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# Editorial: Endotyping and phenotyping prematurity and its complications

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## Editorial on the Research Topic

### Endotyping and phenotyping prematurity and its complications

The mechanisms triggering preterm birth are multifold and largely unexplored. However, evidence is increasingly supporting the hypothesis that the pathophysiological conditions eliciting preterm birth play a major role in the clinical picture and the development of complications of prematurity (1). Most of the complications of prematurity involve different forms of organ injury, expressing themselves as different clinical phenotypes. These phenotypes are highly influenced by the pathological intrauterine environment that manifests themselves as endotypes of prematurity (1). The term endotype refers to “a subtype of a condition, which is defined by a distinct functional or pathophysiological mechanism” (2). A consensus on the different endotypes of prematurity has yet to be reached. Two major pathways leading to very preterm birth have been identified so far: the infection/inflammation endotype and the dysfunctional placentation endotype (3). The infection/inflammation endotype includes chorioamnionitis, preterm labor and rupture of membranes and cervical insufficiency. The dysfunctional placentation endotype includes placental malperfusion, hypertensive disorders of pregnancy (HDP) and/or intrauterine growth restriction. A better understanding of the role of the prematurity endotypes may facilitate the design of more targeted therapeutic and prognostic approaches to the preterm population.

The objective of this research topic was to deepen the knowledge about the association between endotypes of prematurity and phenotypes of complications of prematurity. This topic covered different neonatal organs and systems as they can all be altered by the endotypes of prematurity.

Prenatal environment may affect brain maturation and the process leading to brain injury in preterm infants. The periventricular white matter damage, defined as periventricular leukomalacia (PVL), is the most common form of non-hemorrhagic brain injury in preterm infants (4). PVL is a result of various antenatal, intrapartum, and postnatal insults to the developing brain and represents the most common cause of preterm birth-related cerebral palsy in childhood (4). A better mechanistic understanding of the origins of PVL may help develop preventive and therapeutic strategies. Su et al. used a propensity score matching analysis to evaluate the effect of HDP on clinical outcomes of extremely preterm or extremely low birth weight (EP/ELBW) infants. In this case-control study the incidence of PVL in the

offspring of mothers suffering from HDP was significantly increased. The authors demonstrated that, after matching the six major covariates including sex, gestational age, birth weight, antenatal steroids administration and methods of conception, HDP increased the risk of PVL in EP/ELBW infants however had no significant effect on the survival rate at discharge, or the incidence of other complications. The possible explanation for this result may be related to the hypoxic intrauterine environment typical of HDP. Hypoxia is one of the major upstream mechanisms of PVL (4). In the case of maternal HDP, the fetus is exposed to chronic hypoxia in the intrauterine environment (5). Placental hypoxia leads to fetal oligodendrocyte dysmaturation, resulting in altered myelination, ultimately inducing PVL (6).

Similarly to brain maturation, the nature, timing, and extent of prenatal environment may alter fetal and neonatal endothelial function (7, 8). Changes in the luminal surface, oxidative stress, growth factors imbalance, and dysregulation of permeability and vascular tone are the leading causes of endothelial dysfunction in preterm infants (9). Preterm birth impairs numerous endothelial pathways with potentially severe early and late neonatal adverse outcomes. Amelio et al. reviewed the current knowledge on endothelial dysfunction in relation to the etiology of preterm birth. The type and extent of endothelial dysfunction may vary according to the intrauterine environment. The paper summarizes the available evidence on the type of endothelial damage in the infectious/inflammatory and dysfunctional placentation endotypes of prematurity, focusing on their molecular peculiar features, biomarkers, and clinical impact. In the given context, advancing endothelial characterization could be a promising way to provide patient-tailored care to the most vulnerable newborns.

Individual studies have suggested that prenatal conditions such as chorioamnionitis or HDP may also affect the therapeutic response to pharmacological agents in preterm infants (10). In particular, response to cyclooxygenase (COX) inhibitors, used to treat patent ductus arteriosus (PDA), may vary depending on fetal programming induced by the intrauterine environment. Who, when and how to treat PDA is a challenge for the neonatologist. Multiple factors including gestational age, birth weight, day of life at treatment may influence the effectiveness of PDA treatment. In addition, intrauterine conditions may play a role in the neonatal response to ductal therapy. The meta-analysis from Gonzalez-Luis et al. showed a significant association between exposure to HDP and increased rate of pharmacological closure of PDA. In contrast, neither chorioamnionitis nor being small for gestational age were significantly associated with the response to therapy. Subgroup analyses showed that the higher response to COX inhibitors in the HDP group was significant for indomethacin but not for ibuprofen or for the studies using both drugs. However, meta-regression showed that this difference between the drugs was not statistically significant. These data suggest that the pathologic condition that triggers prematurity may alter the response to pharmacological treatment of PDA and may help address uncertainties around PDA management.

Bronchopulmonary dysplasia (BPD), is a preterm-related chronic lung disease (11) that may involve airways, alveoli, vessels, interstitium, and lymphatic system, giving rise to

different clinical phenotypes, that may be difficult to unveil in clinical practice (12, 13). Cardiopulmonary ultrasound (CPUS) may allow a better understanding of the cardiorespiratory challenges that the neonatologists face on a daily basis, tailoring the diagnostic approach and targeting treatments for BPD (14). The case report from Bruno et al. described four different cardiopulmonary ultrasound patterns of evolving and established chronic lung disease of prematurity and the consequent therapeutic choices. In the reported cases, the histological examination of the placental material and the identification of the endotypes of prematurity were consistent with the CPUS patterns. This approach, if confirmed in prospective studies, may guide the personalized management of infants suffering from evolving and established BPD, optimizing the chances of success of the therapies and at the same time reducing the risk of exposure to inadequate and potentially harmful drugs.

Recently, the public health mitigation measures during COVID-19 lockdowns around the world offered an unprecedented and unique “nature’s experiment” influencing a multitude of host and environmental factors on the feto-maternal unit, and multiple studies suggested changes to preterm birth rates of EP/ELBW population (15). Calvert et al. analysed 52 million births from 26 countries to evaluate changes in preterm birth during the lockdowns (iPOP study) and concluded that large number preterm births were averted globally, warranting further research into causal pathways (16).

A better insight of the relationship between endotypes and phenotypes of prematurity may help target treatments in the view of personalized medicine and in the context of developments in artificial intelligence, potentially improving the outcome of the fragile preterm population.

## Author contributions

MP wrote the first draft of the manuscript, RP, LR, EV revised the manuscript and contributed to the final version. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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