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Psychoneuroimmunology in the context of perinatal depression - Tools for improved clinical practice

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ABSTRACT

Maternal mental health spans in a temporary manner from pre-conception through the phases of pregnancy, childbirth, and the postpartum period (i.e., perinatal). The psychoneuroimmunology (PNI) field has made important contributions to the knowledge of the pathophysiology of poor perinatal mental health, but the PNI lens could be used more broadly to inform clinical practice. This review argues that PNI holds the key to several important aspects of variations in mental health for pregnant and postpartum women. This review describes existing knowledge from studies on immune activation in maternal depression during pregnancy and postpartum, and other important features such as stress reactivity, the microbiome, and its metabolites. The importance of objective measures for screening and prediction is discussed as well as the need for novel therapeutics to treat poor mental health in the perinatal period. The PNI framework could thus be further applied to inform research about the mechanisms of perinatal psychiatric morbidity, which could pave the way for future precision medicine for perinatal mental health issues.

1. Introduction

Major depressive disorders rank among the leading causes of years lived with disability worldwide (James et al., 2018). This review takes the position that maternal mental health is affected by, and can affect, the complex physiological processes associated with reproduction and pregnancy. Precision medicine is an emerging approach to health care that takes into account individual variability, and has been proposed as a way to improve mental health in the perinatal period (Peñalver Bernabé et al., 2020). One promise of precision medicine lies in the identification of predictive and distinct biomarkers that can enable identification of disease subtypes, as well as indicate treatment strategy. Psychoneuroimmunology (PNI) aims to elucidate mechanisms by which the immune system can influence behavior and vice versa. Thus, theoretical knowledge based on the PNI approach can be used as a basis of future individualized care (see Fig. 1).

Maternal mental health has been an important area of study within the PNI field over the past decade; (for early milestone contributions see (Christian, Franco, Glaser and Iams, 2009; Christian, Franco, Iams, Sheridan and Glaser, 2009; Schetter, 2011)). While the PNI field has made contributions to the knowledge of the pathophysiology of poor mental health during the perinatal period (pregnancy and postpartum), a PNI focus could be more extensively used in maternal health care. This review outlines the reasons that a broader use of the PNI perspective, applied to clinical challenges within perinatal mental health, could delineate important aspects of variations in mental health for women, see Fig. 2.

2. Biological changes in the perinatal period with potential importance to mood changes

Depressive episodes during pregnancy and in the postpartum period are common, and sometimes devastating, affecting 10 to 20% of women (Gavin et al., 2005). Antenatal depression affects between 7% and 13% of pregnant women (Bennett et al., 2004), whereas the prevalence of postpartum depression (PPD) varies between 10% and 20% (Gavin et al., 2005; O'Hara et al., 2013; Vigod et al., 2013; Woody, Ferrari, Siskind, Whiteford and Harris, 2017). It is well established that women are at greater risk of depression than men, primarily from puberty and before menopause (Faravelli, Alessandra Scarpato, Castellini and Lo Sauro, 2013). Non-pregnant women with depression have shown a more clear increase in inflammatory markers during depression than men (Birur, Amrock, Shelton and Li, 2017). Interestingly, women are also at higher risk of autoimmune disorders and often have greater symptoms in

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Fig. 1. Dr. Emma Fransson is an Assistant Professor at the Centre for Translational Microbiome Research (CTMR) at the Department for Microbiology, Tumor and Cell Biology, Karolinska Institutet, Sweden and an Associate Professor in medical psychology at Uppsala University, Sweden. After completing training as a clinical psychologist, she started as a PhD candidate at Karolinska Institutet, investigating perinatal inflammation and depressive symptoms in association with preterm birth. After her PhD, she worked at Stockholm University, Sweden, investigating the effect of post-parental divorce on children's mental wellbeing. After a few years, she combined her two current research groups to pursue her main research interest of psychobiological processes in women's perinatal health. Dr. Fransson's current research aims to investigate the importance of the microbiome in preterm birth as well as in women's mental health - along with a program focusing on biological predictors for postpartum depression.

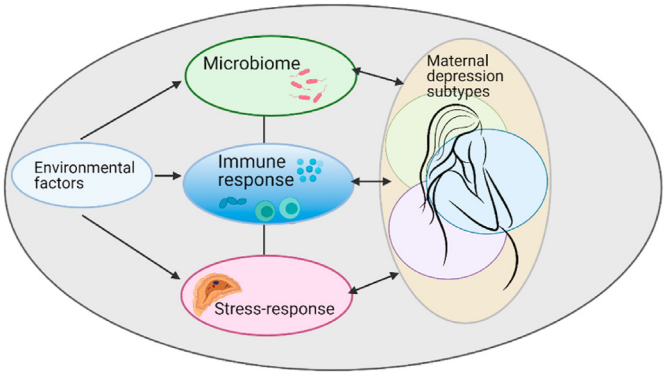

Fig. 2. The psychoneuroimmunology (PNI) approach could be used to further inform the field of perinatal mental health. PNI contributes with the knowledge that not only environmental factors, such as psychosocial circumstances, but also modifiable biological factors (the stress response, the immune response and the gut-brain-axis) have important mechanistic functions for mental health and psychiatric symptoms in pregnant and postpartum women. PNI could be used to further characterize subtypes of maternal depression.

relation to infectious challenges (Lasselin, Lekander, Axelsson and Karshikoff, 2018; Ortona et al., 2016). These differences have been related to differences in sex hormones that may explain differences between women and men in the prevalence of depression.

During pregnancy, levels of sex or gonadal hormones, such as estradiol and progesterone, increase with gestation to levels that are much higher than pre-pregnancy (Glynn, Davis, Sandman and Goldberg, 2016). These sex hormones radically decrease after delivery. In animal models, such rapid estrogen withdrawal has been linked to anxiety and depressive like behaviors and, notably, causing alterations of brain neurogenesis (Hedges et al., 2021; Zhang et al., 2016). Women with a previous history of premenstrual syndrome are shown to have increased risk of perinatal depression (Wikman et al., 2019), indicating that individual vulnerability to changes in hormonal levels might be an important factor in perinatal mood symptoms (Bloch et al., 2000; de Rezende, Garcia-Leal, Silva de Sá, Cavalli and Del-Ben, 2019).

Interestingly, allopregnanolone, a progesterone metabolite, can inhibit proinflammatory processes through modulating GABA receptors (Balan, Beattie, O'Buckley, Aurelian and Morrow, 2019), while IL-6 decreases allopregnanolone synthesis in the brain (Parks et al., 2020). While estrogen deficiency has been suggested as a risk for depressive behavior in animal models (Xu, Sheng, Tang, Lu and Ni, 2015), estrogen has also been shown to increase during acute stress in humans (Pletzer, Poppelaars, Klackl and Jonas, 2021). Notably, immune cells express estrogen receptors (Kovats, 2015), and immune cells from women produce more pro-inflammatory proteins (interferons), compared to cells from men (Berghöfer et al., 2006). Furthermore, estrogen promotes pro-inflammatory activity, such as increasing protein production of Interferon gamma (Fox, Bond and Parslow, 1991; Seillet et al., 2012). However, estrogen has also been found to suppress interferons and other pro-inflammatory products (Escribese et al., 2008). In an animal model resembling the postpartum state, estrogen treatment attenuated depressive-like behaviors (Galea, Wide and Barr, 2001), while in a study of postpartum women, higher levels of estrogen and progesterone in the postpartum period were associated with an increase in mood symptoms and increased pro-inflammatory activity (Sha et al., 2021). These examples highlight the complexity of the relationship between the immune system and estrogen and progesterone, and how the immune response may differ by changes in hormone levels, depending on other contexts (e.g., acute versus chronic stress). Individual differences in the reaction and adaptation to large biological changes during the perinatal period could be important to consider in the clinical understanding of perinatal mental health differences. In a study on both men and women from Georgia, USA, about 45% presented with a pro-inflammatory profile (Raison et al., 2013) and fewer individuals (39%) with indications of an inflammatory phenotype were identified in a study from the UK (Lynall et al., 2020). Identification of biological markers that characterize subtypes may facilitate explanatory models for the pathophysiology of poor mental health in the perinatal period and also indicate the need for altering treatment based on subtype. Of note, this review focuses on perinatal depression, but anxiety and other mood symptoms are often co-morbid with depression and may also explain some of the intra-individual variation.

3. PNI mechanisms of perinatal depression

The perinatal period is a very important time to utilize a PNI perspective that has the potential to improve our understanding of the immune system given the adaptations that occur during the perinatal period (Racicot, Kwon, Aldo, Silasi and Mor, 2014). The implantation phase is characterized by increased immune activation (Mor, Cardenas, Abrahams and Guller, 2011), followed by fetal growth where the maternal immune system adapts to the semi-allogenic fetus (Ernerudh, Berg and Mjösberg, 2011), while processes associated with the delivery (cervical ripening and contractility) are pro-inflammatory (Sennström et al., 2000). Furthermore, the postpartum period consists of three distinct phases, where the two initial stages (the initial 24 h followed by the first six weeks) are characterized by major bodily recovery and associated biological changes (Romano, Cacciatore, Giordano and La Rosa, 2010). Consequently, the entire immune system, not just the sex hormones, undergo remarkable adjustment from pregnancy to postpartum (Bränn, Edvinsson, Rostedt Punga, Sundström-Poromaa and Skalkidou, 2019).

Previous research on women with depression in the perinatal period suggest that characteristics associated with higher risk of having elevated depressive symptoms (such as smoking, history of migraines, history of premenstrual mood symptoms, previous trauma experience, nausea and symphysiolysis during pregnancy) could be attributed to both higher sensitivity to hormonal changes as well as to altered immune function (Welander et al., 2021; Wikman et al., 2019). With regard to other known risk factors for perinatal depression, such as immigrant background or subjective social status, the associations with depression could be mediated by inflammation (Scholaske, Buss, Wadhwa and Entringer,

2020; Spallek, Scholaske, Duman, Razum and Entringer, 2021). Major depression, outside of pregnancy is, for large subgroups, associated with increased pro-inflammatory activity (reviewed in (Osimo et al., 2020)). Furthermore, it has previously been shown that specific sub-types of depressive symptoms, such as anhedonia, are typically associated with an inflamed subtype of depression (Felger et al., 2020).

Studies on pregnant women point at diverse and complex links between the immune response adaptation and perinatal mood. Some studies report on increase in pro-inflammatory activity in early antenatal depression (Christian, Franco, Glaser, et al., 2009; Haeri, Baker and Ruano, 2013), we have shown that antenatal depressive symptoms associate with *lower* regulatory or anti-inflammatory markers in late pregnancy (Edvinsson et al., 2017). In another study, Osborne et al. (2019) found an increase in pro-inflammatory cytokines during the third trimester in women with higher levels of depressive symptoms. It could be hypothesized, that failure to adapt to the immune changes of pregnancy might increase the risk of, or result from, depression. It has previously been suggested that a dysregulation of cytokine production, may be a contributing factor to mood disorders in the perinatal period (reviewed in (Leff-Gelman et al., 2016; Osborne and Monk, 2013; Sherer, Posillico and Schwarz, 2017)). Some individuals may be more sensitive to inflammatory changes that need to occur in the perinatal period, resulting in increased depression. For others, depression is a result of an altered immune system in pregnancy. In line with this, Osborne et al. have argued that a shift away from an anti-inflammatory state characterized by regulatory T cells, shifting to a the more pro-inflammatory T helper 17 (Th17) profile is associated with perinatal depression (Osborne, Brar and Klein, 2019). Furthermore, data from our group and others show that women with perinatal depression differ in characteristics according to trajectories of symptoms (Denckla et al., 2017; Wikman et al., 2019). From an ongoing project aimed at characterizing biological correlates of poor mental health in the perinatal period, we aim to investigate the perinatal trajectories of depressive symptoms and their linkage with trajectories of inflammatory markers (Bränn et al., Manuscript). As shown by others (e.g. (Brewster et al., 2008)), this work reveals expected and large differences in inflammation from mid-to late pregnancy, delivery, and two months postpartum and potential diversities between depression trajectories.

In line with the large number of studies of inflammatory markers in depression in the general population, higher depressive symptoms in the postpartum period (measured around 2 months after the delivery) associate with increased pro-inflammatory activity (Bränn et al., 2018). Maternal negative affectivity, self-harm ideation and antenatal depressive symptoms have been associated with an elevated immune response to the process of delivery (Fransson, Dubicke, et al., 2011; Fransson, Papdopoulos, Sundström-Poromaa, Ramklint and Skalkidou, 2019).

Depressive symptoms during pregnancy and altering the immune adaptation during pregnancy may also result in increased risk of pregnancy complications. Indeed, the disturbance of the prenatal environment by depressive symptoms has been linked to increased risk of preterm birth (Fransson, Örtenstrand and Hjelmstedt, 2011). Notably, we and others have shown that maternal negative affect predicts increased inflammation in infants born preterm (Fransson, Dubicke, et al., 2011; Orr, James and Blackmore Prince, 2002) and maternal depressive symptoms occurring in the prenatal period could be particularly important for future child development (Fransson et al., 2020; Kallak et al., 2021).

4. Other biomarkers for perinatal mental health

The microbial content in the body, the microbiota, are both affected by and can also impact inflammation and immune responses. The term microbiota refers to the microbes; bacteria, viruses and other microorganisms in the different anatomical locations of the human body and the term microbiome refers to the collection of the microflora, together with their genomes (Marchesi et al., 2011). Overall, there is a growing awareness of the potential for microbiota to influence gut-brain communication in health and disease. Increasing evidence points towards a connection between the condition labeled dysbiosis - a shift towards more pathogenic microbes and less diverse commensal microbes (those that live symbiotically with the host) and prevalence of psychiatric conditions (Cheung et al., 2019; Jiang et al., 2015; Liu et al., 2016).

Fecal microbiota transplantation from depressed patients to microbiota-depleted rats can induce behavioral and physiological features characteristic of depression in the recipient animals (Kelly et al., 2016). From animal models and research on human subjects, we have learned about the importance of the commensal microbial species for neurodevelopment as well as for maintaining good mental health (Foster, Rinaman and Cryan, 2017; Heijtz et al., 2011). Accordingly, there are studies demonstrating an association between exposure to specific antibiotics that are known to decrease commensal bacteria in the gut, and the risk for increase in symptoms of depression and anxiety (Lurie, Yang, Haynes, Mamtani and Boursi, 2015). This study indicated that the risk of depression increased by 50% with more than five courses of penicillin. While the relationship might be confounded by the condition for which the antibiotics were prescribed, the results are in line with findings of altered microbial communities and mental health (Rogers et al., 2016).

Notably, the microbiota constitute a modifiable factor that could be a potential therapeutic target. A healthy gut microbiota contributes to an intact intestinal barrier, healthy innate immune functions controlling pathogens, and preventing overgrowth (reviewed in (Borre, Moloney, Clarke, Dinan and Cryan, 2014)). In the dysbiotic state, the risk of losing the intestinal barrier functions increases and alterations might lead to leaky gut. Leaky gut is characterized by increased bacterial components in the circulation, which activates the innate immune response and the production of pro-inflammatory cytokines. Gut dysbiosis may also reduce circulating levels of estrogen, which could further affect mood symptoms (Qi, Yun, Pang and Qiao, 2021). The microbiota are also vital to our metabolism, and are involved in several important metabolic processes necessary for our health, such as short-chain fatty acid production. In an ongoing study investigating the gut microbiota association with symptoms of stress and depression in healthy female volunteers, we show that the relative abundance (the percent composition of a microorganism relative to the total numbers of organisms) of more pathogenic species (e.g. *Escherichia coli*) are related to depressive symptoms. In addition, the increase in the aforementioned bacteria are associated with central functions that are potentially important for development of depressive symptoms (i.e. Histamine, dopamine, and gamma hydroxybutyric acid (GHB) degradation) (Bashir et al., 2021).

Postpartum depression has been investigated regarding presentations of different microbiota profiles, though studies, so far, have been small and sparse. During the course of pregnancy, one study found the intestinal mucosa and inflammation of the gut microbiota increases while diversity decreases; however, mental health symptoms were not assessed (Koren et al., 2012). An animal study found alterations in the gut microbiota linked to lower sex hormonal levels in pregnancy but also without measures of depressive behaviors (Mallott, Borries, Koenig, Amato and Lu, 2020). In a small exploratory study of women followed from pregnancy to postpartum, we report an increase in multiple microbiota related metabolites related to immune activation during the third trimester, followed by a return to baseline postpartum levels (Kimmel et al., 2021). Microbes affect key inflammatory pathways through impacts on metabolites - and microbes are impacted by the effects of psychological stress on key pathways.

Apart from immune or microbiota related biomarkers, investigations into potential biological mechanisms of mood disorders have also identified disturbances in physiological arousal systems as possible underlying factors that could also act as predictors or diagnostic tools (Patriquin and Mathew, 2017; Tafet and Nemeroff, 2016). Two primary arousal systems, the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system (ANS), may substantially influence psychological functioning, with alterations leading to significant behavioral consequences

including psychiatric symptoms. Depression as well as anxiety is often associated with dysfunction in the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system (ANS). Similar to the gonadal hormones and the immune system, the HPA axis undergoes considerable changes during pregnancy (Chrousos, Torpy and Gold, 1998). There has been a suggested attenuation of psychophysiological stress among pregnant women with advancing gestation (Entringer et al., 2010). However, individual differences in the degree of attenuation of stress responses could be an indication of vulnerability to poor mental health. This notion has been supported with reports that women with increased cortisol response to the Trier Social Stress Test (TSST) during pregnancy are more likely to have elevated postpartum depressive symptoms (Nierop, Bratsikas, Zimmermann and Ehlert, 2006).

Heart rate variability (HRV) could be used as a marker of ANS activity and measures beat-to-beat changes in heart rate, using an electrocardiogram (ECG) (Shaffer and Ginsberg, 2017). HRV is mediated primarily by the parasympathetic (i.e. the vagus) and the sympathetic nerves. Parasympathetic tone, inferred from HRV measures, have also been shown to be associated with lower pro-inflammatory activity (Lanza et al., 2006). HRV indices during and after a mild stressor, have been found to exhibit a screening sensitivity of 80% for Major Depressive Disorder compared to the subjective patient-reported screening method (Sun, Shinba, Kirimoto and Matsui, 2016). Relatively higher HRV measures have been associated with lower likelihood of future depressive symptoms in a population-based study (Jandackova, Britton, Malik and Steptoe, 2016). We have recently shown that HRV in late pregnancy is altered in association with past or current anxiety disorders, greater trait anxiety, and greater exposure to past traumatic events (Mary C. Kimmel et al., 2021).

5. PNI in predictive modeling

Pregnancy constitutes a considerable stressor that might unveil a woman's sensitivity to psychiatric morbidity. Despite screening for depressive symptoms, women with poor mental health often remain undetected and untreated (Cox, Sowa, Meltzer-Brody and Gaynes, 2016; Massoudi, Wickberg and Hwang, 2007; Wickberg, Bendix, Wetterholm and Skalkidou, 2020). A systematic review of clinical recognition, treatment and treatment response in perinatal depression shows that only about one third of women with postpartum depression are identified in clinical settings; and very few, about 6–7%, receive adequate treatment (Cox et al., 2016). Although, up to 50% of individuals with depression could experience spontaneous remission within six months (Whiteford et al., 2013); these six months can have long-standing impacts on mother, child and other family members including increasing the risk of developing chronic conditions (Fisher et al., 2019; Wikman et al., 2019; Vliegen, Casalin and Luyten, 2014). In our recent study on postpartum symptom screening in Sweden, foreign-born women, unemployed women, women on sick leave, or single women without partner support were less likely to be offered screening for postpartum depression (Bränn et al., 2021). Those groups comprise the very same groups that are at increased risk of developing postpartum mental health problems (Howard et al., 2014; Wikman et al., 2019). Therefore, novel methods for early identification of at-risk individuals are needed. Asking women is not always enough; some women fear stigmatization, the tools available may not reflect individual experiences, and health care staff bias may impact administration and assessment of results (Corrigan, 2004; Skoog, Berggren and Hallström, 2018). Objective measures of mood symptoms, such as biomarkers studied within the PNI field are, therefore, a vital part of identifying a larger portion of the women at risk of developing postpartum depression.

6. PNI mechanisms as targets for precision interventions

Recently, promising novel approaches for treating postpartum depression have been proposed, such as targeting the GABAergic signaling with brexanolone - an intravenous formulation of the progesterone metabolite, allopregnanolone, a positive allosteric modulator of GABA receptors (Meltzer-Brody and Kanes, 2020; Stewart and Vigod, 2019). However, the most common treatments, apart from psychological interventions that are the main choice for mild to moderate depression, are Selective Serotonin Reuptake Inhibitors (SSRIs) (Davidson, 2010). SSRIs are considered safe to consume during pregnancy but could have similar side effects on pregnancy and fetal development as depression itself (Edvinsson et al., 2019; Hannerfors et al., 2015; Kallak et al., 2021). Moreover, not all women and providers feel safe to use them in the perinatal period and not all symptoms are improved by SSRIs. For example, higher inflammation is associated with poor antidepressant responses in nonpregnant individuals (Haroon et al., 2018). Therefore, there is a need for new therapeutics for mood disorders, in particular for patients in the perinatal period.

Within the PNI research on perinatal mental health, there are many psychoneuroimmunological paths that might be suitable for future therapeutics, such as treatments targeting a dysbiotic microbiome, or anti-inflammatory treatment (Kapulsky, Christos, Ilagan and Kocsis, 2021; Slykerman et al., 2017). For example, in a promising randomized treatment study, Slykerman et al. (2017) showed that probiotic treatment was associated with less postpartum reports of depression and anxiety, compared with placebo. Prebiotics may also prove helpful but require randomized controlled trials (Desai et al., 2021). Considering HRV and the immune system, vagus nerve stimulation may reduce depression (Bonaz, Sinniger and Pellissier, 2017). Future treatment options might also include transplant of anti-inflammatory gut-microbiota types. The common notions of the benefits of exercise and healthy diet could also potentially be used more in clinical recommendations, based on existing evidence of how lifestyle changes could act through lowering inflammation and improving gut microbiota diversity (Bernabé et al., 2019; Jones, Sinclair and Courneya, 2003; Ljungberg, Bondza and Lethin, 2020).

Precision medicine relies on the ability to assess disease risk at an individual level, detect early preclinical conditions and initiate preventive strategies. There is opportunity in PNI to improve the foundation for application of precision medicine in perinatal mental health. To provide personalized care, the timing of symptom onset, as well as the individual immune response to biological changes during pregnancy or to psychosocial challenges, could inform treatment options.

7. Concluding remarks

Becoming a parent involves contextual, psychological, and relational changes that can make diagnosis of depression in the perinatal period difficult. Psychobiological diagnostics could facilitate identification of individuals suffering from poor perinatal mental health who might not be easily identifiable via more traditional methods. The PNI approach could contribute to knowledge needed for early targeted prevention, as biological signs might proceed other symptoms. Moreover, as screening with self-reports for mood symptoms might include bias, such measurement could be complimented with biomarker and neurophysiological assessments that would improve both diagnostics and choice of therapeutics. With more research on individual immune reactivity to the biological changes of the perinatal period, future interventions could potentially be more tailored. During the last decade, diverse biological phenotypes of depression have been explained. Thus, the PNI framework could be further applied to inform research about the mechanisms of perinatal psychiatric morbidity and poor mental health during dynamic periods where immune adaptations are needed.

Declaration of competing interest

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