and functional changes in the systems, leading to diseases in early years of life and those that particularly become overt in adulthood. In this review we take a brief look at the main elements which program the fetal system development and consequently induce a crucial impact on the cardiovascular, nervous and hormonal systems in adulthood.

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Introduction

Strong evidences based on epidemiologic studies indicate that the physiologic functions of the body systems during life is highly under the influence of intrauterine conditions in which the mammalian fetus develops. The morphometric analysis of the human epidemiologic data has shown that the improper fetal growth, which is usually manifested with low birth weight or low ponderal index, is related to the later life diseases, mainly, metabolic disorders such as type 2 diabetes, glucose intolerance, insulin resistance, hyperlipidemia, hypercortisolemia, obesity and cardiovascular problems such as hypertension and ischemic heart disease (1-4). These observations have led to the hypothesis that adult disease arises '*in utero*' as a result of changes in the key organs and systems under suboptimal intrauterine conditions (3, 5) and in the critical stages of development (4, 6) with irreversible consequences (6). This process is known as 'intrauterine programming' (2-7). The timing, duration, severity, and type of insult during development determines the specific physiological outcome (2, 8).

The underlying reason for this phenomenon is not clearly understood (1). Toward understanding the mechanisms of this modified planning based on the human studies some hypotheses have been born (4, 6, 9, 10). In 1989, D. Barker showed the relationship between the lower birth weight and coronary heart disease for the first time (4, 6, 7, 10). In 2001, the "thrifty phenotype" theory was proposed, suggesting that fetal malnutrition may induce physiological adaptations to ensure nutrient supply to the most vital organs at the expense of the others (11). Further extension of this theory emerged in 2004 as "predictive adaptive response", which states that the fetus predicts the environment into which it is likely to be born and adapts to gain a competitive advantage after birth (12).

However, apart from the theories, physiological studies in mammals have shown that the first important line of the fetal growth and development is dependency on nutrient and oxygen supply. The endocrine system, as an internal cue, while dependent on nutrition and oxygenation, by its own has main roles in programming of the developmental stages (2). Nevertheless, there is still a close relationship between the nutritional status during pregnancy and proper functioning of hormonal systems.

Addressing these concepts, in this review we attempt to briefly explain the crucial factors underlying the uterus programming, which are:

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nutrition, oxygenation and maternal and fetal hormones, their interactions and effects on development and functioning of the organs pre and post-natally.

Nutritional programming

The quality of the maternal diet, as potential stressor, may disturb normal fetal development. In this regard, the developmental origins of health and disease (DOHaD) hypothesis, argues the concept of poor nutrition status during pregnancy and its link to the disease process in human population (5). For instance, a series of studies related to the population born in Helsinki in the 1920s and 1930s or the follow-ups of 1944/45 Dutch famine confirmed the association of low birth weight with cardiovascular disease (CVD) and type 2 diabetes (5, 6). In order to further explain the link between malnutrition, low birth weight and CVD and diabetes, we refer to 'Thrifty phenotype hypothesis', which states that maternal or fetal malnutrition can affect fetal growth, metabolism and vascular development. These changes affect the development of fetal organs, such as kidneys (reduction in glomerular filtration rate (GFR) and nephron number), which can lead to hypertension and pancreatic β-cells, leading to diabetes type 2 in adulthood (13, 14). Also, the *in vivo* studies have shown that in abnormal intrauterine environment, such as when deficient of several micronutrients, especially those which act as co-factors or molecular donors in epigenetic processes (such as folic acid and vitamin B_{12}), induce epigenetic modifications (such as DNA methylation) of the key genes which are, for instance, involved in regulation of pancreatic β-cells (6) or normal cardiovascular development (14). A probable link between low birth weight, which can be caused by fetal malnutrition, and CVDs, like hypertension in adulthood, has been recently proposed by introducing endothelial colony-forming cells (ECFCs) as a type of endothelial progenitor with the ability to form tubular and capillary structures. This ability is markedly reduced in infants born with low weight in comparison to normal newborns. These findings provide an important evidence of a relationship between birth weight and the angiogenic properties of ECFCs, and a potential mechanism for the microvascular rarefaction, arteriolar narrowing and decreased vascular branching (15).

To study the maternal diet effect, animal modeling of nutritional deficits are made in a wide variety of ways, including global food, macronutrient and micronutrient (1, 5) restrictions, to provide a better prospect under the controlled environment.

Global food restriction diet

Food restriction diets, in a part or whole gestational period, are widely used in animal experiments. This experimental diet model is compatible with human studies, since it is associated with lower birth weight. Maternal global under-nutrition produces various pathological conditions in adult offspring, such as increased blood pressure (6, 9, 16), probably by reducing nitric oxide (NO) production and endothelial deficiencies (16, 17), glucose intolerance (4-6, 13, 18, 19) likely due to low protein diet (20), sensitivity of the immune system (1, 9), abnormal development of hypothalamic-pituitary-adrenal (HPA) axis (21) probably related to increased basal cortisol and altered HPA responsiveness to challenge (22), insulin growth factor (IGF)-1 and insulin deficiencies (1, 23), adrenocorticotropic hormone (ACTH) response modifications (21) and altered cholesterol homeostasis, which might lead to CVD in offspring (1, 5). Most likely, the hyperglycemic and amino acid-depleted maternal environment made by under-nutrition, act as an early mechanism of programming and initiate metabolic stress: restricting early embryonic proliferation and proper cell lineage and differentiation (9). Maternal under-nutrition consequences are not restricted to the first generation of offspring (17, 20, 22, 24). Studies by Painter *et al* showed that the second generation of women who were pregnant during Dutch famine (1944-1945, last years of World War II), were associated with adiposity and poor health in their adulthood. They did not find any evidence for cardiovascular or metabolic disorders (25). However, studies on guinea pig conducted by Bertram *et al* showed that the first generation of undernourished pregnant females had marked increase in their blood pressure and left ventricular wall thickness, while the second generation only demonstrated increase in the thickness of their left ventricular wall without showing any high blood pressure, when both generations were compared with those born from nourished mothers (22). Maybe the cardiovascular changes were not reported in the second generation of Dutch famine due to lack of echocardiography tests to detect the changes in the structure of the heart without affecting blood pressure. Bertram study also detected higher weight and cortisol levels (modified HPA function) in the second generation of undernourished animals (22). In contrast to animal studies, the studies on the second generation of Dutch famine did not contain any reports on hormonal or psychological changes related to HPA function.

Macronutrient restriction

Maternal low protein diet (MLP) models of fetal programming have been extensively studied in relation to mechanisms that link maternal nutrition with impaired fetal growth and later CVD and diabetes. Elevated blood pressure in offspring,

possibly noted from the time of weaning continued into adult life along with renal dysfunction, is one important consequence of MLP diet (5, 8, 26). Studies have argued the changes in angiotensin II receptor (27, 28) and/or the enzymatic system regulating the male hormone concentration and their role in production of hypertension in MLP offspring (29). Animal studies have also shown that MLP in lactating mothers causes higher thyroid iodine uptake and serum levels of thyroid hormones (THs) in offspring (30). Therefore, according to the studies, it seems more likely that MLP diet produces chronic diseases, possibly by modifying the hormonal system in offspring.

Micronutrient restriction

Includes deficiencies in minerals (calcium, iron), cofactors (folic acid, taurine) and vitamins (A and D) (2). For example, iron restriction prior and throughout pregnancy, leads to offspring with lower birth weight, raised blood pressure after weaning and low nephron number in the kidney (5, 31). Zinc deficiency in pregnancy produces insulin resistant adult offspring (32). Selenium is considered essential due to its participation in major metabolic functions; it is a major co-factor of some enzymes such as glutathione peroxidase (GPx) and iodothyronine 5-deiodinase with critical roles in thyroid hormone homeostasis. Maternal deficiency of selenium leads the neonate into serious conditions such as: chronic lung disease, hemolytic anemia, sick euthyroid syndrome, late-onset sepsis, and neural tube defects in premature infants, as well as Keshan cardiomyopathy, encephalopathy, systemic immune response syndrome and transient hypothyroidism in full term neonates (33). Maternal selenium deficiency is a potential hazard for pre-eclampsia (34). Other antioxidative stress minerals which have an important role in prevention of pre-eclampsia are zinc, copper, iron and calcium (35). Calcium or vitamin D deficiency during pregnancy exposes the mother to a higher incidence of pre-eclampsia (36), abortion (37) and decreased fertility (36). The fetus is entirely dependent on the mother for an adequate supply of 25(OH) D_3, which is believed to cross the placenta. Hypocalcemia and increased parathyroid hormone secretion induce synthesis of 1,25-dihydroxy vitamin D after birth in both full term and preterm neonates (37). Fetal complications are higher risk of infection, neonatal hypocalcaemia (36), low birth-weight, impaired development and rickets (37). An inadequate supply of iodine during gestation, especially mid-gestation, results in damage to the fetal brain. Mid-gestation is a period during which the mother is the only source for the developing fetal brain. Corticogenesis process occurs before mid-gestation, and lack of mother's adequate support with increased levels of THs (because of iodine deficiency) in this period, would lead to mental retardation and cerebral palsy of the neonate. worldwide, the most prominent cause of pregnant women hypothyroidism is iodine deficiency, which is either caused by iodine deficiency, probably because of geographical location, such as Papua New Guinea and Andean regions, where endemic goiter with cretinism occurs (38), or autoimmune thyroid disease, which is common in 2% to 3% of euthyroid pregnant women in Western countries (39).

Oxygenation

Oxygen is a main substrate for energy generation and crucial for fetal and placental growth. O_2 insufficiency, leads to the cessation of fetal growth in favor of brain and heart cellular survival (40, 41). During pregnancy in high altitudes, although the maternal arterial and venal O_2 pressures (PO_2) are notably decreased, the fetal O_2 consumption is not changed. It is suggested that in such hypoxic situation, the placenta switches the glucose consumption from oxidative to anaerobic and therefore, spares the O_2 for the fetal consumption; this is done through a mechanism called metabolic reprogramming. In this way low glucose levels reach the fetus and are likely the cause of decline in the fetal intrauterine growth (40, 42, 43).

Hypoxia induced-intrauterine growth retardation/restriction (IUGR) is also the cause of abnormalities in cardiovascular function in adult offspring (2). To exemplify, in the chick embryo, hypoxia in the mid to late incubation period intensifies the periarterial sympathetic nerve stimulation responses and on the other side, down regulates NO-dependent dilator function in the vessels of the adult birds. In rats, prenatal hypoxia impairs endothelium-dependent relaxation in the mesenteric circulation of the adult offspring (2, 44). The specific mechanisms by which the growth retardation happens are still unknown (40).

Hormones

Hormones affect tissue formation and differentiation in utero, and specific hormone deficiencies are associated with particular types of fetal growth retardation. They act on fetal growth directly via genes and indirectly by changes in placental growth, fetal metabolism, or production of growth factors and other hormones by feto-placental tissues (6). The hormonal concentrations in the fetal circulation change during development and in response to other stimuli such as, under-nutrition, hypoxemia and stress (2, 45).

The key hormones involved in the intrauterine regulatory process are glucocorticoids (GCs), insulin, IGFs and THs (3).

Glucocorticoids

GCs are essential for life. The most notable functions of GCs during development are affecting

tissue differentiation and promotion of maturation of organ systems (3). Maternal steroid treatment is one of the best life-saving treatments in prenatal medicine. Prenatal administration of steroids, reduces the risk of severity of respiratory distress syndrome and improves the survival of preterm infants (46). Nevertheless, in certain circumstances, exogenous administration of steroids may be paid by loss of brain cells, increased neurodevelopmental disability, IUGR, and an increased risk of preterm delivery (47), and since exposure to synthetic GCs in utero results in hyperactivity of the HPA axis in adulthood, it may be linked to the premature onset of cardiovascular and metabolic diseases, such as hypertension and diabetes (46).

GCs regulate and/or modulate many pathways, including those involved in metabolism, response to infection, stress responses, blood pressure maintenance, and fluid and electrolyte homeostasis (47, 48). The placental 11β-hydroxysteroid dehydrogenase enzyme (11β-HSD) regulates and maintains the concentration of GCs in the fetal circulation. However, low expression of placental 11 β-HSD, caused by MLP diet, or maternal stress, which increases the glucocorticoid release, can expose the fetus to higher levels of the hormone (3, 48).

The endogenous GCs are essential for many aspects of normal brain development. Within the developing brain, the limbic system is particularly sensitive to endogenous and exogenous GCs. The exogenous synthesis GCs may modify brain's glucocorticoid receptor expression, which can result in long term modification in HPA axis. Fetal exposure to exogenous GCs during the critical periods of brain development may also exert a profound influence on the limbic system (primarily the hippocampus), resulting in long-term changes in cognition, behavior, memory, co-ordination of the autonomic nervous system, and regulation of a number of endocrine system functions later in adult life. Repeated administration of GCs in pregnancy, may result in decrease in neurogenesis and in the brain weight in fetus and neonate (46).

There is an association between the prenatal glucocorticoid exposure and adulthood hypertension in rats, sheep and non-human primates. The probable underlying mechanisms include alterations in kidney and cardiovascular system structure and function, glucose and insulin levels during the last trimester, as well as alteration in renin–angiotensin–aldosterone system activity (48). Cases of pregnant women with adrenal insufficiencies are not common. Usually the reason for adrenal insufficiency in mothers is adrenal autoantibodies, which are capable of crossing over the placenta. In most cases the neonate is born with some respiratory deficiencies and later needs to be checked for adrenal insufficiency (49).

Insulin

Insulin plays an important role in fetal growth (50). Fetal insulin levels are highly dependent on glucose concentration. Insulin does not have crucial effects on fetal tissue differentiation or maturation, though it enhances tissue accretion via its anabolic effects on fetal metabolism and by stimulating the production of IGF-1 (3). Insulin deficiency reduces and insulin infusion raises plasma IGF-1 levels, but in either way insulin does not affect IGF-2 levels; they both act synergistically to enhance accumulation of glucose and amino acids in fetal tissue (51). IGF-1 specifically enhances insulin sensitivity, particularly via IGF-1 receptors in muscles (52).

Diabetes, glucose intolerance, insulin resistance, dyslipidemia and obesity are related metabolic disorders commonly associated with impaired intrauterine growth (1).

During the fetal life, amino acids determine insulin secretion by pancreatic -cells (1,52). MLP diet causes uneven distribution of pancreatic islet cell proliferation, decreased cell size, insulin content, reduction in mitochondrial glycerophosphate dehydrogenase (mGPDH) activity and islet vascular density at birth, as well as affecting insulin-sensitive tissues and production of insulin resistant offspring (1, 5, 53, 54).

Thyroid hormone imbalances in fetuses and neonates (55), can interact with glucose metabolism. Studies have shown that gestational hypothyroidism causes reduction in insulin secretion, not insulin pool of pancreatic β-cells (56, 57), and high glucose levels in aged adult male offspring versus young and euthyroid rats (19). Moreover, gestational hypothyroid neonate rabbits displayed reduced brain insulin receptors, which could be normalized by T4 treatment (58).

Alternatively, the streptozotocin-induced diabetes in pregnant rat caused the total decrease in T4 and T3 pools to one-third of normal values in offspring. Maternal insulin treatment avoided the TH changes in the fetus (59).

IGFs

The Insulin-like growth factors, IGF-1 and IGF-2 have a key role in regulating feto-placental growth by affecting the metabolism, mitogenesis (by preventing apoptosis and increasing DNA) and differentiation, throughout gestation (3,60). During mid to late gestation, *igf2* gene expression is more abundant than *igf1* gene expression and IGF-2 is 3 to 10-fold higher than IGF-1 in fetal plasma. After delivery, the plasma IGF-1 level raises and IGF-2 level declines. Deletion of either *igf-1* or *igf-2* genes retards fetal growth to a similar extent. Deletion of both genes simultaneously, leads to a newborn with only 30% of normal body weight. Since, both IGFs act on IGF-1 receptor to stimulate tissue accretion, deletion of this receptor gene produces more severe

growth retardation than seen in either of IGFs' gene deletions. In human, homozygous partial deletion of IGF-1 gene is associated with failure in growth, both in utero and post-natal. Deletion of IGF type-1 receptor in murine is proved to be fatal at birth. Over-expression of IGF-2 in murine causes generalized organomegaly with kinky tail, edema and cardiac abnormalities, which might be lethal at birth.

While IGF-1 affects the fetal growth directly, IGF-2 provides the constitutive stimulus for feto-placental growth by indirect action on maternal metabolism and placental development and capacity of nutrition transport to fetus (51,60). Nutrient restriction and arterial blood pO2 and glucose levels, have more pronounced effects on IGF-1 than IGF-2 concentrations in fetal blood. Also, hormones which regulate fetal development, such as insulin, thyroid and GCs have more effects on IGF-1 expression than IGF-2 in fetus. For instance, in hypothyroidism, the low levels of IGF-1 are accompanied by fetal growth retardation (51). Therefore, as A.L. Fowden has thoroughly described in her documents, it seems that IGF-2, as a growth hormone, is more effective during fetal life, with less dependency on extrinsic factors, like nutrition, oxygen and maternal hormones than IGF-1. IGF-1 is more effective in post-natal life, maintaining the continuous growth and development of the newborn with more dependency on nutrient and growth hormone.

Thyroid hormones

THs, triiodothyronine (T3) and thyroxine (T4) play an essential role in normal fetal development of physiological systems, especially central nervous system. Congenital hypothyroidism is a hormonal state of insufficient TH secretion starting in utero and present at birth or post-natally. Maternal iodine insufficiency or defects either in fetal thyroid gland (thyroid dysgenesis: aplasia, hypoplasia or ectopic thyroid gland), the pituitary gland or the hypothalamus can lead to insufficient TH release, which is critical for different periods of prenatal as well as post-natal brain development. Depending on the biochemical severity of thyroid deficiency these infants may develop mild to overt hypothyroidism in the first weeks or months post-natally (61). Mild TH insufficiency in congenitally hypothyroid humans can produce measurable deficits in specific neuro-cognitive functions, and the specific consequences of TH deficiency depend on the precise developmental timing of the deficiency. For instance, if the TH deficiency occurs within the first trimester, offspring will develop reduced visual attention and processing, and gross motor skills, while if it occurs within the second trimester, it would lead to still subnormal visual and slow motor responses and fine motor deficits. If TH insufficiency occurs after birth, language and memory skills are mostly affected (62).

However, iodine deficiency in the most important target groups, which are pregnant mothers, fetuses, neonates, and young infants leads to brain damage resulting in irreversible mental retardation. This is the consequence of thyroid failure occurring during pregnancy, fetal, and early post-natal life. The most serious complication of iodine deficiency is *endemic cretinism* (63), a syndrome within the spectrum of iodine deficiency disorders (IDDs) (64), characterized by irreversible mental retardation, deafness, and spastic diplegia (65). Cretinism mostly occurs as a predominant neurological syndrome (mentioned above) or less commonly, predominant hypothyroidism (characterized by severe hypothyroidism (65) with less severe mental defect and physical growth retardation (64)), or combination of both (63). These consequences are irreversible if not treated soon after birth (65).

THs enter the brain cells in two ways: 1. By crossing the endothelial cells of the blood–brain barrier (BBB) by the OAT1P1C transporter (transports T4>T3), they enter astrocytes, where, T4 can be converted into T3 via deiodinase. THs then enter the neuron by the MCT8 transporter (transports T3>T4) 2. Circulating T4 and T3 may also enter neurons (and astrocytes) directly via these transporters through gaps in astrocyte's end feet. In fact there are some evidences, based on deiodinase 2 knocked out mice studies, indicating that T4 is not only a pro-hormone, but also an active stimulator of neural functions in fetal brain (66). Fetal hypothyroidism is a prevalent gestational thyroid malfunction (37), which results in abnormal development of all fetal/neonate organ systems, a syndrome termed cretinism. Treatment with THs, if initiated within weeks after birth, restores essentially normal development, while treatment after this critical period is ineffective. Extended studies on rat have shown that THs regulate a variety of genes in the neonatal brain. However, expression of most known TH-responsive genes is reduced only 2 to 3-fold in hypothyroid. Therefore, THs deficiency results in multiple morphological alterations in neonatal rat brain. Size of cortical neurons, dendritic branching, axonal density, synaptic number and morphology, and number of neurons in various parts of brain are reduced, as well as defects in cell migration and differentiation. Another striking defect in the hypothyroid neonatal brain is the reduction in myelination, which markedly affects neuronal connectivity, and the establishment of neuronal networks (67).

THs induce changes in the heart parameters by directly affecting transcription of specific and nonspecific cardiac genes (68, 69). Marked changes occur in the myocardium under the control of THs during the last third of gestation. There is a dramatic increase in the number of cardiomyocytes, as well as a transition from mononucleated to binucleated myocytes (a measure of maturation), with increases in right and left ventricle wall masses. Studies have

shown that the fetal heart of thyroidectomized sheep display a decreased binucleated cardiomyocyte population and cell cycle activity (70). THs stimulate the transcription of α-myosin heavy chain (α-MHC) and inhibit that of β-myosin heavy chain (β-MHC). Similarly, the sarcoplasmatic reticulum ATPase isoform 2a (SERCA-2a) and its regulatory subunit phospholamban (PLB) are reciprocally regulated by THs. Neonatal hypothyroidism has been shown to decrease SERCA-2a levels and increase cardiac PLB levels, whereas neonatal hyperthyroidism leaves SERCA-2a levels unchanged, but decreases cardiac PLB expression (71). Fetal or neonatal hyperthyroidism is a rare condition and its incidence has been estimated around 1:4000–40000. The most common causes are maternal thyroid autoimmune disorders, such as Graves' disease and Hashimoto's thyroiditis. Rarer non-autoimmune causes recently identified are represented by TSH receptor mutations leading to constitutively activated TSH receptor. Infants born to mothers with Graves' history may develop neonatal thyrotoxicosis. Fetal/neonatal disease is due to transplacental thyrotrophin receptor stimulating antibodies (TRAb) passage. Thyrotoxic state may have adverse effects on the outcome of pregnancy and both on the fetus and newborn. Thyrotoxic fetuses may develop goitre, tachycardia, hydrops associated with heart failure, growth retardation, craniosynostosis, accelerated bone maturation and increased fetal motility (72).

Changes in heart rate, cardiac index and systemic vascular resistance (73) are prominent effects of fetal thyroid disorders. THs modulate post-natal changes of cardiac excitation-contraction coupling at the level of contractile function and calcium handling (74). Hypothyroid patients are subject to reduced oxidative metabolism, higher rate of oxidative stress, and higher levels of lipoproteins and low density lipoprotein (LDL) in plasma (69).

In vessels, T3 reduces the resistance especially in arteries. Therefore, the cardiovascular system response to hypothyroidism are low cardiac output and pulse pressure, and increased vascular resistance, while the opposite symptoms are seen in hyperthyroidism (39, 71, 75, 76). Furthermore, the response of the vessels is changed to the vasoconstrictors and vasodilators (77, 78). Studies indicate that, gestational hypothyroidism markedly reduces the isolated vascular smooth muscle (VSM) in response to vasoconstrictors compared with euthyroidism (77, 79, 80). This modified reaction of the VSM system may be under the influence of altered adrenergic receptors, NO, and calcium channel systems in developing fetus vascular function (39, 74, 79-85).

Hypertension is an important outcome of THs gestational deficiency. THs stimulate relaxation of VSM by increasing NO production, through the activation of induced nitric oxide synthase-nitric oxide synthase (iNOS), and neural-nitric oxide synthase (nNOS) via the PI3K/Akt-signalling pathway (69, 86). Also, T3 has an indirect control over hypertension through regulation of cytochrome *P450* and by inhibiting oxidative stress within the vessel wall (69, 87). THs also down regulate angiotensin I and II receptor mRNA expressions, and therefore, inhibit hypertension under normal conditions (69, 88, 89).

Based on extended effects of THs in fetal development it would not be surprising to mention a significant influence of these hormones on fetal/neonate skin development. In fact, THs regulate laminin expression in skin negatively, which means an increase in fetal THs levels, would decrease laminin expression. In maternal hypothyroidism the opposite is in effect. Also, maternal hypothyroidism causes significant decrease in epidermis thickness and hair follicle count in neonate (90).

These studies clearly indicate that the fetal developing of endocrine system is closely regulated by balanced maternal endocrine hormonal influence, which otherwise, would lead to serious modifications in the programming of pre and post-natal endocrine systems in offspring.

Conclusion

Intrauterine life is a crucial period of development, in which the intrinsic and extrinsic factors can play an important role in the fate of the post-natal life. Epidemiological studies have shown that inadequate fetal growth, manifested by low birth weight, can lead to chronic adulthood metabolic and cardiovascular disorders. Based on these observations, a hypothesis was raised, indicating that adult diseases may have in utero origin, when suboptimal intrauterine conditions, at critical stages of fetal development, induce irreversible changes, which manifest themselves in post-natal and adult life. This process was called intrauterine programming. The most important factors in fetal growth and development are nutrient and oxygen supply. The physiologic responsiveness of fetal tissues to hormones in a great part is dependent on tissue nutritional and oxygen supply. Epidemiological studies have evidenced through history that poor nutritional status during pregnancy is one of the main causes of later cardiovascular issues such as hypertension and diabetes type 2 in offspring for the next two generations. Animal studies have also shown that restriction in protein, vitamins and mineral elements such as iron, calcium and iodine in the diet during gestation, is the main cause of changes in the fetal cellular function and responses to hormonal release and therefore, serves as the basis for post-natal and adulthood neuronal as well as cardiovascular and metabolic diseases. The key hormones involved in the intrauterine regulatory process are GCs, insulin, IGFs and THs. There is also interaction between the

regulatory functions of these hormones in the fetal tissues and systems.

Overall, the balanced interaction between the intrauterine hormonal responses, which result in normal fetal growth, development and birth, is based on maternal nutritional, oxygen and hormonal supply as well as flawless genetic delivery of information. Any decline in delivery of these critical elements from mother to the fetus results in starting a compensatory mechanism by which the fetal systems try to protect the key organs at the expense of other systems' destructions. This process is regulated by a certain planning which is designed by fetal systems and is called intrauterine programming.

The consequences of this programming depend on whether the developmental deficit is the inadvertent outcome of an insult acting as mutagen or a specific adaptation to an environmental challenge for maximal survival, if they can be passed to the next generations.

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