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Editorial

The next ten years in neonatology: new directions in research

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The last ten years, the next ten years in Neonatology

Guest Editors: Vassilios Fanos, Michele Mussap, Gavino Faa, Apostolos Papageorgiou

"To strive, to seek, to find, and not to yield."
(Ulysses, Lord Alfred Tennyson)

Keywords

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This paper is a prelude to proceedings of the 10th International Workshop on Neonatology to be held in Cagliari, Italy from October 21st to 25th, 2014. These proceedings will be a significant milestone, highlighting the new frontiers of perinatal and neonatal research. Over the five days of this meeting, we aim to (1) examine the roots of the new directions in perinatal and neonatal research; (2) predict the trajectories of advancement in medical technologies, research, clinical care and teaching that will be the future of perinatology and neonatology. The discussion will be in four sections.

Back to the future: the placenta and perinatal programming

More than 20 years ago, an extraordinary man and scientist, David Barker, was ahead of his time by focusing attention on the importance of the fetus and what takes place during intrauterine life [1]. Barker was one of the physicians who in the last decades brought about the greatest changes in medicine, changes so important as to represent a veritable revolution in medical thought. Following his theory, not only is the neonate (and even more so the fetus) not a small adult, but perhaps the neonate is the "father" of the adult person. Most of our destiny in health and disease throughout adult life has been decided and traced in our mothers' wombs [2]. The concept of perinatal programming has become more and more accepted as: "The response by a developing organism to a specific challenge during a critical time window that alters the trajectory of development qualitatively and/or quantitatively with resulting persistent effects on phenotype" [3]. There are several contributions on the outstanding role of early epigenetic mechanisms and the future adult life of each individual. The practical consequences of all the data reported in these studies are as follows. Firstly, not only the mother is involved but also the father, with an intergenerational effect: for example, undernourishment in the uterus perturbs the adult sperm methylome. Thus, *in utero* nutritional exposures during critical windows of germ cell development can impact the male germline methylome, associated with metabolic disease in offspring [4]. Secondly, we are going progressively back to the importance of the placenta: this concept is expressed in non-scientific environments. The placenta is the life support system for the fetus. However, given its vital role, shockingly little is known about the placenta [5]. Only recently, for instance, have scientists started to suspect that the placenta may be non-sterile, as previously thought, but may have its own microbiome [6]. Thirdly, until today no effect of perinatal programming has been observed in the constellation of the so-called metabolic syndrome; however, perinatal programming significantly influences many other organs and tissues, such as the kidney, the lung and the brain in their development, maturation, function, and ultimately in their susceptibility to diseases. The authors, after spending the last few years in studying developmental nephrology [7, 8], recently turned their attention to fetal programming of the human brain and the possible link with the occurrence of neurodegenerative disorders in adulthood [9]. Thus, not only genetics is important (to be able to), but also epigenetics (to be). All appears to occur on the basis of a genetic predisposition inside the womb, where negative events lead to cell hypodysplasia and a reduction of the ramification of essential structures inside the parenchyma (the lung in our case, but also the ureteral bud, the cerebral connectome and so on) [10, 11]. Quoting a fascinating title by Grady [5], we can call these structures the "mysterious trees" of a newborn's life. Placenta is the first of these trees: when it is strongly involved in pathologies, especially at ≤ 26 weeks of gestation, it probably determines a negative influence on all the other trees. We shall give a single example. Some psychiatric diseases in children and young adults are thought to originate from adverse exposures during fetal life, including hypoxia and hypoxia/reoxygenation. A recent study shows, for example, that the placenta is able to release factors, in response to altered oxygen, that can damage developing neurons under experimental conditions [12]. These data appear to confirm what Rees and colleagues point out: "fetal brain damage might arise not only because oxygen delivery to the brain is impaired but because of the accumulation of reactive products in the fetal circulation released from the placenta that affect fetal cerebral vascular resistance and cerebral metabolism" [13]. Thus, placental dysfunction is central to many complications of human pregnancy, including pre-eclampsia, intra-uterine growth restriction (IUGR) and stillbirth. The precise molecular pathophysiology of placental dysfunction in these conditions is not well known. Some authors have detected changes in the intracellular metabolome and metabolic footprint of placental tissue in response to altered oxygen tension and pre-eclampsia [14]. Metabolomics has the potential to identify changes in clinical conditions associated with placental molecular pathophysiology [15].

Paradigm shift: the revolution of metabolomics in perinatalogy and neonatology

In recent years the number of publications on metabolomics in neonatology and pediatrics has greatly increased [16, 17]. This is an evolution, perhaps a silent revolution, that promises to become a powerful discipline widely accepted and with which perinatologists will have to come to grips in the very near future as a part of our world. This is because we strongly believe that the time is ripe to propose the neologisms *neonatomics* and *childomics*: this is in the

title of a further issue published on the occasion of the 10th International Workshop on Neonatology, namely a special supplement of the *Journal of Maternal Fetal Neonatal Medicine*, fully devoted to perinatal metabolomics [18]. It follows a multiannual tradition consisting of the publication of a special issue containing the proceedings of the workshop and a commentary/editorial written by us [19]. Over the past several years, most published (and presented) studies have focused on metabolomics; its applications have been increasingly studied in pregnancy, in labour/delivery, and in the neonatal age.

Regarding the binomial metabolomics and pregnancy, we wish to quote the first paper, to the best of our knowledge, published in obstetrics by Romero [20], and the latest articles that have appeared in the literature. A report on dynamic metabolic signatures and proposed related metabolic pathways in the maternal plasma for normal pregnancies has recently been published: it provides the basis for time-dependent metabolic trajectory against which disease-related disorders may be fought [21]. In another paper, urine samples collected from pregnant women at term of gestation before and/or after the onset of labour, were analyzed using gas chromatography mass spectrometry (GC/MS) and nuclear magnetic resonance spectroscopy (NMR) techniques to identify the different metabolic profile between labor (L) and not labor (NL) status. This paper potentially offers the promise of a robust screening test [22].

Regarding the time of birth, metabolomics has been studied in depth in asphyxia, both in experimental animal models [23-25] and in newborns [26]. What emerges globally from these studies is the prospective, predictive and personalized dimension of perinatal metabolomics [27, 28]. The capacity to respond to and survive an extremely strong and acute stimulus such as asphyxia seems an intrinsic property of each subject, virtually independent of the application or non-application of treatment protocols: some newborns are fragile when faced with strong obstacles and die, while others are resilient and may survive, with or without insufficiency of one or more organs [18]. Their basal metabolisms are quite different. Thus, knowledge of the existence of a marked interindividual basal variability and of the fact that this variability increases greatly following an important stimulus such as asphyxia is of extreme importance in clinical practice. In the near future, some of these neonates, instead of having all of them follow the same protocol (potentially too drastic for some and inadequate and/or not well focused for others), can be saved through application of personalized treatments [18].

Regarding the binomial metabolomics and neonatal period, we have dedicated several papers and reviews to this topic [16, 17]: they are related to intrauterine growth-restricted and small-for-gestational-age neonates, prematurity, mode of delivery, hypoxic-ischemic encephalopathy, persistent ductus arteriosus, respiratory syndrome and surfactant therapy, cytomegalovirus infection, nephrouropathy, inborn errors of metabolism, pharmametabolomics and nutrimetabolomics (including the study of maternal milk and formula). Numerous papers have also been presented in experimental neonatology. In particular, the fluids most frequently used are urine, cord blood plasma, but also milk and stools. Each condition or disease presents a specific discriminating set of metabolites, which can be considered as a 'bar code'. In the near future, urinary metabolomics will probably be one of the tools most used in pediatrics and the metabolome will be 'our world' [18].

Brave new world: the microbiome and microbiomics from perinatal to adult life

Microbial communities associated with the human body, that is, the human microbiome, are complex ecologies critical for normal development and health. The characterization of the human microbiome in various disease states suggests that our microbial environment plays a critical role in both the maintenance of health and the pathogenesis of many diseases [29], including those of the central nervous system [30]. Development of the intestinal microbiota in infants is characterized by rapid and major changes in microbial abundance, diversity and composition. These changes are influenced by medical, cultural, and environmental factors such as mode of delivery, diet, familial environment, diseases, and therapies used. Thus, arriving at a universal standard for intestinal colonization is extremely difficult since the development of the intestinal microbiota is very peculiar for each individual [31]. Factors influencing the development of a personal tailored microbiota in the neonate are well known, with particular emphasis on antibiotic therapy [32]. Coming back to prenatal life, exciting advances in understanding the role of both host and microbiota in parturition and preterm birth are on the horizon [33].

A special area of increasing interest is the correlation between microbiome and metabolomics, the so-called microbiomics [34]. In particular, metabolomic applications to decipher gut microbial metabolic influence in health and disease have been addressed in depth [35]. What we know is that metabolomics

analyses reveal major effects of gut microflora on mammalian blood metabolites. By studying germ-free animals it is clear that the gut microflora has a direct impact on the drug metabolism capacity of the host. Together, these results suggest a significant interplay between bacterial and mammalian metabolism [36, 37]. In particular, in subjects with a genetically predetermined pathology, only the interaction of a given diet with a specific microbiome can form metabolites capable of conditioning all the organs of the body, including the central nervous system (the brain-gut connection) [18, 38].

One can explore protein and metabolite interactomes in order to pinpoint additional molecules associated with brain diseases that had not been picked up initially [39].

Another example regards the kidney. Under physiological conditions, the predominance of symbiotic bacteria, an intact intestinal barrier, defensin production, mucus integrity, and immunoglobulin A (IgA) secretion support the symbiosis between the host and its gut microbiota. An intramural innate immunity controls pathobiont overgrowth inside the lumen of the intestinal tract. The metabolic changes that are associated with the progression of chronic kidney disease (CKD) to end-stage renal disease (ESRD) change the balance of symbionts and pathobionts in a way that favors pathobiont overgrowth, that is, dysbiosis [40]. It is important to understand how the intestinal microbiota and a failing kidney affect each other [41].

It is increasingly recognized that bacterial metabolites, such as phenols, indoles and amines may contribute to uremic toxicity. Some of these metabolites are related to diet/microbiome interaction [42].

Thus, certain metabolites strongly correlate with microbial community structure: this raises the possibility of targeting metabolites for monitoring and/or therapeutically manipulating microbial community function in acute and/or chronic diseases [43]. A very recent experience of the authors on autism [44] confirms some data from the literature [30]. This leaves open prospects and expectations of acting through diet to treat, but most of all to prevent, certain symptoms and thus significantly improve the quality of life of patients.

New inhabitants on the planet earth: adults who were born with extremely low birth weight

The survival of extremely low birth weight infants (ELBW) has improved dramatically. Compared to the past, more ELBWs continue today to survive and go home. An open problem is the long-term outcome of these children [45]. Severe disability has been observed in about 1 out of 3 of ELBWs at 18-24 months, with multiple disabilities in about 1 out of 4 of these children [46]. Long-term follow-up of this high-risk cohort of NICU graduates should be mandatory. Moreover, other problems such as subtle and non-specific neurocognitive disorders have been observed in 50-70% of non-disabled ELBWs with normal intelligence, often emerging after starting school. Again, a triad of disorders, namely Autism Spectrum Disorders (ASD), attention deficit/hyperactivity disorders (ADHD) and emotional disorders have been reported for former ELBWs. Finally, mood disorders (namely depression) have been described [47]. The role of epigenetic DNA modifications as a potential mechanism that explains how early social life experiences become embedded in the circuitry of the developing brain and are associated with lifelong consequences has recently been underlined. Therefore, the identification of potential windows for timely therapeutic interventions in DNA memory-mediated disease states is likely to be more effective and less costly than addressing problems at a later age [48].

A special problem is represented by long-term cardiovascular, renal and metabolic problems [49]. In a number of reports from the literature it has been demonstrated that prematurity and consequent low weight at birth are risk factors for developing hypercholesterolemia, arterial hypertension, obesity, type 2 diabetes, QTc interval prolongation at basal electrocardiogram, early endothelial dysfunction, structural and functional cardiac modifications and increased death rates from coronary heart disease [49]. It has recently been observed that there is a gender effect: preterm birth is associated with higher blood pressure in adult life, with women appearing to be at greater risk than men [50]. Moreover, the metabolic fingerprinting of a birth with extremely low birth weight (ELBW) persists into adult age [51]. Finally, an underestimated problem is the socioeconomic impact on health systems of these adults born ELBW [52].

Conclusions

Great changes in medicine are expected in the next few years with the explosion of knowledge that will include discovery of arrays of biomarkers [53], integration of omics technologies [54], in-depth understanding of microbiomes [55, 56], networked

medicine [57] and individualized medical care [58]. Advances in perinatology and neonatalogy will result from these research trajectories and will require forward thinking, creativity and advanced planning to breach the gap between research and clinical practice and thereby create a powerful partnership for the betterment of our infants and indeed, all of mankind.

Declaration of interest

The Authors declare that there is no conflict of interest.

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