frontiers | Frontiers in Endocrinology

TYPE Editorial
PUBLISHED 19 May 2023
DOI 10.3389/fendo.2023.1206072

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 14 April 2023
ACCEPTED 09 May 2023
PUBLISHED 19 May 2023

CITATION
Vacher C-M, Bonnin A, Mir IN and Penn AA (2023) Editorial: Advances and perspectives in neuroplacentology.
Front. Endocrinol. 14:1206072.
doi: 10.3389/fendo.2023.1206072

Editorial: Advances and perspectives in neuroplacentology

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KEYWORDS

neuroplacentology, placenta, brain, preterm birth, neurodevelopmental disorders, preeclampsia, chorioamnionitis

Editorial on the Research Topic
Advances and perspectives in neuroplacentology

The placenta is essential for pregnancy maintenance and fetal development. It regulates fetal growth by controlling the transport of oxygen, nutrients and waste products between the maternal and fetal circulation. It also serves as a protective and selective barrier filtering the passage of hormones, toxic agents and pathogens that could be harmful for the fetus. Recent studies have revealed a more specific role of the placenta in protecting and shaping the developing brain. The placenta produces a plethora of neuroactive hormones, growth factors, and immune molecules that can influence brain developmental trajectory, in region- and sex-dependent ways. Consequently, placental dysfunction or abruption may program the developing brain for long-term neurological and psychiatric morbidities. The growing body of evidence linking placental physiology and brain development has led to the emergence of a new field coined "neuroplacentology". The current Research Topic explores different aspects of the latest research in neuroplacentology and offers new insights into the array of associations linking placental physiology and brain development.

Preterm birth refers to any live birth before 37 weeks of gestation. Premature delivery, which is marked by the premature loss of the placenta, exposes the immature cerebral tissue to adverse conditions that may compromise its development, lead to injury and potentially predispose the newborn to neurodevelopmental disorders, including a wide range of motor, cognitive, behavioral and emotional disorders (1). Preterm birth is a major public health issue that affects approximately 10% of the surviving newborns worldwide (2). The prematurity rate in the United States has not decreased substantially in recent decades, but the survival rate for preterm infants has improved. Eighty percent of infants weighing 500-1000 g will now survive, but with a significant risk of lifelong disabilities. Despite considerable improvements in neonatal care and therapies in recent years (3), preterm labor is still responsible for 70% of perinatal mortality and accounts for 50% of long-term neurobehavioral morbidities. The relative risks of these adverse outcomes are even higher for those born extremely prematurely (<28 weeks of gestation) (4). Placental conditions preceding preterm birth, such as intrauterine growth restriction, infection

(chorioamnionitis) or preeclampsia, have also been shown to exacerbate the risk and severity of poor neurological outcomes caused by prematurity (5–8). Gardella et al. offer a comprehensive overview of this topic. The authors review and discuss different potential mechanisms linking compromised placental support and postnatal neurological outcomes in the context of fetal growth restriction and prematurity. White matter injuries are common complications of preterm birth, particularly in extremely preterm infants, due to the exposure to factors such as hypoxia, inflammation, oxidative stress and withdrawal of placental support (9–16). Marable et al. present an analysis of placental transcriptomes from a cohort of extremely low gestational age newborns (ELGANs) diagnosed with white matter injury. This study reveals that white matter damages among extremely preterm infants are associated with placental transcriptional signatures linked to endocrine disorders, metabolism, inflammation, immune response, and autism spectrum disorders.

Preeclampsia, a gestational hypertensive disorder occurring in 3 to 8% of pregnancies worldwide (17), is a leading cause of maternal and fetal morbidity and mortality. Preeclampsia is linked to clinical neurodevelopmental outcomes in children, including cognitive and psychiatric vulnerabilities, motor impairments, and stroke risk (18). It also increases the risk of fetal growth restriction and placental abruption, ~15% of preterm deliveries being due to preeclampsia (19). There is a pressing need to understand the mechanisms leading to the neonatal outcomes of preeclampsia because there are no well-established measures for primary prevention, delivery remaining the ultimate treatment. The etiology of preeclampsia is not fully understood, but recent research suggests a contributing role of placentally derived angiogenic factor release into the maternal circulation. In particular, an imbalance between PlGF (Placental Growth Factor) and sFlt-1 (soluble Fms-like tyrosine kinase-1) has been associated with the onset of the disorder (20, 21). Interestingly, higher sFlt-1/PlGF ratio in the maternal serum has also been linked to higher risk of fetal growth restriction, preterm labor, and reduced APGAR (Appearance, Pulse, Grimace, Activity and Respiration) score (which assesses for signs of hemodynamic compromise at birth) (22). However, the predictive value of sFlt-1/PlGF ratio for neurological vulnerabilities of prematurity has never been evaluated. In this Research Topic, Middendorf et al. show, in a cohort of 88 preterm infants, that low birth weight was associated with increased maternal sFlt-1/PlGF ratio and worse motor score (as measured by Motor Optimality Score-Revised, MOS-R). However, no direct correlation between sFlt-1/PlGF ratio and motor impairments was found. Evaluating the developmental progress of the cohort through follow-up assessments may provide additional insights into the long-term outcomes of the preterm infants beyond their initial assessment.

The placenta plays a critical role in regulating the *in-utero* immunological state during pregnancy. It helps maintaining the balance between an active immune response against potential intrauterine infections and an immunosuppression that preserves semi-allogeneic fetal development. This optimal balance between pro- and anti-inflammatory signals in the intrauterine milieu is temporally regulated by the placental secretion of cytokines (23, 24), which can influence fetal brain development (25). Infection of the placenta and its membranes, known as chorioamnionitis, is a major cause of preterm delivery (26–29), and may place the fetus at risk for long-term neurological outcomes (30–40). In the current Research Topic, Leon et al. report elevated rates of histological signs of placental inflammation in term infants with perinatal stroke. This finding represents a substantial advancement in our knowledge of the perinatal stroke etiology. The authors stress the importance of continued research in prenatal assessment of placental health, using biomarker signatures or magnetic resonance imaging, to identify perinatal stroke risk early and initiate interventions when possible. Chorioamnionitis is characterized by elevated pro-inflammatory cytokines such as interleukin-1β (IL-1β) (41), leading to excessive inflammatory processes and subsequent fetal brain injury (42). In an experimental model of chorioamnionitis induced by Group B Streptococcus (GBS), Ayash et al. demonstrate that the targeted blockade of IL-1β activity using IL-1a receptor antagonist (IL-1Ra) alleviates placental inflammation and the resulting Fetal Inflammatory Response Syndrome (FIRS). Furthermore, prenatal IL-1 blockade reduces or prevents some of the neurobehavioral impairments resulting from FIRS in the female offspring, but not in males. These findings open new avenues on the therapeutic potential of IL-1Ra to prevent some of the neurobehavioral alterations resulting from placental inflammatory diseases. This study also highlights the importance of considering biological sex when studying the mechanisms that contribute to the etiology, manifestation and treatment of neurodevelopmental disorders.

The increasing prevalence of obesity among women of child-bearing age has been an issue of growing concern in recent years, with studies showing that it may contribute to an elevated risk of pregnancy complications (43). This is particularly true for women of lower socioeconomic status and certain racial groups, with socio-demographic features and stress being identified as potential factors (44–46). Among Black women, higher rates of premature births and small-for-gestational age infants have been reported (2), which may in part be linked to placental conditions. In this context, the study by Williams et al. sheds new light on the complex interplay between maternal health markers (i.e., body mass index and inflammation), race, placental function, and infant outcomes. These findings have important implications for the development of targeted interventions aimed at reducing modifiable pre-pregnancy factors, such as body mass index (BMI) or stress, to reduce pregnancy complications that can ultimately improve maternal and infant health outcomes.

The placenta not only exposes the fetus to negative signals in pathological conditions, but also produces protective factors. A growing body of evidence indicates that the placenta supports fetal brain development through the release of neuroactive and neuroprotective signaling molecules (47–51). Allopregnanolone (ALLO) is a neuroactive metabolite of progesterone (52) that acts as a potent positive allosteric modulator of the $GABA_A$ receptors ($GABA_A$-Rs) (53). In the fetal brain, ALLO levels peak in mid-to-late gestation and are greater than at any other period in life due to a high placental production (54). ALLO administration has been shown to exert neurotrophic, neuroprotective and anti-inflammatory actions in a number of experimental models of neurological conditions, including perinatal brain injury (55). Placental ALLO insufficiency has been associated with altered brain myelination and male-specific autistic-like behavior in a

conditional knockout mouse model (51). Using the same model, Bakalar et al. further show that the lack of placental ALLO disrupts corticogenesis and female somatosensory function. These findings suggest that placental neurosteroids regulate fetal brain development and long-term behavior differently in males and females. Placental hormones may thus target specific structures, circuits and cells, and deviation from physiological conditions might have sex-biased, enduring neurobehavioral consequences.

In conclusion, this Research Topic provides new insights into the mechanisms underlying the placental origin of short and long-term neurological disorders. This special issue shows that the risk and degree of placental and brain disorders are influenced by a complex interplay of factors, such as the timing of insult, biological sex and social determinants of maternal health. Identifying placental risk factors for perinatal brain injuries and neurodevelopmental impairments represents a central aspect of the research in neuroplacentology. The latest advances in this topic highlight the importance of evaluating circulating placental factors, placental histology and transcriptional signatures to identify the individuals at risk and mitigate the impact of injury on fetal brain, through the development of new interventions and preventive strategies. In this regard, the development of more advanced, non-invasive tools and sensors is needed to monitor placental development and detect prenatal anomalies, allowing for timely interventions.

Author contributions

C-MV supervised and wrote the editorial article. AB, IM and AP reviewed and approved the editorial manuscript.

Funding

AB is supported by NIH (R01NS121190, R01DK125415), BrightFocus Foundation (A2019279S), and the Cure Alzheimer's fund; INM is supported by a Children's Clinical Research Advisory Committee (CCRAC) award; AAP is funded by NIH (R21HD109623, R01HD092593).

Acknowledgments

We want to thank all the authors for their contribution, all the reviewers for the time they devoted to the evaluation of the manuscripts, and the Frontiers in Endocrinology team who helped to the preparation of this Research Topic.

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.

Publisher's note

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