Prenatal Depression, Breastfeeding, and Infant Gut Microbiota

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Depressive symptoms are common during pregnancy and are estimated to affect 7–20% of pregnant women, with higher prevalence found in those with a prior history of depression, in ethnic minorities, and those with increased exposure to stressful life events. Maternal depression often remains undiagnosed, and its symptoms can increase adverse health risks to the infant, including impaired cognitive development, behavioral problems, and higher susceptibility to physical illnesses. Accumulating research evidence supports the association between maternal physical health elements to infant gut health, including factors such as mode of delivery, medication, feeding status, and antibiotic use. However, specific maternal prenatal psychosocial factors and their effect on infant gut microbiota and immunity remains an area that is not well understood. This article reviews the literature and supplements it with new findings to show that prenatal depression alters: (i) gut microbial composition in partially and fully formula-fed infants at 3–4 months of age, and (ii) gut immunity (i.e., secretory Immunoglobulin A) in all infants independent of breastfeeding status. Understanding the implications of maternal depression on the infant gut microbiome is important to enhance both maternal and child health and to better inform disease outcomes and management.

Keywords: prenatal depression, breastfeeding, birth mode, infant, gut microbiota, gut immunity

INTRODUCTION

The World Health Organization (WHO) lists depression as the leading cause of disease burden for women of reproductive age (Davalos et al., 2012). Depression before and after birth is often accompanied by symptoms of sadness and anxiety, anhedonia, appetite loss, sleep disturbance, confusion, and mood lability (Bernard-Bonnin et al., 2004). An estimated 18.4% of women experience prenatal depression, with 12.7% having major depressive episodes, and 13% experiencing postpartum depression. Women in their reproductive years are especially at high risk for major depression, with increased risk present during pregnancy or within the first 12 months post-delivery (Figueiredo et al., 2014). When left undetected, maternal depression results in reduced mother-child quality interactions, including reduced breastfeeding, impaired response
to the infant's hunger cues, and less contingent stimulation. Prenatal depression is a significant contributor to shorter breastfeeding duration (Dias and Figueiredo, 2015).

In addition to its negative impact on maternal health, prenatal depression can have long term consequences on children's physical and mental health, and cognitive and socio-emotional development (Bernard-Bonnin et al., 2004). Depression alters the intrauterine environment, including elevation in circulating cortisol, which can negatively affect the developing fetus (Lewis et al., 2015). Various epidemiological studies suggest the association of maternal depression and the development of a compromised infant immune system susceptible to illnesses including asthma, allergy, and other atopic diseases (Smejda et al., 2019). Fetal exposure to prenatal depression predicts elevated inflammatory biomarkers at age 25. Prenatal depression can also extend its influence to the critical “window of opportunity” during the infant’s first year of life and the beginning stages of gut microbiota development when it is most sensitive to perturbation (van den Elsen et al., 2019).

Several factors have been identified as key to shaping early microbiota composition and function, including birth mode, antibiotic use, and infant nutrition (Milani et al., 2017). Next to birth mode, breastfeeding has the most critical influence in young infants. Breast milk shapes the gut microbiota composition of infants by providing nutrients for bacterial growth (Bravi et al., 2016; Moosavi et al., 2019). Infants who are partially breastfed and even those who receive small amounts of formula supplementation display significant shifts in their gut microbial composition (Forbes et al., 2018). Additionally, breastfeeding also shapes infant immune development to support oral tolerance induction and allergy prevention (van den Elsen et al., 2019).

Many studies support the importance of early-life factors, including maternal and infant factors, in establishing nascent gut microbiota that consequently contribute to infant nutrient acquisition, pathogen exclusion, immune system regulation, and other health and developmental outcomes. This brief review aims to present evidence from the literature that examines maternal prenatal depression’s relationship with infant gut microbiota and immunity, taking into account maternal prenatal diet and infant diet.

**Prenatal Depression Affects Infant Gut Microbial Composition Dependent on Breastfeeding**

To understand the link between maternal depression, breastfeeding, and infant gut microbiota, it is essential to consider the decision-making process that women undergo when choosing to breastfeed. Breastfeeding behavior has two stages (Meedya et al., 2010). First is the intention or the decision to breastfeed, which is shaped by sociodemographic, clinical, and psychosocial factors; and second is initiation, which is dependent on the intention, as well as lactation coaching, birth mode, and perinatal complications. The overwhelming majority of women make decisions on whether to breast or formula feed during the prenatal period; intention is one of the strongest predictors of breastfeeding initiation (Bogen et al., 2010). A comprehensive systematic review revealed that prenatal depression may or may not reduce breastfeeding intention (Dias and Figueiredo, 2015). It does not appear to reduce breastfeeding initiation, pointing to the success of lactation coaching. However, depression during pregnancy predicts shorter breastfeeding duration. Hence, prenatal depression may make no difference on whether a woman intends to and/or initiates breastfeeding, but it is certainly a factor in whether she continues to breastfeed. Lastly, prenatal depression appears to have a more substantial impact on breastfeeding duration than postnatal depression (Dias and Figueiredo, 2015).

Building on previous studies of maternal perinatal depression and the infant gut microbiome (Zijlmans et al., 2015), we compared whole gut microbiota community composition in infants at mean age 3.7 months according to maternal depression status in the CHILD Cohort Study (Box 1). Differences were found in Bray-Curtis measure of microbial beta-diversity between infants of mothers with and without prenatal depression (Figure 1 and Table 1; Beals, 1984). Notably, these observed gut microbial community differences were independent of breastfeeding status, and of many maternal and household factors known to influence infant gut microbiota, including breastfeeding difficulty. There were interactions in maternal mood differences according to breastfeeding status that will be discussed later. Further, infant gut microbial abundance differed according to maternal history of depression, classified as during pregnancy, in the past and never (Figure 1 and Table 2). Gut bacteria in the families of the phylum, Firmicutes families – Erysipelotrichaceae, Lachnospiraceae, and Ruminococcaceae were more abundant in infants of mothers experiencing depression during pregnancy versus infants whose mothers never had depression and those with depression in the past. Based on pairwise comparisons of abundance, only Ruminococcaceae and Lachnospiraceae showed a statistically significant difference between all three depression categories ($p < 0.01$), including enrichment in infants whose mothers had depression in the past versus those who did not. These butyrate-producing bacteria are strict anaerobes that normally become more abundant in later infancy. Many have been found to be elevated in the gut of adults with depression and of mice following fecal transplantation from adults with depression, although not uniformly so (Barandouzi et al., 2020).

Interestingly, CHILD study infants born to women with prenatal or history of depression had significantly fewer Proteobacteria in their gut microbiota, specifically the Enterobacteriaceae, than infants whose mothers never had depression (Table 2). Typically, Proteobacteria peak in abundance during early infancy — a phenomenon called the "Proteobacteria bloom," and then slowly decline after the first 3 years of life as gut microbiota start to resemble that of an adult (Shin et al., 2015). This Proteobacterial bloom plays a crucial role in infant immune mechanisms, including homeostasis and tolerance to environmental pathogens, and prepares the infant gut for colonization by strict anaerobes in later infancy. As summarized by Campos-Rodriguez et al. (2013), evidence is accumulating from several studies that maternal prenatal...
depression affects phylogenetic diversity of second trimester gut microbiota, and in turn, gut microbial colonization of offspring. More recently, Hu et al. (2019) found psychosocial stress during pregnancy, specifically anxiety, also to be associated with a less diverse microbial community in meconium (first stool) of the newborn (Hu et al., 2019). Since passage of meconium predates breastfeeding in many infants, their results point to classifications that CHILD study results were consistent with theirs, on the correlation between higher pregnancy-related anxiety with lower levels of meconium Enterobacteriaceae. Further, a small study of longitudinally collected fecal samples after vaginal birth found enrichment with some enterobacterial genera but a reduction in other enterobacteria over the first 4 months of life (Madan et al., 2016; Yang et al., 2019). Next to birth mode, breastfeeding status explained the next highest variation in community diversity (r-squared, 4.5%) in CHILD study infants at mean age 3.7 months (Table 1). Yet, independent of 15 adjusting covariates, including infant feeding status, prenatal depression ranked 4th to explain 0.5% of the variation in gut microbial diversity among all infants.

It is also important to know how prenatal depression impacts the gut microbiota of infants within feeding groups (e.g., exclusive, partial, and no breastfeeding). Similar gut microbial dysbiosis has been reported in 3–4 months old infants following maternal prenatal stress in the presence or absence of breastfeeding (Zijlmans et al., 2015). In the CHILD study, no gut microbiota compositional differences were found by maternal prenatal mood status in fully-breastfed infants at 3–4 months, in whom the major determinant of gut microbial diversity was birth mode (Table 1). In contrast, prenatal depression was associated with statistically significant changes to total microbial diversity of infants who were not exclusively breastfed (Table 1). Enrichment with Lachnospiraceae and Ruminococcaceae, and depletion of Enterobacteriaceae are characteristic of 3–4 months gut microbiota during partial or exclusive breastfeeding.
full formula-feeding when compared to exclusive breastfeeding, and independent of birth mode (Forbes et al., 2018). Prenatal depression further enhanced the abundance of Lachnospiraceae and Ruminococcaceae in CHILD study infants (Table 2). Importantly, next to cesarean birth (r² up to 9.7%), prenatal depression ranked 2nd in explaining the variation in gut microbial diversity in the partially (1.1%) and fully formula-fed (2.7%) groups (Table 1).

Shifts in the normal development of infant gut microbiota, such as the premature depletion of Proteobacteria or enrichment of butyrate-producers, increase risk for gastrointestinal and allergic diseases, and future overweight (Milani et al., 2017; Forbes et al., 2018; Korpela and de Vos, 2018; Tun et al., 2018). There is a growing appreciation of signaling pathways of the “gut-brain axis” that involve gut microbiota. Since the prenatal and postnatal periods are important phases of development for both the brain and gut, significant potential exists for maternal distress to have long-term effects on both gut microbiota and neurodevelopment (Codagnone et al., 2019). In summary, human evidence is amassing on the detrimental impact of prenatal depression on gut microbiota in offspring. Since prenatal depression results in shorter breastfeeding duration, and because breastfeeding is a strong predictor of microbiome composition, the evidence implies that prenatal depression harms the infant gut microbiome by reducing duration of breastfeeding. In this section, we also pointed to the limited research on differential impacts of maternal depression according to breastfeeding status, which presents additional risk of adverse outcomes in infants not exclusively breastfed in early life.

PRENATAL DEPRESSION AFFECTS INFANT GUT IMMUNITY INDEPENDENT OF BREASTFEEDING

The early establishment of the infant gut microbiome has a significant influence on postnatal development of the gut mucosal immune system, and early infancy is a critical window of influence for both systems (Milani et al., 2017). The innate and adaptive immune systems both develop in concert with gut microbiota, and both are required to achieve host-gut microbiota homeostasis. Secretory IgA (sIgA) is a mucosal immunoglobulin of the adaptive immune system that acts as the first line of defense against invading pathogens by coating bacteria (Corthésy, 2013). It also binds to members of the gut microbiota, promoting homeostasis by preventing overgrowth by a single species. Since infants are unable to produce sIgA in significant amounts during the early days of postnatal life, they are highly dependent on their mother’s breast milk as a source for sIgA (Maruyama et al., 2009). Suboptimal binding of Proteobacterial microbiota...
TABLE 1 | Univariable and multivariable PERMANOVA analysis of infant gut microbiota at 3–4 months in the CHILD cohort.

|                         | Univariable | Multivariablea |
|-------------------------|-------------|----------------|
|                         | Pr(F) | R2 | Pr(F) | R2 |
| All infantsd             |        |    |        |    |
| Prenatal depression     | 0.001  | 0.0057 | 0.006  | 0.0048 |
| Birth mode              | 0.001  | 0.0523 | 0.001  | 0.0597 |
| Breastfeeding status    | 0.001  | 0.0457 | 0.001  | 0.0448 |
| Exclusive breastfeeding from birth up to 3–4 months |        |    |        |    |
| Prenatal depression     | 0.706  | 0.0020 | 0.566  | 0.0031 |
| Birth mode              | 0.001  | 0.0701 | 0.001  | 0.0759 |
| Exclusive breastfeeding at 3–4 months but not in hospital after birth |        |    |        |    |
| Prenatal depression     | 0.701  | 0.0043 | 0.633  | 0.0058 |
| Birth mode              | 0.001  | 0.0756 | 0.016  | 0.0577 |
| Partial breastfeeding at 3–4 months |        |    |        |    |
| Prenatal depression     | 0.003  | 0.0133 | 0.023  | 0.0111 |
| Birth mode              | 0.001  | 0.0602 | 0.001  | 0.05801 |
| No breastfeeding at 3–4 months |        |    |        |    |
| Prenatal depression     | 0.040  | 0.0116 | 0.022  | 0.0274 |
| Birth mode              | 0.001  | 0.0510 | 0.001  | 0.0971 |

*Adjusted for maternal age, race, pre-pregnancy BMI, prenatal diet (healthy eating index/HEI), recurrent UTI, and smoking, birth mode, infant sex, antibiotics, length of hospital stay, BF difficulty medication, older siblings, dog in household, and study site.

P-value corresponds to the beta-coefficient and is for each of the variables.

R2 value is specific to each of the covariates.

Association of prenatal depression in all infants (i.e., not stratified by breastfeeding status at 3–4 months).

Bolded values are statistically significant.

to sIgA has been associated with gastrointestinal conditions such as necrotizing enterocolitis in preterm infants, and even future allergic disease (Dzidic et al., 2017; Hornef and Torow, 2020).

Gut microbiota and sIgA binding are selective, such that several members of the Firmicutes (e.g., lactobacilli, Lachnospiraceae, and Ruminococcaceae) are preferentially bound to gut sIgA (Macpherson et al., 2018). Specific gut microbiota, like the lactobacilli, and their metabolites can also promote the infant’s own production of sIgA by gut mucosal cells and increase sIgA binding to microbiota (Kukkonen et al., 2010;
the number of IgA-producing cells has real potential to affect in utero breastfed infants (see above section), risk of *Clostridium difficile* colonization and gut slgA levels in young infants have been reported (Drall et al., 2019). As such, an imbalance in infant gut microbiota from the depletion (e.g., lactobacilli or enterobacteria) or enhancement of specific microbiota (e.g., members of the Lachnospiraceae) subsequent to prenatal depression has capacity to affect slgA binding and/or production with further disruption to host-gut microbiota homeostasis. Animal experimental models have confirmed a causal association between psychological stress and adaptive gut immunity. When young mice are exposed to repeated restraint stress (stress due to immobilization), significantly lower intestinal slgA levels and number of IgA-producing cells in intestinal mucosa are observed (Campos-Rodriguez et al., 2013). The natural stress experienced by mice when they change cages or social groups has also been found to lower fecal slgA levels. Posited pathways for prenatal distress include greater transmission of glucocorticoids to the developing fetus that reduces the number of IgA-producing cells (Campos-Rodriguez et al., 2013; Lewis et al., 2015). Equally plausible are postnatal slgA changes secondary to gut microbial dysbiosis from prenatal distress. More recently, restraint stress in a murine model raised the extent of gut IgA binding of microbiota like the Lachnospiraceae; this result was replicated in fecal samples from adults with irritable bowel syndrome, a condition often aggravated by stress (Rengarajan et al., 2020).

Kang et al. (2020) published the first human report regarding the independent association between maternal depressive symptomatology during pregnancy and compromised gut immunity in offspring. This recent study which examined infant fecal slgA concentrations in relation to maternal depression trajectories, revealed that infants born to mothers in the prenatal trajectory (high depressive symptoms scores primarily during pregnancy) were twice more likely to have lower slgA concentrations than infants of mothers with low symptom scores. At 4–8 months of age, the reduction in fecal slgA concentrations among infants of mothers in the prenatal trajectory amounted to a large effect size of 0.53. Importantly, in the presence of prenatal depression, they were equally likely to be low in infants not breastfed, who fully depend on self-production of slgA, and in exclusively breastfed infants. The latter results are consistent with previous findings by Kawano and Emori (2015) in which maternal psychological states affect immune properties of breast milk. This breast milk study demonstrated that women who scored highly on measures of anxiety, depression, and anger tended to have lower slgA concentrations in their milk.

In summary, maternal depression during pregnancy can compromise offspring adaptive immunity through direct actions of cortisol on fetal development of IgA-producing cells and indirectly, through postnatal changes to infant gut microbiota and altered slgA production or binding. Consequently, lowered gut slgA concentrations or abundance of IgA-stimulating gut microbiota can impair microbe-slgA interactions, increasing the risk of *C. difficile* colonization and allergic disease. Even if prenatal depression does not alter gut microbiota in exclusively breastfed infants (see above section), *in utero* action to reduce the number of IgA-producing cells has real potential to affect IgA-gut microbiota binding in exclusively breastfed infants. Finally, women experiencing distress have lowered slgA amounts in breast milk and they are less likely to breastfeed for a longer duration.

**PRENATAL DEPRESSION INFLUENCES THE INFANT’S GUT MICROBIOME INDEPENDENT OF PRENATAL DIET**

To maintain a healthy pregnancy, adequate nutrition is needed to nourish both mother and fetus. A narrative review by Bouillé et al. (2021) confirmed that worldwide, women with depression or stress during pregnancy eat an unhealthy diet, high on fat, and low in fruits and vegetables. Aspects of the prenatal diet related to fat consumption have been associated with changes to pregnancy and infant gut microbiota (Chu et al., 2016; Mandal et al., 2016). Notably, greater self-reported fruit intake during pregnancy has been linked to enhanced neurodevelopment in the CHILD study (Bolduc et al., 2016).

In the above-mentioned CHILD study, a “healthy” prenatal diet (i.e., an HEI score of above 80) was strongly associated with gut microbial diversity in infants at 3–4 months (r² = 0.37%, p = 0.009). This univariate association remained only within non-breastfed infants, in whom prenatal diet explained a greater percentage of the variation in beta-diversity (r², 1.08%, p = 0.04). Prenatal diet associations with infant gut microbiota were lost altogether in multivariate models that included prenatal depression (Table 1). These results demonstrate that maternal depression influences the infant gut microbiome even following adjustment for prenatal diet quality. They also indicate that a healthy maternal prenatal diet is especially important to infants who are not breastfed, the benefits of which may be affected by depression during pregnancy.

**CONCLUSION**

Evidence is accumulating on the association between maternal prenatal depression and gut microbial diversity in early infancy. Characteristic of the altered gut microbial community structure and important to the infant’s adaptive immunity are disruptions in the typical Proteobacterial bloom, and enrichment with microbiota in the families *Ruminococcaceae* and *Lachnospiraceae*. The latter is seen in infants who develop overweight. We reported new evidence that prenatal depression-related differences in microbial diversity are more likely to manifest in infants with partial or absence of breastfeeding. On the other hand, prenatal depression appears to affect slgA independent of infant feeding type. Future study is needed to more fully characterize gut microbiota changes at the genus level, and to include viral and fungal, and other communities as well. This micro-level characterization also requires testing for metabolism end-products to determine the specific pathways by which maternal depression affects the infant gut microbiome/virome/mycobiome and future health.
Breastfeeding has many psychological benefits; our review suggests that breastfeeding can be protective against the impact of maternal depression on infant gut microbiota. It also emphasizes the importance of pregnancy depression screening to identify women at risk for breastfeeding cessation since type of infant feeding strongly influences gut microbial composition. The review also underscores the importance of prenatal counseling on depression and dietary intake to promote future gut health of the newborn. Finally, obtaining evidence on the detrimental impact of prenatal depression on infant gut microbiota is critical to inform strategies that identify and timely target women with depression during pregnancy, as their infants will benefit from breastfeeding coaching to prolong its duration.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Alberta Health Research Ethics Boards. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AK contributed to the conception and design of the study. HT, CR, PM, and JS organized the database. NR wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Bernard-Bonnin, A.-C., Canadian Paediatric Society, Mental Health, HT, CF, PM, and JS organized the database. NR contributed by the participants’ legal guardian/next of kin.

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ACKNOWLEDGMENTS

We thank the CHILD Cohort Study (CHILD) participant families for their dedication and commitment to advancing health research. We also thank Forbes and Azad for their contribution to the data analysis and interpretation.
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