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The fascinating theory of fetal programming of adult diseases: A review of the fundamentals of the Barker hypothesis

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Abstract

The theory of fetal programming of adult diseases was first proposed by David J.P. Barker in the eighties of the previous century, to explain the higher susceptibility of some people toward the development of ischemic heart disease. According to his hypothesis, poor maternal living conditions during gestation represent an important risk factor for the onset of atherosclerotic heart disease later in life. The analysis of the early phases of fetal development is a fundamental tool for the risk stratification of children and adults, allowing the identification of susceptible or resistant subjects to multiple diseases later in life. Here, we provide a narrative summary of the most relevant evidence supporting the Barker hypothesis in multiple fields of medicine, including neuropsychiatric disorders, such as Parkinson disease and Alzheimer disease, kidney failure, atherosclerosis, coronary heart disease, stroke, diabetes, cancer onset and progression, metabolic syndrome, and infectious diseases including COVID-19. Given the consensus on the role of body weight at birth as a practical indicator of the fetal nutritional status during gestation, every subject with a low birth weight should be considered an "at risk" subject for the development of multiple diseases later in life. The hypothesis of the "physiological regenerative medicine," able to improve fetal organs' development in the perinatal period is discussed, in the light of recent experimental data indicating Thymosin Beta-4 as a powerful growth promoter when administered to pregnant mothers before birth.

Keywords

Prevention, Barker hypothesis, The Developmental Origins of Health and Disease, low birth body weight, renal failure, atherosclerosis, COVID-19, neuropsychiatric disorders

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Introduction

To understand the early origins of the theory on fetal programming of diseases we must go back to the 80s of the previous century when David J.P. Barker and C. Osmond published a pivotal paper in which maternal and fetal malnutrition during gestation was correlated with the susceptibility to the development ischemic heart disease in adulthood.[1] More than 10 years before this article, a Norwegian researcher from the University of Trömso, Anders Forsdahl, had advanced the hypothesis that poor living conditions in childhood might represent an important risk factor for the insurgence of atherosclerotic heart disease later in life.[2–4] Following Forsdhal and Barker studies, mainly focused on the early origins of atherosclerosis-related cardiovascular diseas,[5,6] the newer Barker's studies took into consideration the influence of maternal malnutrition during gestation on programming of persisting multiple metabolic and structural changes in the newborn. Specifically, Barker[7] hypothesized that low birth weight might influence insulin resistance, cholesterol metabolism, blood coagulation, and blood pressure in adulthood. This new revolutionary approach, aimed at better understanding the susceptibility to develop adult diseases by analyzing the early phases of fetal development, was subsequently defined as the "Barker Hypothesis."[8,9]

More recent articles have confirmed that pathological events occurring during gestation may have a significant influence on the onset of pathological events later in life. The period of the intrauterine life and the first 2 years of life, also called "the first 1000 days," are generally considered by the scientific community the crucial time window for development of human organs and for neurodevelopment.[10] According to these studies, the most important intrauterine factors modulating the increasing risk of the newborn to undergo several diseases later in life, are maternal endocrinological disorders, intrauterine exposure to toxins, infectious diseases during gestation, placental dysfunction, and decreased nutrient availability due to a poor maternal nutritional status.[11] More recently, maternal-fetal stress during gestation has been indicated as one of the principal causes of inefficient fetal growth, low birth weight, increased death loss, and aberrant metabolism persisting later in life.[12] In a modern interpretation of the Barker hypothesis, Thomas Block and Assam El-Osta introduced the theory of the "Metabolic Memory."[13] According to these authors, adverse early life events such as gestational diabetes and maternal obesity, might modify the fetal epigenome, which might represent metabolic memories leaving a permanent signature. Among them, the modifications of 5-methylcytosine (methylation) are hypothesized to represent the metabolic memory of adverse events occurring in the intrauterine life. The hypothalamus is indicated, in this modern elaboration of the Barker hypothesis, as the central regulator of the metabolic memory and the principal responsible for the obesity risk in adulthood. With the definition of "developmental plasticity," Barker lays stress on the concept that human beings, in their early intrauterine life, are highly plastic and able to adapt their developmental programs to the different environmental conditions encountered during gestation. From this perspective, the concept of developmental plasticity is linked to a pivotal gestational phase during which the developing organs and tissues exhibit heightened sensitivity to environmental alterations, culminating in the creation of a phenotype that is specifically adapted to a particular environment. In practical terms, it becomes clear that a single genotype has the capacity to give rise to a variety of distinct morphological and metabolic phenotypes, contingent upon the varied environmental circumstances experienced during the prenatal period.[14]

Aim of the narrative review

In this context, we performed a selective review of the evidence supporting the Barker hypothesis, with the twofold aim of: (1) providing an historical overview of its evolution and (2) offer a perspective on the implication for diagnosis, prevention, and treatment of complex disorders.

The role of undernutrition in fetal programming of adult diseases

The hypothesis of the fetal origins of adult diseases assumes that undernutrition before birth might determine persisting changes in a range of metabolic and structural parameters in the newborn. The Barker hypothesis may be summarized as follows:[7]

1. All human beings are programmed. The generative program for making a person is contained in genes.
2. The main feature of fetal growth is cell division, and it depends on maternal nutrients and oxygen availability.
3. Maternal undernutrition during pregnancy slows cell division and fetal growth.
4. Low birth weight reflects structural and functional adaptations of the fetus to undernutrition, adaptations that may be permanent and persist through the whole life.
5. Disproportionate growth can occur, given that each different fetal tissue has critical periods of growth at different times.
6. Undernutrition may permanently reduce the number of cells in particular organs, changing the program of our body.
7. The body's memories of early undernutrition in utero may lead to persisting changes in blood pressure, insulin response to glucose, cholesterol metabolism, renal function, and immune response.

8. Body's memory of undernutrition during gestation may lead to persisting structural changes in multiple organs, including low nephron number in kidneys and low burden of Langerhans islets in the pancreas.
9. Memories of early malnutrition in utero are translated into pathology, including susceptibility to undergo chronic kidney disease and renal failure, type II diabetes, adrenal failure, neuropsychiatric disorders, metabolic syndrome, atherosclerosis, coronary heart disease, stroke, and cancer.

Re-allocation of scarce resources during pregnancy

Another interesting interpretation of the Barker hypothesis concerns the suggestion that, when resources in utero are restricted, the appropriate development of vital organs such as brain, lungs, and heart is protected trough a preferential allocation of resources at detriment of kidneys and pancreas. This re-allocation of scarce resources represents the basis for pathological development of the kidneys and is considered the prenatal cause of higher vulnerability to chronic kidney diseases later in life.[15] The major results of this trade-off between kidney and brain during fetal development are represented by a decreased nephron number, which is a structural change in renal architecture that predisposes neonates to an increased risk of renal failure.

The consequences of the Barker hypothesis are not restricted to a better comprehension of the origins of human diseases. It might represent a useful tool in the prevention of multiple common adult-onset diseases.[16] According to this interpretation of the Barker hypothesis, a better understanding of the prenatal origins of adult-onset common diseases such as atherosclerosis, coronary heart disease, type II diabetes, metabolic syndrome, and hypertension, might allow the identification of at-risk subjects from birth. The identification of a cohort of subjects at high risk, utilizing the simple question "which was your birthweight?," might allow the medical community to organize a follow-up of these subjects, able to identify the early signs of metabolic changes in the target organs. In this view, the primary prevention of multiple chronic diseases of the adult life should start form the initial phases of gestation, given that an optimal intrauterine environment is fundamental in shaping individuals resistant to chronic diseases during the whole life.[17]

The reinterpretation of the Barker hypothesis by the author: The role of geographical maps

In an article published on 2007, more than 20 years after the first proposal of the theory of the developmental origins of adult diseases, Barker[18] reiterated that undernutrition in utero permanently modifies the body's metabolism, structure, and function, leading to increased death rates among low birth weight newborns, as well as to a higher susceptibility to develop coronary heart disease later in life. In this article, Barker recapitulated the origins of his revolutionary theory. He started from the current knowledge that coronary heart disease (CHD) should result from unhealthy lifestyles, including a fat-rich diet. Therefore, it was widely believed that CHD mortality should fell during the war. Barker et al. re-examined CHD mortality among middle-aged people in England and Wales from 1931 to 1967. They discovered that even in 1940, despite large changes in lifestyle during the war (famine), there was little to suggest that trends in CHD might be much influenced by the conflict.[19] These findings first evidenced that the simple correlation between a fat-rich diet and atherosclerosis might leave changing incidence of CHD and CHD geography largely unexplained.

It is surprising that it was geographical studies that gave the early clue that CHD might be linked to impaired fetal growth and not to a fat-rich diet during gestation. Starting from previous studies on geography of CHD in Britain[20] and confronting them with older studies on the social etiology of infant mortality in England and Wales,[21] Barker evidenced that CHD rates were twice as high in the poorer areas of the Country and in subjects from the low social class. Specifically, in an atlas of mortality in England and Wales 1968–1978, Gardner et al.[22] evidenced a higher mortality for CHD in the poorer rural areas and in the northern industrial towns, contrasting with a lower mortality rate from CHD in the South and East of England and in the richest zones of United Kingdom, including the city of London. Looking for a possible explanation for this geographical relationship between CHD, poor social conditions, and past infant mortality, Barker took into consideration multiple factors, including cigarette smoking, dietary fat consumption, and other adult lifestyles, but geographical studies did not highlight any strict relationship between these factors and CHD.

A breakthrough in the diffusion of the hypothesis that adverse environmental influences in utero might increase susceptibility to CHD came from the relationship between the mortality ratios for stroke and CHD in the 212 local authorities' areas of England and Wales and the neonatal mortality rates during 1911–1925. With this study, Barker[18]. revealed that both stroke and CHD mortality ratios increased with increasing neonatal mortality. On these bases, the principle that the nutritional, metabolic, and hormonal environment afforded by a pregnant mother might program the structure and metabolism of the developing fetal organs was, eventually, established.[7]

The Developmental Origins of Health and Disease (DOHaD)

A further step in the acquisition of the Barker hypothesis by the scientific community is represented by the birth of

an international society aimed to study the Developmental Origins of Heath and Disease (DOHaD).[23] DOHaD represents an expansion of the Barker hypothesis and includes multiple predictive adaptative responses of the fetus to a broad range of environmental factors. According with the DOHaD hypothesis, in addition to undernutrition, overnutrition, altered nutrition, and maternal stress during gestation should be also considered important potential environmental factors able to interfere with the physiological fetal programming, ending with an increased susceptibility for adult-onset cardiovascular, metabolic, psychiatric, and pulmonary disorders. Recent studies revealed that the intrauterine environment during gestation is impacted by multiple factors relative to the maternal health status, including maternal inflammation.[24] For example, a diabetic intrauterine environment might induce, in the fetus, epigenetic changes that predispose the newborn to develop metabolic disease later in life.[25]

The role of trace metals in fetal programming

A role in fetal programming of adult diseases has been recently assigned to maternal trace metal status, with particular attention to magnesium maternal accumulations.[26] In this study, the authors analyzed the essential role of magnesium in fetal development during gestation. This trace element is fundamental in over 600 enzymatic reactions implicated in protein synthesis, mitochondrial functions, neuromuscular activity, bone formation, and immune system competence. Magnesium status is particularly relevant in fetal development during the intrauterine life. Moreover, magnesium plays a fundamental role in the newborn growth during the perinatal period. Evidence is also reported indicating that magnesium deficiency can influence fetal programming and disease presentation in childhood or adulthood. According to this work, the maternal magnesium status should be monitored during pregnancy, to study its role in fetal programming of adult diseases. The data reported in this article indicate the existence of a strict connection between magnesium status and human pathology starting from intrauterine life and extending into adulthood, including susceptibility to undergo a severe form of COVID-19 infection.[27]

The role of placental dysfunction in fetal programming

Looking for the intermediate lesions of the developmental origins of adult diseases, a study aimed at identifying the factors responsible for the linkage between changes in the developmental programs of the fetal life and the insurgence of diseases later in life, Li et al.[28] focused on the role played by the placenta and the umbilical cord. This study paid special attention to the relevant role of the fetoplacental vasculature as the most important connection between the fetus and the mother during gestation. Changes in placental and umbilical vasculature could be responsible for relevant changes in maternal-fetal perfusion, leading to fetal altered perfusion and maldevelopment. The pathological changes induced in the placenta and in the umbilical cord by maternal disorders such as hypertension and diabetes are indicated as the possible responsible for the fetal origin of adult diseases (FOADs), the last evolution of the Barker hypothesis. Given that, even in physiology, maternal-fetal allocation of resources is the result of a cooperation, but sometimes it originates a conflict between the fetal requests and maternal needs,[29] the presence of adverse environmental conditions during gestation might exacerbate this conflict, leading to deprivation of nutrients for the fetus.

This hypothesis has been recently reinforced by the study of D'Errico and Stapleton,[30] which indicated placental metabolic and structural changes as the proof of the developmental onset of adult cardiovascular diseases. Placental insufficiency is hypothesized to represent the most important linkage between maternal dysfunctions (malnutrition, depression, anxiety, stress, hypercholesterolemia, diabetes, epilepsy, smoking, infections, alcohol, medicines, infections, inflammation) and restriction of in utero resources, with severe consequences on fetal development (low birth weight) and on the susceptibility to develop multiple chronic diseases later in life.

Endothelial dysfunction and vascular remodeling: A link between adverse intrauterine environment and vascular diseases later in life?

Among the multiple open questions regarding the signaling cascades starting from environmentally induced intrauterine growth restriction (IUGR) and low birth weight, ending with important influences on adult health or disease status, the most relevant is probably the identification of the cells involved and of the structural modifications occurring in fetal organs. An answer to this question might rely on the identification of the endothelium as the structure at the basis of vascular remodeling that modifies the elastic properties of the arterial wall. The sequence of events hypothesized to may lead to a susceptibility of low-birth weight infants to develop cardiovascular disease later in life, is the following: (1) endothelial dysfunction (starting in the intrauterine life); (2) changes in thickness of the intima and media of aorta, carotid arteries, and coronary vessels; (3) changes in arterial stiffness; (4) hypertension. The identification of high-risk newborns, by the evaluation of central pulse way velocity, laser Doppler skin perfusion and by the measure of arterial blood pressure could allow "at risk" neonates to undergo a strict long-term follow-up, to prevent the insurgence of hypertension and cardiovascular disease later in life.[31]

Low birth weight: The first sign of fetal programming of adult diseases

This growing body of reports confirms the Barker hypothesis that fetal nutrition during the intrauterine life, as indicated by birthweight, plays a relevant role in early prenatal life to program the susceptibility and the risk for adverse health outcomes later in life, both in childhood and in adulthood. The link between changes in the early development and susceptibility to adult diseases might be represented by the ability of epigenetic factors to change the expression of some key genes during gestation, leading to permanent alterations of cell proliferation and differentiation processes, ending with persisting structural and metabolic changes in tissues and organs. The impairment in structure and function of multiple organs during gestation might have, according with Barker, relevant clinical consequences. Changes in the development of multiple organs might explain the susceptibility of some individuals to undergo multiple chronic diseases, including coronary heart disease, stroke, diabetes, hypertension, obesity, metabolic syndrome, neuropsychiatric disorders, and others.

A further confirmation of the value of the Barker hypothesis came from an elegant study, carried out on 19 twin pairs with disproportionate birthweight, followed from birth to the age of 16. This study evidenced the relevant role of the intrauterine growth pattern on bronchial reactivity and lung function later in life. Twins with a low birth weight showed lower values of forced ventilatory volume % (FEV%) and of forced expiratory flow (FEF), as compared to twins with higher birthweight.[32]

Fetal programming of atherosclerosis

Barker based his hypothesis on epidemiological studies estimating the occurrence of coronary heart disease in men and women whose body weight at birth was recorded. Death rates from coronary heart disease paralleled birthweight, felling progressively from small for date newborns (<2500 g) to those who were in the normal range.[33,34] Further studies aimed to determine whether people born in the period of famine during the Spanish civil war might undergo an increased incidence of coronary heart disease, confirmed that data were compatible with those expected by the Barker hypothesis.[35] A recent article by Peter Libby, entitled "the changing landscape of atherosclerosis," confirmed many of the Barker's observations on the role played by multiple epigenetic factors in programming human diseases. Speaking about a considerable evolution in recent times of concepts related to atherosclerosis, Libby reported some non-traditional drivers of atherosclerosis, including air pollution and environmental stress.[36]

Looking for an association between disturbances in fetal growth and later insurgence of coronary heart disease, Barker et al. found a positive correlation between low birth weight and impaired glucose tolerance,[37,38] insulin resistance,[39] non-insulin dependent diabetes,[37] serum cholesterol levels,[40,41] hyperlipidemia,[42] and hypertension[38] developed in adulthood. A more recent study evidenced also racial disparities in the association between birth weight and insurgence of high blood pressure in childhood,[43] showing that low birth weight was positively associated with systolic and diastolic blood pressure in black children but not in white children. These racial disparities, according to the authors, might be related to the fact that black mothers were more likely to live in poverty as compared with white mothers.

The risk stratification of subjects who will develop a mild form of atherosclerosis and patients who will undergo a severe disease is an open problem in clinical practice. In a recent paper, the multiple evidence that might explain the increased susceptibility to develop severe forms of atherosclerosis, including stroke and cardiac infarct, in subjects who underwent intrauterine growth restriction (IUGR) have been analyzed.[44] In this study, evidence indicating an association between a low birth weight (LBW) and an adult phenotype which might favor a severe outcome of atherosclerosis was discussed. According to this hypothesis, young and adult subjects born too small (IUGR) or too early (pre-terms) might represent a subgroup of "at risk subjects" for the clinical events due to the early insurgence of atherosclerotic plaques. In other words, small for date and preterm infants should be considered as more susceptible subjects toward severe forms of atherosclerosis. Given that low birth weight (LBW) is generally utilized, in clinical practice, as a surrogate of IUGR, the weight at birth should be included among those indispensable clinical data collected in every patient presenting with atherosclerotic lesions. According to the hypothesis that structural arterial changes might represent the link between LBW and susceptibility to develop atherosclerotic plaques later in life, we suggest that the prevention of atherosclerosis should start at birth. The aim of this new approach to the prevention of atherosclerosis should be the reinforcement of the structure of the arterial wall, allowing LBW newborns to avoid the most severe complications of atherosclerosis later in life.

Fetal programming of kidney diseases

Human nephrogenesis is a complex process characterized by the interplay between multiple stem/progenitor cells, with several molecular pathways involved in kidney development.[45,46] In recent years, multiple immunohistochemical studies have shown the involvement of multiple markers of stem/progenitors in the developing human kidney including WT1, CD44, the anti-apoptotic protein Bcl2, PAX2, MUC1, and CD10.[47,48] A disturbed intrauterine growth, ending with a reduced nephron endowment, has been associated with the susceptibility to undergo renal

dysfunction and end-stage kidney disease later in life.[49] According with this hypothesis, the following sequence of events has been proposed: (1) malnutrition during gestation; (2) negative influence on the development of the cardiovascular system; (3) susceptibility to undergo hypertension; (4) glomerular hyper perfusion; (5) vascular lesions in middle-sized and small kidney arterial vessels; (6) glomerulosclerosis; (7) kidney failure.[50] Altered intrauterine growth has been also associated with a pathological nephrogenesis, ending with a reduced number of nephrons at birth. Interindividual differences in the nephron burden may be relevant: according with recent hypotheses, the number of glomeruli might range from 200,000 up to 2 million.[51] Very recently, a marked interindividual variability has been reported regarding the expression in the developing kidney of the L-1 cell adhesion molecule (L1CAM), a cell adhesion molecule that plays a major role in human development.[52] According to this work, a deficient expression of L1CAM in critical structures for kidney development, such as the distal tubules in close proximity with the fusion point with a collecting tubule, might lead to the insurgence of renal maldevelopment and to a low nephron burden.

A reduced number of nephrons represents a factor that might link low birth weight to a greater susceptibility to develop hypertension and progressive kidney disease later in life.[53] Significant differences in nephron number in newborns of the same gestational age have been reported by our group, confirming the major role played by environmental factors during gestation in kidney development, therefore explaining the marked interindividual differences regarding the nephron burden.[54] More recent studies have confirmed previous data regarding the role of an adverse fetal environment on kidney maldevelopment, leading to changes in renal phenotypes, with consequences on renal structure and metabolism, including modifications in the renal-angiotensin system and its components.[55]

Fetal programming of the metabolic syndrome

Data from the Barker's group regarding the relationship between undernutrition before birth and programming of metabolic changes persisting later in life were also confirmed by a prospective study carried out on 55 small for gestational age (SGA) children followed for 12 years after birth. At age 12 years, most SGA children showed relevant long-term consequences, with an increased incidence of hypercholesterolemia.[56]

Interestingly, also plasma fibrinogen concentrations in adulthood were found to be related to maternal malnutrition during gestation, particularly in male newborns.[57] In this study, fibrinogen serum levels were related to weight and abdominal circumference at birth in males and fell by 0.12 g/l for each pound increase in birthweight and by 0.10 g/l for each inch increase in abdominal circumference.

In more recent years, these findings were confirmed by a study carried out on 725 people, aged 50 years, born around the time of the Dutch famine 1944–1945.[58] This study assessed the effect of maternal malnutrition during different stages of gestation on plasma concentration of fibrinogen in adulthood.

Fetal programming of type II diabetes

Diabetes in pregnancy has been shown to induce long-term effects in offspring, with a higher incidence of type II diabetes in the adult offspring of diabetic mothers.[59] The prevalence of type II diabetes and impaired glucose tolerance in men aged 59–70 years ranged from 40% when body weight was less than 2500 g, to 22% when body weight was 3450–3860 g, to 14% when body weight was more than 4000 g.[7] The "thrifty phenotype" hypothesis was the result of further JP Barker's speculations on the permanent changes in glucose-insulin metabolism produced by poor fetal and infant growth.[60] It was based on epidemiological associations between fetal undernutrition and the subsequent development of type 2 diabetes and the metabolic syndrome later in life. According with the thrifty phenotype hypothesis, poor fetal growth might cause a reduction in insulin secretion, and an increase in insulin resistance, ending with the insurgence of obesity, type 2 diabetes, and metabolic syndrome in adulthood.

An intriguing interpretation of the Barker hypothesis suggests the ability of changes in nutrient availability during gestation in determining developmental adaptations that readjust the set points of physiological responses in the postnatal period. Accordingly, the developmental adaptations might prepare the newborn to an adverse environment after birth, whereas a high nutritional support in the postnatal period (a typical approach to SGA neonates) might create metabolic conflicts, increasing the risk of the insurgence of multiple diseases later in life.[61]

Fetal programming of all-cause death

Although initially concerned with cardiometabolic phenotypes, the Barker hypothesis has been progressively extended to other systems, including neural development and psychiatric phenotypes.[62] The Barker hypothesis has been recently utilized for the comprehension of the interindividual variability regarding the susceptibility to develop cancer in human beings.[63]

Moreover, the Barker hypothesis has been confirmed by the report of association between low birth weight and all-cause natural death in young adults, indicating intrauterine growth restriction (IUGR) as a predisposing factor of early death in adulthood.[64] The role of fetal mal-programming in permanently modifying the structure and metabolism of organs and tissues has been extended, in recent years, to other organs and systems, including the hematopoietic system.[65]

Fetal programming of neuropsychiatric disorders

The implications of early life stress have been also reported to include neuropsychiatric disorders occurring in childhood or in adulthood.[66,67] In particular, maternal prenatal depression has been associated with the insurgence of neuropsychiatric adversities in children.[68] Prenatal insults might disrupt normal brain development, triggering epigenetic changes that contribute to the development of a psychiatric phenotype. First, a role for fetal programming has been indicated in Parkinson's and Alzheimer diseases.[69] The identification of neuropathological changes caused by fetal programming have also been proposed as useful markers for the early detection of psychiatric disorders early in life. These permanent neuropathological changes, related to epigenetic factors acting during gestation, are indicated, by recent studies, as responsible for the development in childhood and adulthood of multiple neuropsychiatric disorders, including schizophrenia.[70] The period of gestation in which maternal disorders, including depression, anxiety, epilepsy, and in which maternal lifestyle changes occur, also plays a fundamental role in determining the tendency to develop a peculiar disease later in life.[71] At critical periods of embryonic and fetal development, an insult related to maternal disease or incorrect lifestyle, might result in specific developmental adaptations, with permanent metabolic and/or structural changes in target organs which could favor the insurgence of different diseases in adult life.[72]

A very recent study on the role of fetal programming on the function of the human brain introduced a new actor in this field: ionizing radiations.[73] In this study, the fetal programming of neural genetic activity and behavior in multiple neural regions is reaffirmed as an important factor in neurology. The cerebral cortex, the prefrontal cortex, the cerebellum, the hippocampus, and the hypothalamic–pituitary–adrenal axis are suggested as the brain areas which are particularly susceptible to fetal programming of adult neurological and psychiatric diseases. In this article, ionizing radiations are introduced as an indirect driver of phenotypical changes in the newborn brain. According to the authors, gestational exposure to stressors could predispose the newborn brain to peculiar behavioral phenotypes and might lead to harmful outcomes.

Fetal programing of the severe forms of COVID-19

At admission to the hospital, the stratification of patients affected by coronavirus disease 19 (COVID-19) between subjects who will undergo a severe disease and subjects who will develop a mild form of the infectious disease remains inaccurate. Recently, a paper from our group proposed that the Barker hypothesis might explain the increased susceptibility to a more severe form of COVID-19 in some subjects. According to this hypothesis, COVID-19 subjects who underwent intrauterine growth restriction (IUGR) might represent a group at higher risk of undergoing severe consequences following SARS-CoV-2 infection.[9] Specifically, we suggested an association between a low birth weight and an adult phenotype which might favor a severe outcome of SARS-CoV-2 infection. Lower lung functional capacity, increased respiratory morbidity, changes in fibrinogen and Factor VIII serum levels, dysregulation of the hemostasis and thrombosis system, acquisition of a pro-thrombotic phenotype, low nephron number with decreased ability to sustain renal function and increased renal morbidity, heart remodeling with a less efficient cardiac function, endothelial dysfunction favoring the insurgence of multiple organ failure, remodeling of arteries with changes in the elastic properties of the arterial wall predisposing to the insurgence and progression of atherosclerosis, dysfunction of the innate immune system, a risk factor for immune diseases in adulthood. Taken together all these data are at the basis of the hypothesis that adult subjects born too small (IUGR) or too early (preterms) might represent a subgroup of "at risk subjects," more susceptible to develop severe forms of COVID-19. Given that a low weight at birth may be considered a surrogate of IUGR, low birth weight should be included among the indispensable clinical data collected in every patient presenting with SARS-COV-2 infection, to better stratify at risk patients at admission to the hospital.

The role of the Barker hypothesis in disease prevention

Barker and coworkers suggested that, to enact a preventive approach to CHD, the natural step was the identification of groups of men and women that identified as "high risk subjects" before the onset of the disease. To this end, by applying the same geographical approach, Barker found a strict association between low birth weight and death from ischemic heart disease.[74] The association between a low body weight at birth and the insurgence of CHD later in life has been confirmed by further studies carried out in different populations.[75–77] These reports were paralleled by other studies, which evidenced a strict relationship between a low birthweight and an increased risk of stroke.[78–81] Further studies in the Helsinki birth cohort have shown that the susceptibility to hemorrhagic stroke in the adult life originates in the prenatal intrauterine environment, and that this susceptibility is not, or scarcely, influenced by the postnatal environment.[82]

Conclusions and future perspectives

This overview has highlighted that the Barker hypothesis on the fetal origins of adult-onset diseases, and the

subsequent DOHaD theory, may change the approach of the scientific community to the prevention of some of the most important human diseases, including atherosclerosis and all its clinical systemic consequences in vital organs such as heart, brain, and kidneys. The prevention of these "adult-onset" diseases, now it is clear, should start from the intrauterine life.[83] Gynecologists play a fundamental role for encouraging a maternal healthy lifestyle, reducing maternal obesity, preventing maternal hypertension, discouraging maternal smoking, and alcohol assumption during gestation. Neonatologists are asked to accurately monitor all infants with evidence of IUGR, low birth weight, and preterm neonates. Neonatologists are asked to act immediately after birth, in a window in which regeneration in some organs is still active. According with this fascinating new approach, defined "physiological regenerative medicine," the administration of natural substances in the perinatal period might stimulate the ongoing nephrogenesis, increasing the nephron burden of the newborn and decreasing his/her susceptibility to undergo renal insufficiency later in life. Very recently, experimental data have been published in support to this intriguing theory. Thymosin beta 4 (TB4), a small peptide physiologically present in human fluids[84] and tissues[85] has been proposed as a powerful growth promoter able to stimulate the development of multiple fetal organs when administered to pregnant mice in the days before delivery.[86] Given that TB4 is a physiological peptide, normally detectable in human beings, it could be considered for future clinical trials aimed at restoring the damages caused in fetal organs by environmental changes occurring during gestation. The "physiological regenerative medicine" approach[87] might transform neonates susceptible to major chronic diseases later in life, into resistant ones.

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