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The Relationship Between Perinatal Mental Health and Stress: a Review of the Microbiome

Nusiebeh Redpath[1] · Hannah S. Rackers[2] · Mary C. Kimmel[2]

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Abstract

Purpose of Review Our current understanding of the underlying mechanisms and etiologies of perinatal mood and anxiety disorders (PMADs) is not clearly identified. The relationship of stress-induced adaptations (i.e., the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS), the immune system) and the microbiota are potential contributors to psychopathology exhibited in women during pregnancy and postpartum and should be investigated.

Recent Findings The stress response activates the HPA axis and dysregulates the ANS, leading to the inhibition of the parasympathetic system. Sustained high levels of cortisol, reduced heart variability, and modulated immune responses increase the vulnerability to PMAD. Bidirectional communication between the nervous system and the microbiota is an important factor to alter host homeostasis and development of PMAD.

Summary Future research in the relationship between the psychoneuroimmune system, the gut microbiota, and PMAD has the potential to be integrated in clinical practice to improve screening, diagnosis, and treatment.

Keywords Heart rate variability · Psychosocial stress · Depression · Anxiety · Pregnancy · Microbiota

Introduction

Stress is a state in which an individual's homeostasis is threatened by perceived or real adverse physical or psychological conditions [1]. The perinatal period encompassing pregnancy, parturition, and postdelivery is innately stressful. A healthy pregnancy demonstrates resilience and adaption to physiological, psychological, and social demands of the perinatal period and maintenance of maternal well-being beyond the postpartum period. Perinatal mood and anxiety disorders (PMADs), occurring in 10–20% of women, may result when a woman is unable to successfully adjust to stressors whether due to physiologic factors or exposure to severe or chronic external stressors [2, 3]. The burden of disease from perinatal mental illness is shared by all communities of the world. The non-psychotic PMADs are among the most common morbidities during pregnancy and postpartum period [4]. In current practice, the diagnosis of PMAD is defined by syndromic criteria, thus highly dependent on a clinician's assessment and results of screening scales. The intensity and severity of depressive or anxiety-associated symptoms can change throughout the course of pregnancy and postpartum period [5, 6]. Adding to the complexity of diagnosis, normative physiological changes exhibited in pregnancy often reflect symptoms of depression (i.e., fatigue, appetite changes, sleep deprivation). Anxiety and/or depression can be missed or inaccurately diagnosed [7•]. Furthermore, an individual's presentation may not fully meet the symptomology criteria or reach the diagnostic threshold of screening tools. Similarly, some women may underreport symptoms due to stigma and worry regarding how they are perceived as parents [8]. PMADs remain at risk of being undiagnosed, underdiagnosed, and untreated, which increase the risk of poor health outcomes in mother and child.

Research has identified sociodemographic, psychological, and biological risk factors contributing to the manifestation of

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✉ Mary C. Kimmel
mary_kimmel@med.unc.edu

[1] Department of Maternal and Child Health, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[2] Department of Psychiatry, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

PMAD; however, many are non-specific to the diagnosis [7•, 9]. Many demographic predictors have either direct or indirect association to elevated maternal stress level including lower education level, socioeconomic status, and poorly received social support. Women who have experienced childhood trauma are also at increased risk of experiencing antenatal anxiety [7•]. Significant predictors representative of genetic and environmental factors combined are a personal past history of mood and/or anxiety disorder and a family history specifically of PMAD [7•, 10, 11]. The biological risk factors of PMAD have yet to be elucidated, although there are indications that stress-induced adaptations in the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS), and the immune system are potential contributors to PMAD. Historically, studies on PMAD have focused mainly on the genetic, behavioral, and social risk factors; however, contributions of the gut microbiota (i.e., bacteria, viruses, and fungi that thrive in the intestine) in relation to the central nervous system has gained significant attention. Current research focuses on the microbiota-gut brain axis, a bidirectional communication between the microbiota and brain [12, 13••, 14]. Although the direct link between gut bacteria and brain is poorly understood, stress has been observed as a critical mediator.

Stress leads to the dysfunction of the intestinal barrier, enhancing the permeability of the mucosal membrane leading to a "leaky gut" [12, 13••, 14]. The loss of the integrity of the mucosa facilitates the transmucosal migration of commensal bacteria or bacterial products [12, 15•]. Furthermore, stress may lead to a deviation of "normal" microbial composition known as microbial dysbiosis [13••, 16]. Dysbiosis has been associated with psychological disorders, including stress, anxiety, and major depressive disorder (MDD) [14, 17•]. Across pregnancy, several studies have shown an observed shift of maternal intestinal microbial composition [18, 19]. Jasarevic et al. suggest the maternal intestinal microbiome favors taxa that are able to meet the nutritional and metabolic demands of pregnancy and prepare for lactation [18]. Similarly, Koren et al. [19] found in human subjects that gut bacteria change over pregnancy to meet metabolic demands of pregnancy. Yet DiGiulio et al. [20] found that microbiota community, taxonomic composition, and diversity in distal gut remained stable throughout pregnancy and postdelivery. The discrepancies in these findings can be accounted by the variation in study sampling and design [13••]. Researchers have also attributed stress during pregnancy as a mechanism for altering the maternal gut microbial composition and influencing neural activity in stress-responsive areas of the brain [14, 18, 21]. The composition of gut microbiota from mice exposed to prolonged restraint stressor was significantly different from the community from non-stressed control mice [21].

The microbiota is associated with activation and alteration of the HPA axis, the ANS, and the immune system [14, 22, 23]. The ANS and HPA axis respond to demands placed on the body during stressful events to maintain homeostasis [22]. The balance between the sympathovagal system and HPA axis is modulated by the inverse relationship between the amplitude of heart rate variability (HRV) and plasma level of cortisol, respectively. The imbalance between the HPA axis and ANS is represented by decreased parasympathetic activity (low HRV) and increased cortisol levels [12, 24]. Germ-free mice were observed to have an exaggerated response of the HPA axis to stress; this was reversed by reconstitution with microbial communities [12]. The experimental manipulation of intestinal microbiota has shown to increase corticosteroid reactivity and/or glucocorticoid levels as well as influence depressive and anxious behaviors in mice [25].

Microbial communities are likely important regulators of a host's stress response; vice versa, microbial communities are affected by the host response to acute and chronic stressors.

This review will assess the relationship of PMAD to stress by examining the physiological response to stress including the changes in the HPA axis and the ANS during the perinatal period. It will explore the relationship between HRV as a measure of stress reactivity and the microbiota as a mechanism for the development of depression and anxiety mood disorders during pregnancy and the postpartum period. The search terms used in the review included heart rate variability, psychosocial stress, depression, anxiety, pregnancy, microbiota, and postpartum, and they are supplemented with known relevant articles. The association of measures of stress reactivity and microbiota holds tremendous potential for clinical efficacy to overcome barriers to screen, diagnose, and treat PMAD.

Stress Reactivity: Normal Physiology and in PMAD

Hypothalamic-Pituitary-Adrenal Axis

The HPA axis plays a key role in regulating the release of cortisol by integrating both the neural and endocrine systems. First, the activation of the HPA axis stimulates neurosecretory cells in the hypothalamus to release corticotropin-releasing hormone (CRH) to stimulate the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary hormone [1, 26]. As a result, ACTH enters into circulation and stimulates the cortex of the adrenal gland to produce corticoid and glucocorticoid hormones, the most prominent of which is cortisol [22, 26]. As shown in the behavioral test, the Trier Social Stress Test (TSST), cortisol is a physiological biomarker of stress and used as an index to account for acute stress with a recovery phase occurring 90 min following a stressor [27, 28].

In addition, the cortisol awakening level response is able to serve as a marker of HPA axis function during pregnancy independent from the mother's subjective response to a stressful experience [29]. The negative feedback from the elevated levels of cortisol inhibits further release of corticotropin by the anterior pituitary corticotrophs [26].

During pregnancy, response to the HPA axis is reduced with a dysregulation of the negative feedback response [30, 31•]. Over the course of fetal gestation, the placenta secretes increasing amounts of CRH into both fetal and maternal bloodstreams. After 25 weeks of gestation, the CRH levels rapidly increase to levels usually only observed during stress [30, 32, 33•]. Placental CRH stimulates release of cortisol and overcomes the HPA axis negative feedback system [32, 34]. High levels of cortisol are sustained throughout pregnancy and into the postpartum period as an adaptive function to promote fetal development, conserve energy for lactation, improve the function of the immune system, and enhance maternal defense [6, 30, 31•]. Minuscule elevations of maternal cortisol cross the placenta and substantially elevate fetal concentrations and prime the developing fetal brain to respond to stress after birth [35, 36]. These hormones can alter the structure and function of the developing brain [35]. However, a balance is required as the fetal brain is vulnerable to excessive exposure to glucocorticoid. Studies have noted elevated levels of cortisol predict premature delivery and psychomotor developmental problems such as growth delays and maladaptive behaviors [34].

The delivery of the placenta sets an acute withdrawal of placental CRH and levels of cortisol gradually decline [33•]. The duration by which HPA function returns varies; however, best estimates suggest between 2 and 3 months [30]. A delay in return of the normal function of the HPA axis during the postpartum period may contribute to the onset or worsening of postpartum depression (PPD) [31•]. The hormonal profile observed of depressed patients, including those with PPD, has shown hypersecretion of cortisol and abnormal diurnal secretion [6]. Thus, the sustained elevated levels of cortisol are suspected to increase maternal vulnerability to PMAD during pregnancy and postpartum but are not diagnostic due to the likely complex etiologies of PMAD. Investigations focused on HPA axis function in individuals with depression have conflicting results. Some studies find hyperreactivity and others hyporeactivity of the HPA axis [33•]. Furthermore, the assessment of cortisol is time dependent, including time of sample extraction, recent exposure to stressor, and lastly, whether levels are measured during euthymic state of a woman with histories of PPD or MDD [33•]. In addition, other methods to assess HPA axis function are limited. The TSST remains the gold standard of assessment of acute stress under laboratory conditions; however, it is impractical for clinical use [28].

The Autonomic Nervous System

The key components of the ANS, the sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS), provide a coordinated network of nerve signals, neurotransmitters, and target organs to maintain homeostasis, stress response, and bodily functions [12]. In general, the actions of the sympathetic and parasympathetic divisions of the ANS work paradoxically. The ANS interplays a negative feedback loop between the SNS and PSNS to modulate homeostasis between the opposing divisions of the nervous system [37]. Exposure to chronic stress can shift the balance to a more sympathetic-predominant state as a result of parasympathetic withdrawal. The persistent diminished parasympathetic activity can deteriorate the regulatory capability to react to stress as measured by reduced HRV [24].

Pregnancy is a heightened period of stress due to physiological changes. In late pregnancy, as an adaptive response to hemodynamic changes and aortocaval compression caused by the uterus, the ANS shifts toward a sympathetic-predominant state to increase cardiac output [24]. After delivery, the non-pregnant state returns and recovery of the parasympathetic activation occurs. However, if this recovery process is not fulfilled, postpartum women are more vulnerable to external stressors and may develop psychiatric disorders [24].

Heart Rate Variability

The vagus nerve carries the largest collection of preganglionic parasympathetic fibers and plays a pivotal role to bridge the two systems of the ANS to send messages toward the sinoauricular node for normal cardiac variability [12, 37]. The conventional description of cardiac variability is through monitoring HRV, which can be used as a marker to assess vagal and ANS activity [37–40]. Increased sympathetic activity or decreased parasympathetic activity can reduce HRV; likewise, decreased sympathetic activity or increased parasympathetic activity will result in increased HRV [41•].

HRV is the variations of both instantaneous heart rate and interval between two consecutive heartbeats (the R-R interval) known as interbeat intervals [37, 41•, 42]. The respiratory sinus arrhythmia (RSA) represents a consistent state of interbeat intervals [37]. The ratio between these components is an index of sympathovagal interaction: the high frequency, reflecting phasic vagal activity, and low frequency, related to sympathetic and vagal outflow [12]. The monitoring of HRV is a non-invasive measurement and can be a diagnostic technique to correlate PPD and anxiety to changes in autonomic homeostasis [41•].

While the link between HRV and perinatal mental illness has yet to be conclusive, a myriad of research has shown an association between reductions in HRV and vagal tone (reflected by RSA) with subjects with MDD or generalized

anxiety disorder (GAD) [40, 41•, 43•, 44]. In one study, the severity of depression was found to be negatively correlated with HRV [43•]. Overall, this demonstrates lower parasympathetic activation among people with anxiety or depression. Furthermore, one study suggested the compounding effect of anxiety to depression as the deficit of HRV was greater in a subgroup of patients with comorbid anxiety [41•]. A large-scale cohort study in the Netherlands showed subjects with an anxiety disorder, whether afflicted with panic disorder, social phobia, or GAD, all had significantly lower total HRV and lower RSA when compared with healthy controls [40]. Previous research has found a link between anxiety and cardiovascular activity. An enhanced cardiovascular response to stress was found in people who frequently reported feeling anxious and worried, and these people recovered more slowly from stressful events [44]. In summary, an increased HRV is reflective of a heathy ANS response to external stressors. In contrast, a reduced HRV suggests increased sympathetic tone and vagal withdrawal: a marker of autonomic inflexibility [43•]. Dysregulation of the ANS plays an important role in stress-related mental disorders [38].

The Immune System

During pregnancy, an adaptive change in the immune system function is required to maintain a balance between protection against pathogens and tolerance to fetal development [45]. More recent research supports psychological stressors in humans as a cause of increasing circulating cytokines [45, 46]. The production of proinflammatory cytokines as a response to acute stress can initially be beneficial followed by glucocorticoids that then downregulate immune activity [33•]. However, if stress is prolonged and the effects of glucocorticoids are insufficient, the elevated levels of circulating inflammatory cytokines can lead to excessive inflammation [26, 46]. Individuals with high anxiety levels and high perceived stress had elevated levels of interleukin-1 receptor antagonist (IL-1ra). Patients with clinical depression showed elevated levels of IL-1ra and interleukin-6 (IL-6) [39]. IL-6 and IL-1B were significantly and positively associated with depressive symptomatology among women recruited during the second trimester of pregnancy [47]. Women with trauma histories were found to have elevated tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine, and IL-6 levels [46, 47].

The vagus nerve plays an important role in regulating inflammation by decreasing the production of proinflammatory cytokines and facilitating the migration of leukocytes to sites of inflammation [45, 48]. Stress results in vagal inhibition, increasing sympathetic outflow, adrenomedullary activity, and inhibiting immune cell function to control inflammation [12, 48]. Because HRV is an index of cardiac vagal regulation, HRV is inversely related to levels of inflammatory markers [48]. If regulation is reduced by an increased SNS activity in stress-related disorders, as mentioned previously, inflammation control fails and the gut barrier could be compromised.

Increasing evidence also suggests microbial dysbiosis is an important component to a proinflammatory state. One study showed that stressed mice exhibited microbial changes and increases in cytokines. The latter of which were inhibited in mice treated with antibiotics demonstrating that the microbiota is necessary for the changes in the immune system and increase in cytokines to occur [21]. Stress also induces changes in the abundance of certain taxa and impacts the community structure of the microbiota. A decrease in *Bifidobacteria* was found in stressed offspring and then another study showed prebiotics supplementation could increase *Bifidobacteria* and decrease inflammation [49•, 50]. Other studies have indicated a greater amount of proinflammatory gut bacteria and reduced levels of anti-inflammatory gut bacteria from individuals with MDD [14, 51]. Anti-inflammatory effects of bacteria, such as *Faecalibacterium*, have been associated with lower production of inflammatory cytokines with relative low proportions among MDD group [14, 52]. In comparison, Alistipes and *Enterobacteriaceae* are characterized by proinflammatory activity within the gut and increased levels of Alistipes in the MDD group [14, 51]. Lipolysaccharide (LPS), a bacterial endotoxin, when found in the bloodstream is linked to stress-induced anxiety in pregnant dams [53, 54]. LPS increases intestinal permeability and promotes the translocation of commensal bacteria [15•]. As a result, the immune system and HPA axis are activated, elevating corticosterone, elevating Th1 cytokine and TNF-α, and upregulating Toll-like receptor (TLR) activity [15•, 54]. TLRs have been found to influence autonomic regulation by decreasing parasympathetic tone (vagal inhibition, low HRV) and increasing cardiovascular risk from elevated blood pressure and heart rate [12, 55]. In addition, there is a sex difference in neuroimmunomodulation. One study found females with low HRV had 4.4 times greater levels of C-reactive protein, an acute phase reactant, than male subjects [56]. Sex differences may indicate a role for gonadotropins estrogen and progesterone that undergo significant alterations during the perinatal period [13••]. Although the exact immune response and involved biomarkers during stress are debatable, a relationship between the psychoneuroimmune system and the gut microbiota has been clearly identified.

Transgenerational PMAD, the Microbiota, and Stress Responses

The perinatal period is a critical time for both mother and child; stress can lead to adverse effects on both mother and child not only during the critical perinatal period but also over their lifespans. The maternal stress response impacts the in utero environment and influences fetal programming, a phenomenon associated with fetal development and long-term adverse effects, such as newborn behavioral abnormalities,

childhood psychiatric disorders, and non-communicable diseases later in life [35, 57–59]. A particular focus is the impact of cytokine levels to the developing fetal brain. Gur et al. found microbial dysbiosis in response to prenatal stress in rodents is associated with elevation of IL-1B, a cytokine found to block the induction of brain-derived neurotrophic factor (BDNF). BDNF supports neuronal survival and growth in utero; and the reduction of BDNF is associated with long-term alterations in behavior and microbiome in female offspring. Female offspring from stressed dams had a significant decrease in BDNF in the amygdala in adulthood, suggesting that prenatal stressor had effects in the development of adult anxiety-like behavior and cognitive changes [49•].

A transgenerational mouse model study by Walker et al. investigated the relationship between prenatal stress to elevated stress and anxiety in offspring. The administration of LPS during early pregnancy induced anxiety-like behavior and increased cytokines and corticosterone levels in maternal serum. Neonates exposed to persistent LPS in utero demonstrated increased activation of the HPA, elevated corticosterone concentration, and showed reduced maternal behaviors with their own offspring [53, 54]. The relationship between microbial communities of mother and child combined with their HPA axes and ANS responses may provide insight into the familial risk PMAD [10].

Discussion

Clinical Implications and Directions for Future Research

The perinatal period is a critical time by which multiple factors have an influence on the well-being of mother and child. As shown in Fig. 1, the relationship between the stress response and microbiota–brain axis can be pivotal to the development of anxiety and depressive symptoms during pregnancy and postpartum. Combined markers of the HPA axis, the ANS, and microbial intestinal composition could aid the development of a more effective and focused screening, prevention, and treatments.

The surveillance of PMAD can be increased by assessing ANS dysregulation by HRV. Some individuals may underreport symptoms and not fulfill the criteria for diagnosis, and yet continue to experience chronic stress that negatively impacts mother and child. In this subset

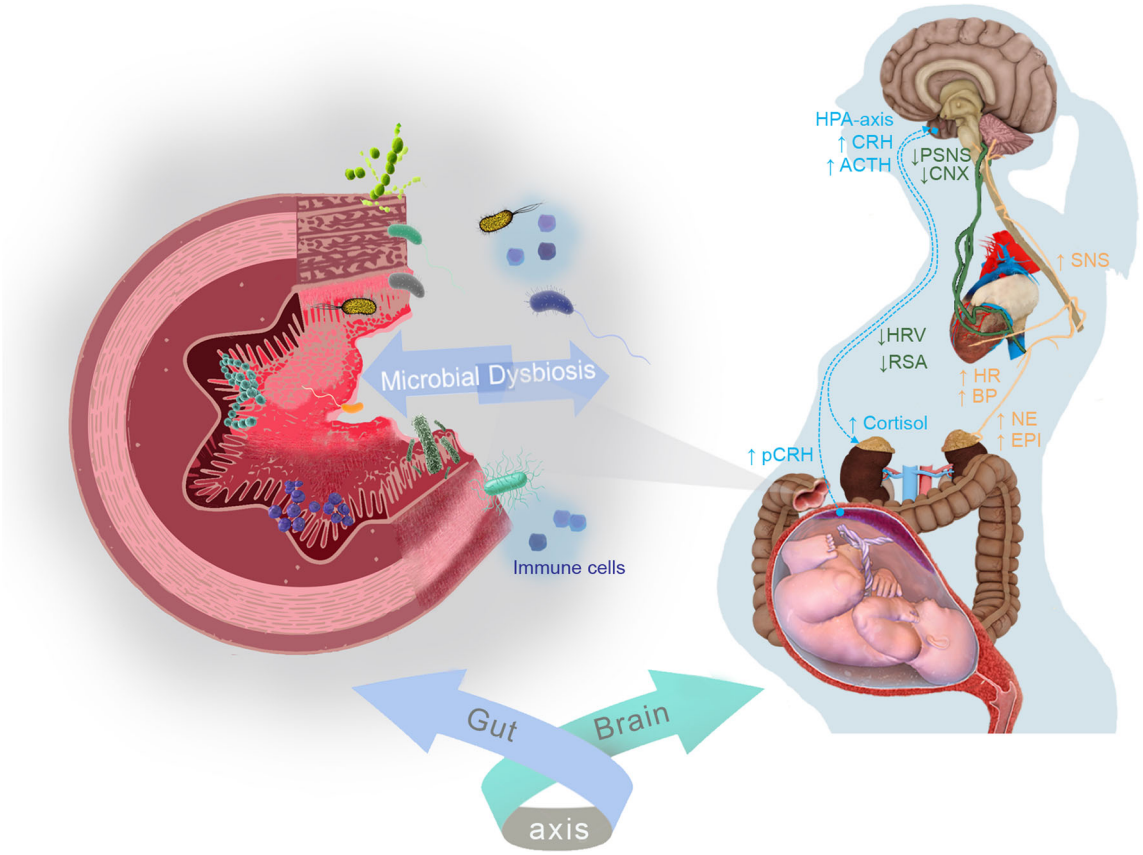

Fig. 1 Microbiota gut–brain axis in perinatal mood and anxiety disorders: the bidirectional communication between the nervous system and microbiota is an important concept to understand how stress alters the gut microbiota. The key pathways that influence the development of PMAD include the activation of the HPA axis, subdivisions of the ANS, immune response, and lastly, microbial dysbiosis that alters the composition and diversity of the intestinal microbial community

population, HRV may be an applicable screening tool for identifying PMAD. HRV is an objective, non-invasive, and low-cost predictor of parasympathetic modulation and can be used in a clinical setting. In one study, bipolar disorder participants wore T-shirts with sensors to acquire ECG and respiration signals in order to predict mood states [60]. By gathering heartbeat dynamics related to the parasympathetic activity, the study suggests monitoring HRV is a promising method to forecast mood states and optimize care of the patient. Another study used HRV to screen for MDD. They found the analysis of HRV indices had a higher screening sensitivity of 80.0% compared to the subjective patient-reported screening method [61]. It has been proposed HRV could be a biological marker utilized as a component of clinical evaluation and risk stratification of patients with mood disorders. This marker of stress reactivity has the potential to provide insight to a maladaptive response to stress during pregnancy or postpartum in people with anxiety or depression. In addition, HRV has been found to be a promising complementary method to treat PMAD. HRV biofeedback has shown to decrease anxiety symptoms of perinatal depression in hospitalized patients [62].

Although low HRV is an indicator of maternal PMAD, the shortcomings of this measurement are the next steps for intervention. The protocol for HRV data collection has varied in different studies, further indicating the need for standardization in methodology to facilitate the interpretation and comparison of results. At present, the minimum number of R-R intervals needed to have a reliable measure has not been determined nor a universal definition or algorithm to determine the ideal cutoff for each HRV measure [63, 64]. It is not clear which covariates can influence the HRV index results; however, some studies have mentioned age, smoking status, or ethnicity as factors [63–65]. Once the confounding variables are identified; a method to adjust HRV values is needed. There is no definitive guide for clinical management with reduced HRV; however, further research into perinatal microbiome can be combined to provide a solution.

Although the research and clinical application of the microbiota are at an elementary stage, microbial composition may provide a method of identification, targeted prevention strategies, and treatment recommendations for women vulnerable to experiencing PMAD. The changes of the microbial composition and diversity among individuals have been associated with MDD [14, 46, 51]. With robust sampling, analysis of microbial composition may lead to biomarkers indicative of mood disorders including PMAD. There is also emerging literature focusing on the role of probiotics in attenuating stress. An experiment providing probiotics to rats found a reduced HPA response to acute psychological stress [12]. The administration of *Lactobacillus rhamnosus*, an anti-inflammatory probiotic, reduced stress-induced corticosterone, anxiety, and depression-related behavior in mice [66]. The introduction of *Bifidobacterium longum* and *Bifidobacterium breve* in anxious mice was found to reduce anxiety, similar to a selective serotonin reuptake inhibitor [67]. In a human randomized control trial, the effects of perinatal supplementation of the probiotic *Lactobacillus rhamnosus* HN001 improved depressive anxiety symptoms compared to those in the placebo group [68].

Conclusion

The prevention and/or diagnosis of PMAD is challenging as the underlying pathophysiology is not fully understood. Maternal stress alters host homeostasis by inflammation, activation of the HPA axis, and dysbiosis of intestinal microbiota. The interrelationship of the immune system, microbiota, and neuroendocrine system serves as a potential contributor to the manifestation or exacerbation of perinatal mental illness. Furthermore, the association of maternal stress to alterations of microbiota and in utero neurodevelopment may explain the transmission of maternal mental illness to following generations. Further research is needed to further explore the interaction between the gut microbiota, the CNS, and pregnancy. Despite studies indicating an association between the gut microbiota and mood disorders (depression and/or anxiety), this relationship is poorly understood in pregnancy. Ultimately, an improved understanding of the underlying role of the microbiota gut–brain axis in perinatal mental illness will improve identification of women at risk, refine current diagnostic criteria, and implement tailored and effective treatments to mitigate PMAD and reduce the risk of poor health outcomes in mother and child.

Compliance with Ethical Standards

Conflict of Interest Nusiebeh Redpath declares no conflict of interest.

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- •• Of major importance

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