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The Long-Term Effects of Gut Microbiota of Premature Babies and Adult Health

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Preterm intrauterine growth restricted (IUGR) infants compared with their appropriate for gestational age (AGA) counterparts carry a double burden. Both groups of infants experience catch-up growth mainly in the first 2 years of life. Later, they may be predisposed to develop cardio-renal-metabolic adverse sequelae [1], particularly in cases of "excessive", unhealthy growth. The type of catch-up growth depends on several factors, including fetal programming, early nutrition, and gut microbiota [1]. Although many of the implicated factors have been extensively explored, the literature on preterm gut microbiota is restricted. Therefore, we aimed to search existing evidence concerning differences between the microbiota of AGA and IUGR preterm infants. The following parameters were considered: composition of their gut microbiota, their microbiota-depended catch-up growth, and the later resulting deleterious effects.

It is known that preterm infants present a divergent gut microbiota compared to term infants. This is mainly due to their immature intestinal tract and immune system [2]. Furthermore, different microbial exposures at birth and postnatally, including mode of delivery, antibiotic administration, absence of lactation, and formula feeding, are implicated. Thus, the gut microbiota of preterm infants is characterised by delayed colonisation, decreased number of bacterial species, and lower diversity. Possible abundance of pathogenic facultative anaerobes (e.g., Enterobacter, Escherichia, Klebsiella) and scarcity of commensal strictly anaerobic organisms (e.g., Bifidobacterium, Bacteroides, Clostridium) may occur [3].

Focusing on preterm infants, limited studies showed differences in gut microbiota between AGA and IUGR infants. It has been reported that preterm small for gestational age (SGA) infants on postnatal day 30 presented in their stool lower Klebsiella and Enterobacter abundances. Additionally, the bacteria from this group clustered separately from those of the AGA group [4]. Studies in animal models confirm differences in the gut microbiota of IUGR and AGA offspring. Relatively, pathogenic bacteria, including Enterococcus and Enterobacteriaceae, were higher in the faecal samples of 2 to 11-week-old fetal growth restricted (FGR) pups of Sprague Dawley rats [5].

Concerning rapid catch-up growth and higher body mass index (BMI) in preterm SGA infants, increased risk has been documented for renal injury. This is due to their smaller nephron number, higher renal dysfunction, decreased glomerular filtration rate (GFR) and increased microalbuminuria. Also, increased risk exists for higher blood pressure, insulin resistance, obesity, and cardiovascular problems even in childhood [6].

The effect of the gut microbiota on catch-up could rely on various mechanisms. Thus, changes in the expression of genes associated with growth and modifications in metabolic pathways could be implicated. Relatively, research has shown that the gut microbiota impacts the somatotropic axis by regulating insulin-like growth factor 1 (IGF1) and growth hormone production [7]. Furthermore, it has been documented that increased body weight was associated with decreased Lactobacillus and

increased short-chain fatty acids (SCFAs). The latter are involved in the synthesis of lipids and glucose [8]. Seminal research had already stressed the critical role of the gut microbiota in shaping lean and obese phenotypes [9]. Later literature reports that several pathologies, comprising obesity and metabolic syndrome, present an imbalanced gut microbiota [10].

Hence, divergent and more pathologic early gut microbiota may be implicated in excessive catch-up growth. Moreover, it may predispose to worse cardio-renal-metabolic sequelae in preterm IUGR, compared with preterm AGA subjects. Therefore, prematurity associated with IUGR versus prematurity associated with AGA should be considered a more deleterious condition, seen also from the gut microbiota perspective.

Interventions might target a balanced microbiota that could train the immune system, influence growth hormone production, and protect the gut barrier. Such interventions comprise a healthy diet during pregnancy, vaginal delivery, breastfeeding, and possibly manipulation of intestinal microbiota by dietary or biotherapeutic means.

Nevertheless, focusing only on the microbiota may be a bit simplistic. Several mechanistic factors should be considered in this complex relationship between early microbial colonisation and the developmental origins of health and disease. Interactions between the host and the microbial milieu in specific environments obviously play a role. Altered gene expression profiles (transcriptomics) and epigenomics with DNA methylation changes, histone modifications in genes related to metabolism and growth likely play important roles. Multiomic integration via metabolite and proteomic expression should be considered. Incorporation of these mechanisms into a systems biology approach can provide a more in-depth understanding of mechanisms of action. At the same time, it may provide biomarkers for those individuals at greatest risk.

Summing-up, an improved perception of the mechanisms along with early identification will enable the development of targeted strategies for prevention which may include nutritional, pharmaceutical, and environmental modulators.

Author Contributions

A.M-.P. conceptualised the paper and wrote the manuscript. D.D.B. and J.N. revised and edited the manuscript. All three authors have read and consented to the last version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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