Perinatal mental health research: towards an integrative biopsychosocial approach

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EDITORIAL

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Stress-related perinatal mental disorders are common complications of childbearing, with perinatal depression and anxiety disorders being most frequent with prevalence rates of up to 20% reported among parents across the perinatal period (Howard & Khalifeh, 2020). Perinatal stress exposure not only directly impacts the mental health status of the parent and her/his partner but is also known to exert long-term effects on the offspring's disease susceptibility. Understanding the complex biopsychological mechanisms underlying stress-related mental disorders and their potential intergenerational transmission is a crucially important prerequisite towards early identification and prevention in this critical time in life.

The continuous refinement of a comprehensive biopsychosocial model of perinatal mental disorders represents an important next step for several reasons. Firstly, investigating combined psychological, social, as well as *biological* factors provides a more holistic understanding of the respective disorders and will consequently aid an improved identification of individuals at risk. Also, the study of how alterations of biological systems are implicated in the development of perinatal mental disorders will advance our understanding of critical mechanisms explaining how perinatal stress leads to adverse perinatal mental health outcomes and promotes intergenerational effects on the offspring. Furthermore, investigating the role of several biomarkers in different perinatal mental disorders, such as perinatal anxiety, depression, or childbirth-related posttraumatic stress disorder, in both mothers and their partners, will enable differentiation of shared and specific biological mechanisms, again aiding improved identification. Finally, this more integrative grasp of the aetiology of perinatal mental disorders will support the development of personalised interventions targeting both biological risk profiles and the psychosocial context (e.g. social support, individual resilience).

Although recent years have seen initial progress towards integrative approaches in perinatal health research, psychosocial and biological mechanisms are still largely investigated separately (Yim & Dunkel Schetter, 2019). The perinatal period and the transition to parenthood are characterised by unique physiological changes and psychological demands that are inherently stressful. Additionally, in the context of perinatal mental illness unsuccessful adjustment to stressors may cause further strain, which may in turn lead to a dysregulation of stress-related biological systems, including the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system and the immune system (Redpath et al., 2019). Among the wide range of biological mechanisms potentially underlying perinatal mental health disorders, most studies have focused on HPA axis dysregulation in patients with postpartum depression (PPD). For example, previous studies have documented alterations in corticotropin-releasing hormone levels during pregnancy, total cortisol output and cortisol reactivity among PPD patients (Garcia-Leal et al., 2017). Yet, findings remain heterogenous and highlight the need to further characterise HPA axis dysfunction in PPD and other perinatal mental disorders using

innovative methods and longitudinal designs. Recent methodological developments such as the retrospective assessment of *long-term* glucocorticoids in hair may provide a useful complementary tool to be combined with other established strategies to measure HPA axis activity. Furthermore, since hair sampling in offspring immediately after childbirth allows a reflection of glucocorticoid exposure mainly incorporated in the intrauterine period, this provides the unique opportunity to also study intergenerational effects of perinatal mental disorders on offspring's HPA axis regulation (Kress et al., 2019).

In addition to examining singular biological risk indicators, integrating influences of several indicators simultaneously as well as their cross-system interactions holds important value for capturing the complex aetiological processes of perinatal mental disorders. For instance, simultaneous measurement of the steroid hormones cortisol and dehydroepiandrosterone-sulphate, both indicators of HPA axis functioning, allows more complex physiological processes to be depicted, such as their ratio as an index of stress system balance. First evidence indeed suggests that pregnant women with severe anxiety are characterised by an altered cortisol and dehydroepiandrosterone-sulphate levels as well as an increased cortisol and dehydroepiandrosterone-sulphate ratio (Leff-Gelman et al., 2020). Taking this integrative approach further involves combining knowledge from several biological systems which are known to interact with the HPA axis. The immune system undergoes substantial adaptive changes during pregnancy. Moreover, prolonged stress and depressive symptoms during pregnancy have been associated with increased inflammation indexed by elevated levels of pro-inflammatory cytokines such as interleukin-6 (Redpath et al., 2019). Considering that stress affects both the HPA axis and the immune system and these in turn show complex interactions, research examining both stress-related neuroendocrine and inflammatory indicators could uncover important cross-system influences. In this context, the maternal gut microbiome, which is closely linked to inflammatory processes and HPA axis dysregulation, has emerged as another promising mechanism in the development of perinatal mental disorders and their intergenerational transmission (Redpath et al., 2019). On a neuropeptide level, endocannabinoids exert widespread modulatory influences on multiple biological systems, including the stress response and the immune system, and have also been implicated in depressive and anxiety disorders (Navarrete et al., 2020). Hence, investigating endocannabinoid system markers in perinatal mental disorders may offer new insights for aetiological understanding and intervention.

Finally, perinatal mental disorders directly impact the inner social network of the affected individuals and exert detrimental effects on multiple health outcomes of their partners and offspring. Intriguingly, maternal perinatal stress and psychopathology have also been associated with persistent changes in the offspring's immune system and HPA axis functioning (Heim et al., 2019). In this regard, epigenetic signatures, such as DNA methylation, have emerged as a key molecular pathway to explain this process of fetal programming. To investigate these intricate influences, multi-method, whole-family, longitudinal birth cohort studies like the Dresden Study on Parenting, Work and Mental Health (Kress et al., 2019) hold great promise. By understanding the psychosocial and

biological mechanisms underlying perinatal mental health problems, novel mechanism-driven intervention strategies can be derived to promote young families' wellbeing as well as to aid precision medicine in perinatal mental health.

In summary, integrating a multitude of biological factors from different interacting stress-related biological systems in perinatal mental health research has the potential to improve identification of individuals at risk in a family network and to promote evidence-based interventions that target both psychological and physiological outcomes. A successful implementation of this approach can meaningfully contribute to preventing suffering for parents and their offspring during this critical time.

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