REVIEW ARTICLE

Neonatal and Long-Term Consequences of Fetal Growth Restriction

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Abstract: **Background**: Fetal Growth Restriction (FGR) is one of the most common noxious antenatal conditions in humans, inducing a substantial proportion of preterm delivery and leading to a significant increase in perinatal mortality, neurological handicaps and chronic diseases in adulthood. This review summarizes the current knowledge about the postnatal consequences of FGR, with a particular emphasis on the long-term consequences on respiratory, cardiovascular and neurological structures and functions.

Result and Conclusion: FGR represents a global health challenge, and efforts are urgently needed to improve our understanding of the critical factors leading to FGR and subsequent insults to the developing organs.

1. INTRODUCTION: FETAL GROWTH RESTRICTION (FGR) IS A MAJOR GLOBAL HEALTH CONCERN

Fetal Growth Restriction (FGR) refers to a condition in which the fetus is unable to achieve its genetically determined potential size, responsible of increased rates of stillbirth, neonatal mortality and morbidity [1]. Multiple terms have been used to define it, as intrauterine growth restriction/retardation or small for gestational age (SGA, defined as a birth weight less then the 10th centile in the population of reference but not necesseraly associated with abnormal growth kinetic), generating confusion in terms of incidence and diagnosis. Recently, to distinguish between constitutionally small babies (SGA) and those with growth restriction, FGR has been proposed as a standard definition in scientific literature [2].

Globally, FGR affects nearly 10% of all pregnancies [2-5]. In Europe, the incidence of low birth weight infants is between 3.0 % (Island) and 8.8 % (Cyprus) [6]. In France, perinatal mortality and complications and long-term handicap due to FGR are responsible for costs estimated to reach about 235M€ for just the first year of care [7]. This is a public health challenge in both industrialized and developing countries [4]. Indeed, of the 135 million children born in low/middle income countries in 2010, an estimated 29.7 million were born at term following FGR and 2.8 million were born preterm and growth restricted [7].

Currently the FGR rate is the highest, in over 20 years and is likely to rise further due to the increasing number of infertility treatments, multiple pregnancies, professional workload, older motherhood and exposure to FGR-inducing agents such as stress, nicotine, malnutrition [8, 9]. Maternal malnutrition during pregnancy is a major determinant mimicking placental insufficiency and negatively affecting feto-placental growth. Given the fact that the incidence of maternal malnutrition is higher than 10% in developing countries and accounts for a significant proportion of FGR in industrialized countries as well, it is crucial to better delineate its effect on genomic regulation, brain maturation and function.

The consequences of FGR are influenced by its severity, the gestational age at the onset (defined as early, *i.e.* <32 weeks gestation or late, *i.e.* ≥ 32 weeks gestation) [2], and the etiologies implicated (genetic, placental, maternal and fetal factors). Moreover, FGR is related to preterm delivery, leading to an increased risk of disability in surviving infants [1]. Thus, early diagnosis of FGR is very important to establish an adequate surveillance of the fetal status, minimizing risks of premature birth and intrauterine hypoxia.

This review examines the impact of FGR on the long-term function of developing organs, both in animal models and human cohorts.

2. FGR AND THE DEVELOPING LUNG

Impaired fetal nutrition and oxygen deprivation, both usually related to FGR, can modify the normal lung development at any stage (from embryonic, pseudoglandular, canalicular, saccular to alveolar), making the lung more vulnerable to postnatal insults [10].

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In the past, infants born following FGR were considered to have more mature lungs, as a result of intrauterine exposition to higher levels of glucocorticoids. Conversely, cinical studies have shown that premature SGA infants are at higher risk for developing both neonatal respiratory distress and Bronchopulmonary Dysplasia (BPD) when compared with premature infants with a birth weight Appropriate for Gestational Age (AGA) [11, 12]. Nowadays, FGR is recognized as a risk factor for BPD and its long-term consequences, as asthma and bronchiolitis [13-15]. Recent studies have identified an association between FGR and the development of wheezing at the age of 3 years [16], independently to gestational age at birth. Moreover, infants born with a FGR or a low birth weight may develop a lower lung function in the spirometry analysis performed at school age [17-19].

Different animal models have been developed to identify the mechanisms implicated in the origin and evolution of respiratory pathology in FGR. Poor fetal nutrition and oxygenation can alterate surfactant quantity and activity [20], alveolar cell proliferation and alveolar walls and air-blood barriers [21]. In preclinical studies, sheep and rats born following FGR show smaller lungs, with no evidence of postnatal catch-up [22]. Adult animals exposed to FGR have fewer [23] and larger alveoli, developing emphysema [22]. Maritz and collaborators reported an accumulation of extracellular matrix leading to an increased thickness of both septa and air-blood barrier in the sheep at 8 weeks and 2 years of age [24]. FGR is also associated with atypical elastin production, and consequent derangement of the normal architecture of the lung [25, 26]. A dysregulation of gene's expression involving cell growth and differentiation, as IGF-1, PPAR-γ [25], and p53 [27], is responsible for increased thickness and cellularity of the pulmonary parenchyma. Furthermore, hypoxia FGR-related, affecting alveolar endothelium and VEGF pathway, could play a role in the pulmonary dysfunctions, as observed in FGR animal models [28, 29]

From these preclinical studies, promising therapeutic strategies have recently emerged. Maternal dietary supplementation in Docosahexaenoic Acid (DHA) can restore normal quantity of the enzyme SETD-8, which regulates cell proliferation and gene function, modifying lung development in rats [30].

3. FGR, SYSTEMIC INFLAMMATION AND IMMUNITY

Recent studies have highlighted the effect of FGR on development and function of the immune system in neonates [31, 32]. Infants born following FGR demonstrate an increased vulnerability to infections [33], especially to late-onset sepsis [34, 35].

In addition to the effects on platelet count (thrombocytopenia) and red blood cells (increased number of nucleated red blood cells and polycythemia), FGR is associated with significant changes in white blood cells counts and immune response. Numbers of B and T-cells, neutrophils and levels of IgG are lower in the cord blood or thymus of FGR infants [36-38] Infants with FGR have lower numbers of T-regs (CD3+, CD4+, CD25^{high}, and FoxP3^{high}) and fewer functional T-regs compared to AGA infants [39] and they present as well some changes in thymus size and histopathology [31,

40]. The importance of T-regs as effectors of self-tolerance and regulators of immune activation is well characterized for primary diseases associated with autoimmunity and allergy. This may have implications for specific postnatal complications, including necrotizing enterocolitis, which disproportionately affect premature and FGR infants [41].

Some studies have focused attention on the dysregulation of immune cells response in FGR neonates. In whole blood cell cultures from FGR infants, after stimulation using lipopolysaccharide, the concentrations of IL-6 and IL-10 are significantly lower [36]. Furthermore, altered cytokine profiles have been reported in newborn serum [42] and antenatally in placenta and fetus [43].

Similar findings have been reported in preclinical studies. FGR piglets present decreased T and B lymphocytes counts and proliferation in peripheral blood [44] and lower cytokine concentrations (IFN-γ, IL-4, IL-10, IL-1α, and IL-8) [45].

Yet conflicting data but increasing evidence support the hypothesis that FGR is a pro-inflammatory status, similar to preeclampsia [46, 47], that may induce several impairments of the developing organs. Indeed, while there is no evidence of increased cytokines levels soon after birth, severely growth restricted preterm neonates demonstrate a significant rise in the concentrations of pro-inflammatory circulating cytokines during the second postnatal week [48]. In umbilical cord serum from FGR neonates at birth, IFN-γ concentration is increased and it has been proposed as a neonatal marker of FGR [49].

A recent randomised trial has tested GM-CSF administration to infants born following FGR; although an increase of neutrophil counts, the authors report no effect on other short and long-term outcomes, in particular, no benefit on the incidence of secondary sepsis [50].

Further research is required to elucidate the physiopathological alterations implicated in the immunity and inflammation response in FGR infants. Whether the quantitative deficiency in innate immunity plays a role in adverse outcomes needs to be investigated in future trials.

4. FGR AND CARDIOVASCULAR AND METABOLIC FUNCTIONS

The oxygen and nutrients deprivation induced by placental insufficiency may result in several metabolic alterations in the neonatal period, like hypo- or hyperglycaemia, hypocalcaemia, jaundice. Large epidemiological studies have highlighted the association between FGR and risk of type 2 diabetes mellitus, obesity, hypertension, dyslipidaemia, and insulin resistance (the metabolic syndrome), that ultimately lead to the premature development of cardiovascular diseases [51, 52].

FGR is responsible for changes in the structure and the physiology of developing organs, with adverse long-term consequences. This concept of fetal programming [51, 53, 54] is recognized to be the link between in utero environment and chronic diseases in adulthood. The theory of the developmental origin of health and disease (DoHaD) is hypothesized to relate the permanent epigenetic modifications induced by FGR (methylation, acetylation of DNA, histones

modification) to the effects on gene expression in adulthood [55-58]. The potential adverse outcomes associated with this concept include circulatory and metabolic adaptations to spare the developing brain, short stature in children and adults, premature adrenarche, and the development of polycystic ovarian syndrome.

The reduction of β-cell mass, present in a rodent model of FGR, is correlated to an increased risk of diabetes mellitus [59]. These FGR models show a down-regulation of PDX-1 expression (a transcription factor involved in pancreatic islet development), as a result of specific alterations in DNA methylation and histone acetylation [60]. Also in humans, changes in target specific genes implicated in growth or metabolic phenotypes and genome-wide approach both demonstrated the deep impact of FGR on epigenetics [61, 62].

The risk of cardiovascular diseases observed following FGR has been related not only to the higher incidence of metabolic syndrome, but also to specific cardiovascular complications and dysfunction. Indeed, FGR has been associated to increased blood pression and heart rate [63, 64] and early atherosclerosis [65, 66]. The abnormal aortic and carotid wall thickness detected in FGR fetuses and infants could be the result of vascular remodelling beginning before birth, which may contribute to the occurrence of cardiac dysfunction during adulthood [67, 68]. The pathogenesis is still unclear, but animal models of FGR have demonstrated morphological changes in myocardium and vascular wall, with consequent myocardial dysfunction, vascular remodeling and fibrosis [69, 70].

Furthermore, the renal anatomy and function are usually impaired by FGR, as shown both in animal models, which present a reduced number of nephrons [71] and in clinical studies [72], with a greater risk of hypertension and progressive renal failure [73].

5. FGR AND THE DEVELOPING BRAIN

FGR severely affects the fetal brain development and brain functions and recent advances have highlighted this effect [74, 75]. The fetal brain is particularly vulnerable to the effects of abnormal fetal growth, that is associated to neurological disorders including cerebral palsy, epilepsy, learning and attention difficulties, neurobehavioral disabilities, and other cognitive impairments [76-78].

5.1. FGR and Neurodevelopmental Impairments

Babies born at 32-42 Gestational Weeks (GW) with a birth weight for gestational age below the 10th percentile are 4-6 times more likely to have cerebral palsy than children with a birth weight in a reference band between the 25th and 75th percentile [1]. A similar pattern is observed in those with unilateral or bilateral spasticity, as well as those with a dyskinetic or ataxic disability. In babies born at less than 32 GW, the relationship between birth weight and risk of cerebral palsy is less clear. Cerebral palsy is reported up to a 30-fold increased when FGR is associated with major birth defect [79, 80]. This is consistent with magnetic resonance imaging (MRI) studies suggesting that approximately 75% of brain lesions associated with cerebral palsy occur in the early or middle part of the third trimester, time period usu-

ally affected in case of FGR and adverse intrauterine environment [81]. Moreover, several follow-up studies at school-aged reveal a significant association between FGR and neurodevelopmental impairments, from minor cognitive deficiencies to neuropsychological dysfunctions [76, 80, 82]. Comparison within monozygotic twin pairs at school age showed that the FGR twin is at increased risk for cognitive deficiencies, with reduced verbal IQ when compared to the other twin [83].

The neurodevelopmental consequences of FGR are related to the severity of FGR, when it began during prenatal period and the gestational age at delivery [84].

Constient with findings reported in humans, rats with severe FGR exhibit white matter damage that persist to adulthood [85] while moderate FGR is associated with only transient hypomyelination, mild microglial activation and astrogliosis [86], with behavioural deficits noted at 8-weeks of age [87].

Preterm birth is likely to exacerbate the neurodevelopmental impairment associated with FGR [76, 88]. This is supported by the French cohort study EPIPAGE, showing that neurocognitive deficits and behavioural disorders in children born between 29 and 32 GW are significantly higher in infants with FGR, even mild, compared to infants born with normal birth weight [80]. Therefore, low birth weight has been recently proposed as a factor able to better predict the occurrence of cerebral palsy in moderate to late premature infants [89].

5.2. FGR and Cerebral Blood Flow

During prenatal chronic hypoxia, fetal blood flow is selectively redirected to the brain and to maximize oxygen and nutrient supply [90, 91]. Even if brain sparing mechanism has been initially considered protective, several studies demonstrate that fetuses with brain sparing, diagnosed by prenatal ultrasound, have worse neurodevelopmental outcomes compared to FGR infants without brain sparing [78, 92-94]. In case of blood flow redistribution, improved brain perfusion is not uniform, preferentially directed in favour of basal ganglia. Other brain areas, including frontal lobe, can therefore be severely altered, leading to neurobehavioral disability [95] .

5.3. Brain Injury Induced by FGR

Brain injury following FGR is consequent to a combination of grey and white matter damage as revealed by several clinical imaging studies [96, 97].

Cortical grey matter volume in FGR infants is found reduced by 28% compared to equivalent healthy term-born infants [88]. A delayed cortical development and altered cortical gyrification is described in FGR infants soon after birth [98], and found at least up to 1 year of age with significant developmental disabilities [97]. Post-mortem analysis has detected a decreasing neuronal cells density in the developing cortex [99]. These findings are consistent with several preclinical studies [85-87, 100-105]. Disturbance in cell proliferation and migration of neurons and final neuronal loss are found also in the hippocampus [105, 106]. Interestingly, these morphological changes observed in the hippocampus

and in the septo-hippocampal circuit may be responsible for impairment in hippocampal-related behaviours, such as learning and memory [107].

Furthermore, impaired myelination and abnormal connectivity are recognized as common features following FGR in (i) different animal models of placental vascular disease [105, 108], (ii) in a rat model of maternal undernutrition [109], and (iii) in human preterm infants with FGR [110, 111].

5.4. Mechanisms Underlining FGR-associated Brain Injury

Mechanisms involved in FGR-related brain damages have been explored in preclinical studies focused on excitotoxicity, oxidative stress, necrotic and apoptotic degeneration and neuroinflammation [75, 90]. Hypoxia and undernutrition activate a cascade of cellular and biochemical events that lead to immediate or delayed cell death, with potential effects on immature neurons and neuroglia [90, 91]. Rodent models of FGR have revealed glial reactions including increased microglial activation and increased density of reactive astrocytes [103, 112]. Neuroinflammation is a key factor in the disruption of oligodendroglial maturation [113] and was reported in several animal models of FGR [86, 112]. Recently, in a FGR model induced by prenatal malnutrition, transcriptomic analysis performed at birth reveals a deregulation of genes controlling neuroinflammation in both oligodendrocytes and microglia [109]. These findings support the concept of the double hit insult both in rodents and humans: the initial hit associated with the occurrence of FGR can sensitize the deleterious effects of second postnatal hits, *i.e.* systemic inflammation and epigenetic changes [114-116].

In order to be able to provide therapeutic intervention for the fetus or infant at risk of brain damage, it is important that FGR infants are identified timely. This can be challenging, as fetal brain injury may be initially undetectable during gestation. Advanced neuroimaging is now providing the opportunity to identify and then monitor the evolution of brain injury in compromised foetuses and neonates. Another approach would target reliable circulating markers of brain damage in pregnant women and newborns [117, 118].

CONCLUSION

FGR is a leading cause of neonatal morbidities and neurocognitive disabilities in children. In France, the estimated excess medical costs attributed to FGR reach 235M€ for just the first year of care [9]. This underscores the need for the development of research programs to improve our knowledge of the developmental trajectories altered by FGR, a top priority that is currently under-recognized in global health. Strategies able to prevent FGR-related damage to the developing organs and system during the perinatal period would have immediate and significant clinical, educational and financial benefits for patients, their families and society.

LIST OF ABBREVIATIONS

GM-CSF = Granulocyte-Macrophage Colony-Stimulating Factor

IFN-γ = Interferon γ

IGF-1 = Insulin-Like Growth Factor 1

IgG = Immunoglobulin G

IL = Interleukin

IQ = Intelligence Quotient

PPAR-γ = Peroxisome Proliferator-activated Receptor γ

VEGF = Vascular Endothelial Growth Factor

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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