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Fetal programming of COVID-19: may the barker hypothesis explain the susceptibility of a subset of young adults to develop severe disease?

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Abstract. – The risk stratification of young adults between subjects who will develop a mild form COVID-19 and subjects who will undergo a severe disease remains inaccurate. In this review, we propose that the Barker hypothesis might explain the increased susceptibility to severe forms of COVID-19 in subjects who underwent intrauterine growth restriction (IUGR). In this paper evidence indicating an association between a low birth weight and an adult phenotype which might favor a severe outcome of SARS-CoV-2 infection are presented: lower lung functional capacity; increased respiratory morbidity; changes in fibrinogen and Factor VII serum levels and 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, a risk factor for the insurgence of the 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. These data suggest that young and adult subjects born too small (IUGR) or too early (pre-terms) might represent a subgroup of "at risk subjects", more susceptible toward severe forms of COVID-19. Given that LBW may be considered a surrogate of IUGR, this phenotypic marker should be included among the indispensable clinical data collected in every patient presenting with SARS-COV-2 infection, irrespectively of his/her age.

Key Words:
Fetal programming, COVID-19, Barker hypothesis, IUGR.

Introduction

The clinical spectrum of patients with COVID-19 is broad, ranging from asymptomatic subjects to

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mild-moderate disease, ending with severe and critical illness, characterized by respiratory injury and multiple organ failure (CDC, December 7, 2020)[1]. Subjects aged 65 years or older, affected by different types of chronic disease (cardiovascular disease, chronic lung disease, diabetes, cancer, obesity, chronic kidney disease), with smoke habitus and under immunosuppressive therapy, have been identified as at-risk groups for critical illness[2,3]. Unfortunately, also subjects aged less than 65 years, even if with a lower prevalence, and some young patients, without underlying co-morbidities, might undergo severe or even fatal forms of the infection[4]. As a consequence, there is the need for identifying these apparently healthy young/adult subjects at higher risk for developing severe COVID-19[5], in order to administer effective targeted therapies early in the course of the infection. Very recently, low birth weight (LBW) has been indicated as a potential risk factor for severe COVID-19 in non-elderly patients[6], introducing the concept that COVID-19 vulnerability might be programmed before birth.

The Barker Hypothesis

In the eighties of the previous century, David J.P. Barker published a pivotal paper[7] in which maternal and fetal malnutrition during gestation was correlated with the susceptibility to undergo ischemic heart disease later in life. Barker based his hypothesis on epidemiological studies carried out on the occurrence of coronary heart disease in subjects whose body weight at birth was recorded. Death rates from coronary heart disease paralleled birthweight, reducing progressively from small for date newborns (< 2.500 g) to those who were in the normal rang[e8,9]. Over the years, the Barker hypothesis has been confirmed by evidence collected in multiple human diseases. In particular, altered intrauterine growth has been associated with a susceptibility to undergo end-stage kidney disease later in life. The following sequence of events has been proposed: 1) malnutrition during gestation; 2) negative influence on kidneys development; 3) low nephron number at birth; 4) glomerular hyperperfusion; 5) vascular lesions in middle and small kidney arterial vessels; 6) glomerulosclerosis; 7) kidney failure[10]. Moreover, in recent years, aluminum exposure of fetal tissues during gestation has been suggested as a relevant factor able to determine a predisposition toward the development of neuropsychiatric disorders later in life[11]. In addition, there is substantial evidence showing that specific environmental determinates, acting during the prenatal and perinatal phases, such as infections (rubella, influenza, Toxoplasma gondii (T. gondii), herpes simplex virus type 2, nutritional deficiencies (e.g., famine, folic acid, iron, vitamin D), paternal age, fetal/neonatal hypoxic and other obstetric insults and complications, maternal stress might increase the risk of developing schizophrenia[12].

Relationship Between LBW and Severe Outcome of COVID-19

Recently, Crispi et al[6] published an intriguing study, indicating LBW as an independent risk factor for severe disease in non-elderly adults affected by COVID-19. According with the authors' hypothesis, aligned with a long-standing research in this field, the knowledge of LBW might help to identify a subgroup of young/adult subjects apparently in good health but at higher risk for the manifestation of severe forms of the disease. This finding might offer new opportunities for a more accurate stratification and early interventions in young people infected by SARS-CoV-2, aimed to prevent severe complications, such as thrombotic events.

However, an open question remains: which is the relationship between LBW and a severe course of COVID-19? The first answer regards the biological implications of LBW. In at term newborns, LBW (<2,500 g) has been indicated as a robust surrogate of intrauterine growth restriction (IUGR), and a strong predictor of long-term morbidity[13]. LBW may be also related to preterm labor, prematurity being associated with suboptimal development of multiple fetal organs, including lungs[14], kidneys[15] and brain[16,17,18,19]. According with the Barker hypothesis, and the developmental origin of diseases in adulthood (DODA), LBW might be associated with lower lung functional capacity[20,21] and with increased respiratory morbidity[22]. Moreover, prematurity is widely accepted as a risk factor for a greater predisposition to develop lung disease later in life, starting with the predisposition to develop neonatal respiratory distress syndrome (NRDS) immediately after birth[23]. In survivors born pre-terms, the predisposition to develop lung disease might persist through the entire life[24]. In this perspective, LBW might represent and could reflect, the "first hit", occurring during gestation, and should represent a predisposition to develop diseases in childhood or in adulthood. Later exposure to other environmental factors in the postnatal life, including vi-

ral infections, might represent the "second hit", necessary for the presentation of the disease. This might represent an additive model where predisposition and external causes interact to produce a critical condition.

The Relationship Between Fetal Programming and the Molecular Pathways Triggered by SARS-CoV-2

Trying to explain the correlation between LBW and a severe outcome of COVID-19, implies to consider the multiple molecular pathways triggered by SARS-CoV-2[3,25]. The first one is related to the hemostasis and thrombosis system, which has been indicated as a target of SARS-CoV-2 infection, ending with diffuse intravascular coagulation (DIC) in a subset of COVID-19 patients. However, the hemostatic abnormalities found during SARS-CoV-2 infection are not identical to those of classical DIC[26]. In fact, most of patients show the ISTH (international Society Hemostasia and Thrombosis) laboratory criteria for a diagnosis of DIC, but do not present with severe bleeding[27]. The main features are represented by an important local pulmonary thrombosis[28], a phenomenon now recognized to happen even in other clinical conditions[29]. Moreover, SARS-CoV-2 infection can also induce other widespread thrombotic manifestations, due to a direct endothelial damage caused by the viral infection[30]. Nevertheless, a massive inflammatory and coagulative response may be very dangerous because it can lead to a diffuse thrombotic angiopathy.

As reported above, endothelial susceptibility due to LBW may represent a critical background for the SARS-CoV-2 attachment. The thrombotic phenotype of COVID 19 is essentially due to the involvement of endothelial cells which, after virus entry trough the ACE2 receptor, change their anti-thrombotic properties to a pro-thrombotic phenotype. The endothelial cells of people who have in their background a LBW could be more prone to react to the cytokine storm elicited by SARS-CoV-2 infection.

It was demonstrated that both fibrinogen levels and Factor VII in adults are influenced by maternal malnutrition during gestation and by LBW[31-33]. According with these studies, LBW might be considered a robust surrogate for dysregulation of the homeostasis and thrombosis system, and a predictor of insurgence of thrombotic events later in life. Failure in an adequate controlling of the homeostasis of some coagulative factors seems therefore an outcome of LBW.

Fetal Programming of Kidney Disease

One of the most robust links between LBW and fetal programming of adult disease is represented by the association between preterm delivery and IUGR with a reduced number of glomeruli per kidney[34]. The variability in nephron number among subjects is wide, ranging from about 200,000 up to values more than ten times higher, about 2,700,000[35]. Human kidney development is a complex process, regulated by multiple integrated molecular mechanisms[36,37]. Among these, mesenchymal-epithelial transition of metanephric stem cells represents a fundamental step in human nephrogenesis[38]. Ongoing nephrogenesis in the fetal kidney is demonstrated, at histology, by the presence of aggregates of mesenchymal stem/progenitor cells in the sub-capsular region, giving rise to the "blue strip"[39]. A key point in glomerulogenesis is that it is restricted to the intrauterine life, with the disappearance of the nephrogenic zone, the blue strip, at 38-40 weeks of gestation[40]. The intimate mechanism underlying the abrupt interruption of nephrogenesis after delivery is still unknown. The recent discovery that glomerulogenesis develops in a hypoxic environment, the nephrogenesis zone being devoid of blood vessels[37], suggests that the exposition to high oxygen levels after birth might favor the block of nephrogenesis. As a consequence, the nephron burden at birth will represents the entire nephron number for the whole life. Nephron endowment at birth can shape our susceptibility to renal dysfunction later in life[41]. A study focused on the analysis of the nephron number in autoptic kidneys of neonates with different gestational age, evidenced a marked interindividual variability among newborns. Interestingly, in this study, nephron number was not strictly bound to the gestational age, suggesting a major role played by epigenetic gestational factors in nephrogenesis[15]. Thus, preterm and small for date newborns may not be able to independently sustain renal function after birth and later in life, due to the scarcity of nephrons in their kidneys.

The knowledge of the block of the regenerative ability of the human kidney after birth was at the basis of a new theory defined "physiological regenerative medicine"[42]. According with this theory, the perinatal period might represent a fascinating window of opportunity for favoring ongoing nephrogenesis in preterm infants. This approach has been reinforced, in more recent years, by other authors[43,44], opening a new perinatal approach for the prevention of kidney diseases later in life.

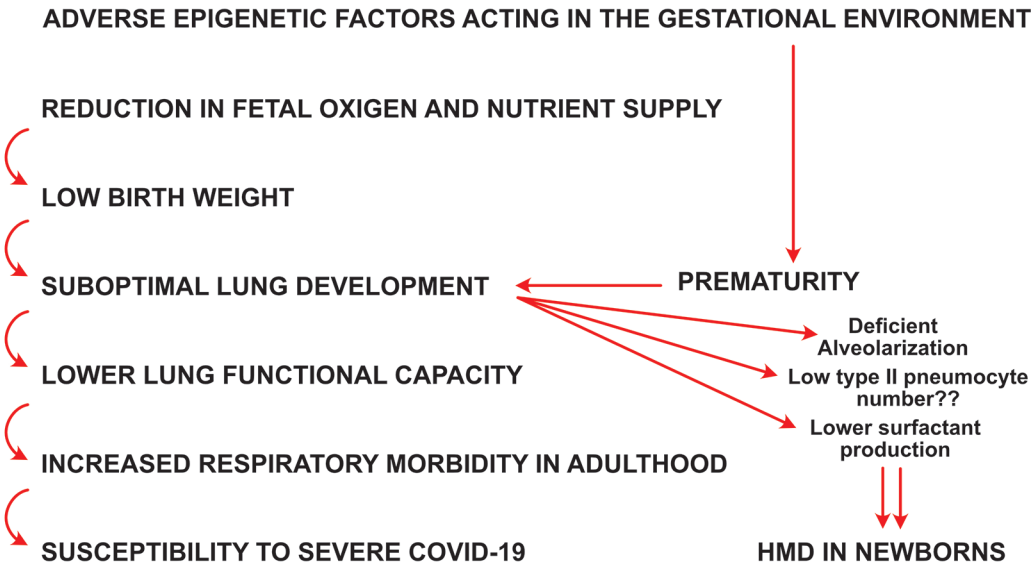

Figure 1. Schematic representation of adverse epigenetic factors acting in the lungs during pregnancy.

Fetal Programming of Lung Disease

Prematurity and intrauterine growth restriction may have relevant consequences even on lung development; LBW has been associated with long term changes in the respiratory system[21] with a wide range of alterations in pulmonary structure and function, including impaired alveolarization[45], ending with a reduced number of alveolar chambers[46]. Other authors reported the effects of IUGR on cellular and molecular events occurring in the developing lungs, such as impaired type II alveolar cell maturation with reduced surfactant activity[47]. Restricted lung growth, associated with LBW, has been shown to predispose children to lower lung function, and represents a risk for respiratory diseases later in life, including asthma[20]. Moreover, restricted fetal growth has been indicated as a risk factor for developing chronic obstructive lung disease in adulthood[48] (Figure 1).

Fetal Programming of Cardiovascular Diseases

In the first papers of David J.P. Barker[7] on the relevant role played by the intrauterine environment on the susceptibility to develop chronic diseases later in life, maternal and fetal malnutrition during gestation was correlated with the susceptibility to undergo ischemic heart disease in adulthood. In following papers, Barker et al[9] focused on the fetal origins of coronary heart disease. More recently, multiple studies[49,50] have shown that fetal growth restriction results in heart remodeling, ending with a less efficient heart in childhood. These data confirm the existence of long-term cardiovascular consequences caused by fetal growth restriction and LBW.

Among the multiple open questions regarding the relationship between low birth weight, and susceptibility to develop severe adult diseases, one concerns the identification of the cells involved. Endothelium has been indicated as the target of maternal malnutrition, and fetal endothelial dysfunction during gestation has been implicated in the occurrence of multiple organ failure in the newborn[51].

Endothelial damage has been proposed as the structure at the basis of the vascular remodeling which might modify the elastic properties of the arterial wall[52]. The sequence of events hypothesized 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[53]. The recently reported ability of SARS-CoV-2 to aggravate atherosclerotic lesions, ending with an increased incidence of myocardial infarct and stroke during the COVID-19 pandemic[54], might be explained with the endothelial dysfunction induced by maternal stress during gestation.

Fetal Programming of Immune Diseases

In recent years, the immune system has been included among the multiple physiological sys-

tem in which intrauterine fetal programming may have relevant consequences persisting in adult life[55]. Social and psychological maternal stress during pregnancy may cause significant changes in cytokine production persisting after birth[56]. Evidence[57] indicate that negative prenatal exposure represents a risk factor for the development of immune diseases later in life. Moreover, maternal farm exposure during gestation has been associated to changes in the fetal immune system, ending with changes in regulatory T lymphocytes after birth[58]. Intrauterine growth restriction may also be associated with dysfunction of the innate immune system in preterm infants, characterized by the inability to determine an appropriate immune response[59]. Collectively, these data suggest that immune diseases in childhood and in adults may have developmental origins[60]. It could be interesting to know whether the immune response is not well either controlled or balanced against foreign challenges. In other words, is an excess of the immune system response during SARS-CoV-2 infection a result of a not well-regulated immune system? This could explain why the burden of the disease is so different among the patients who have a contact with the virus ranging between an asymptomatic condition and a fatal outcome. Ideally, a test investigating both the individual immune harmonization and the response to a foreign attack would be very useful to assess the individual immune capacity in front of a "friendly fire".

Fetal Programming of Thrombotic Disease

Intra-uterine growth restriction may have relevant consequences even on the hemostasis and thrombosis system. Plasma levels of fibrinogen and Factor VII in adults have been shown to be related to birth weight and, in particular, to growth restriction during gestation[32]. A study[61] aimed at verifying the association between IUGR and susceptibility to develop thrombotic events later in life revealed an association between polymorphisms for factor V Leiden and prothrombin, ending with a thrombophilic phenotype in adulthood.

Conclusions

The COVID-19 pandemic permits to study the response of millions of human beings born with a LBW to a strong stress: the SARS-CoV-2 infection. The evidence here summarized first indicate that COVID-19 should be introduced in the spectrum of human diseases whose severity might be subject to fetal programming. In particular, a growing body of data[6] suggest a possible role for fetal programming in shaping the susceptibility of young adult subjects, apparently in good

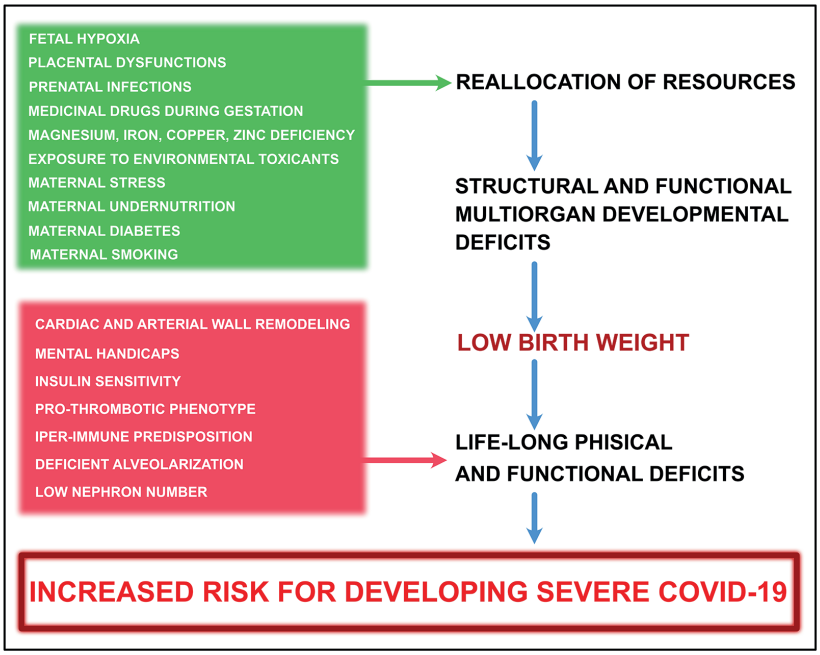

Figure 2. Schematic representation of factors the causing increased risk for developing severe COVID-19.

health, to undergo a severe clinical course when infected by SARS-CoV-2[6]. Thus, according with the Barker hypothesis, considering the relevant consequences of fetal growth restriction persisting in the adult life, LBW should be added to the other risk factors associated with disease severity and mortality previously reported in COVID-19 patients[62] (Figure 2). This hypothesis is supported by multiple relevant findings, which indicate LBW as an important index of fetal growth restriction. As described in this work, LBW is associated with suboptimal development of multiple critical organs, including lungs, heart, vessels, kidneys and brain. Intrauterine growth restriction is associated with an adaptative fetal response, which includes the following disturbances:

- Lower lung functional capacity[20];
- Increased respiratory morbidity[22];
- Changes in fibrinogen and Factor VII serum levels and dysregulation of the hemostasis and thrombosis system[32];
- Acquisition of a pro-thrombotic phenotype, with higher susceptibility to develop thrombotic events[61];
- Low nephron number, with decreased ability to sustain renal function, ending with increased renal morbidity[41];
- Heart remodeling, ending with a less efficient cardiac function[49];
- Endothelial dysfunction, which represents a risk factor for the insurgence of the multiple organ fealure[53];
- Remodeling of arteries, with changes in the elastic properties of the arterial wall, a structural change predisposing to the insurgence and progression of atherosclerosis[53];
- Dysfunction of the innate immune system[59], which represents a risk factor for immune diseases in childhood and adulthood[55].

Our working hypothesis, aligned with a long-standing research line in the field of fetal programming of adult human diseases[42,19,63,15,17,44,64,18,43,41,37,16], indicates that young and adult subjects born too small (IUGR) or too early (pre-terms) should be considered as a distinct subgroup of "at risk subjects" for the development of severe, if not fatal, forms of COVID-19. The adaptative fetal response to reduction of oxygen and nutrient supply during gestation is responsible for a specific phenotype regarding metabolism, function and structure of critical organs. This phenotype might favor the insurgence of the cytokine storm and the development of diffuse thrombotic events, two critical events in the most severe forms of COVID-19. Given that self-reported LBW has been demonstrated to be a good surrogate of IUGR65, its acquisition should be included among the indispensable data from every subject with SARS-CoV-2 infection. The identification of a new "at risk" group, among young/adults undergoing COVID-19 might allow the identification of the severe form of the disease in the early phases, with significant advantages in the therapeutic approach. Moreover, knowing individual birth weight could be used for identifying subjects at a higher cardiovascular risk in the general population starting from the pediatric life. In these subjects, more precise prevention of cardiovascular disease could be afforded by a periodical follow up in their life overall checking for minimizing other adjunctive risks factors, such as obesity, smoking and wrong diet.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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