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Gut Microbiota in Postpartum Depression: Pathogenesis and Treatment Perspectives – a review

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Abstract

Introduction and purpose: Postpartum depression (PPD) is a prevalent and serious mood disorder following childbirth, affecting approximately 10-20% of new mothers worldwide. PPD not only impacts a mother's mental health but also her relationship with her infant, her family, and the psychosocial development of the child. While numerous factors (genetic, hormonal, psychosocial, immunological) contribute to its pathogenesis, growing evidence underscores the central importance of the gut-brain axis and gut microbiota dysbiosis. This article aims to summarise current knowledge on crucial role of gut microbiota in the onset, progression and therapeutic possibilities of PPD.

Description of the state of knowledge: Gut microbes influence PPD through the gut-brain axis, impacting neuroendocrine systems, immune responses, and neurotransmitter production. In particular, alterations in gut microbiota composition such as reduced levels of short-chain

fatty acid-producing bacteria and an increased abundance of pro-inflammatory taxa have been linked to immune dysregulation, heightened stress responses, and altered neurotransmitter metabolism in PPD. Studies show that microbial dysbiosis correlate with PPD symptoms, while interventions like probiotics and dietary changes offer promising therapeutic avenues.

Summary: This review summarizes current evidence on the gut–brain axis in depression, observed gut microbiota changes in PPD, mechanistic pathways linking dysbiosis to postpartum mood disturbances, and emerging microbiota-targeted therapies, including probiotics and fecal microbiota transplantation (FMT).

Key words: Gut microbiota, Postpartum depression (PPD)

INTRODUCTION

Postpartum depression (PPD) is one of the most common complications of childbirth, occurring in roughly 10–15% of women in the first year after delivery [1]. Rates can vary with socioeconomic and medical factors – for instance, the prevalence of PPD ranges from about 10% in high-income countries to over 20% in some low- and middle-income countries [2,3]. PPD is typically characterized by persistent low mood, anxiety, irritability, sleep disturbances, and impaired mother–infant bonding [4]. If left untreated, PPD can have far-reaching consequences: it not only impairs the mother's quality of life but also negatively affects her child's emotional and cognitive development and the well-being of the family [5-7]. In severe cases, PPD can lead to maternal suicidal ideation, and indeed suicide has been reported as a leading cause of maternal death in the postpartum period [8]. These serious outcomes underscore the importance of prompt recognition and effective management of PPD.

Despite its prevalence and impact, the exact causes of PPD remain incompletely understood. The postpartum period involves dramatic physiological changes – a sudden drop in reproductive hormones (estrogen, progesterone) after childbirth, alterations in immune function, and the stress of adapting to new motherhood – all of which are thought to contribute to PPD in susceptible individuals [9,10]. However, traditional risk factors (such as hormonal fluctuations and psychosocial stressors) do not fully explain why some women develop PPD while others do not. Moreover, current treatments for PPD are limited. Standard antidepressant medications (e.g. selective serotonin reuptake inhibitors) can be effective for many women, but some mothers are reluctant to take pharmacotherapy due to concerns about infant exposure during breastfeeding and medication side effects. Psychotherapy is often preferred but may not be accessible or sufficient for moderate to severe cases [11]. Thus, there is an urgent need to explore novel pathophysiological pathways and treatment strategies for PPD [12].

One promising area of research is the role of the gut–brain axis and the gut microbiota in mood disorders. The gut microbiota – the trillions of microorganisms residing in the gastrointestinal tract – is now recognized as a key regulator of host physiology, including brain function and behavior. Through the bidirectional communication network of the gut–brain axis, gut microbes can influence central nervous system activity by releasing metabolites and neuroactive compounds, modulating immune responses, and interacting with the neuroendocrine system [13-14]. Notably, dramatic shifts in gut microbiota composition occur during pregnancy and the postpartum period, due to changes in hormones, metabolism, and diet [15]. It has been hypothesized that a gut dysbiosis might contribute to the development of PPD in vulnerable women [16]. Recent studies have found that gut microbiota disturbances are correlated with PPD. This review will examine the current evidence linking the gut microbiota with postpartum depression. We first overview the gut–brain axis in the context of depression. We next explore the mechanistic pathways by which gut dysbiosis might mediate PPD – including immune/inflammatory pathways, neuroendocrine (HPA axis) dysregulation, and microbial metabolite effects on neurotransmitters and hormones. Emerging therapeutic approaches aiming to restore a healthy gut microbiota in PPD (such as probiotics and fecal microbiota transplantation) are also reviewed. Finally, we outline key gaps in knowledge and future research directions needed to translate this burgeoning area of research into clinical application. By elucidating the role of gut microbes in PPD, we may advance toward novel interventions to improve outcomes for mothers and their children.

DESCRIPTION OF THE STATE OF KNOWLEDGE

The Gut-Brain Axis and Depression

The concept of a microbiota–gut–brain axis has transformed our understanding of how peripheral biology can influence mental health. The gut microbiota communicates with the central nervous system through multiple routes – including neural (vagal) pathways, immune signaling, and microbial metabolites that enter circulation – thereby potentially modulating mood and behavior [4]. Under normal conditions, the intestinal microbiota contributes to homeostasis by aiding metabolism and producing essential molecules. For instance, gut bacteria ferment dietary fibers to produce short-chain fatty acids (SCFAs) such as butyrate, which have neuroactive properties including promoting brain-derived neurotrophic factor (BDNF) expression and supporting hippocampal neurogenesis [17]. Gut microbes also synthesize or trigger the release of neurotransmitters and neuromodulators – examples include γ-aminobutyric acid (GABA), serotonin (5-HT), dopamine, and histamine – many of which can

affect brain function either directly or via the enteric nervous system [18]. In addition, the gut microbial signals help maintain the gut mucosal barrier and keep systemic inflammation in check [19].

Gut microbiota dysbiosis have been linked to several psychiatric conditions, most prominently major depressive disorder (MDD) [17]. Clinical studies have found that adults with depression often show altered gut microbiota profiles compared to non-depressed individuals [20]. Common findings include an increased relative abundance of pro-inflammatory taxa (such as phylum *Bacteroidetes* and *Proteobacteria*) and a decrease in beneficial butyrate-producing bacteria (such as *Faecalibacterium* in the family Ruminococcaceae) [20]. Notably, one study reported that *Faecalibacterium* abundance was negatively correlated with depression severity, suggesting a protective role of this genus in mental health [17,20]. Causal relationships are supported by animal research: transplantation of "depression-associated" microbiota from MDD patients into germ-free mice can induce depressive-like behaviors in the recipient animals [19]. Germ-free mice (raised without any microbiota) themselves exhibit a hyperactive stress response and anxiety/depression-related behaviors, alongside neurobiological abnormalities such as elevated corticosterone levels and reduced BDNF in the brain [20]. These deficits can be partially reversed by introducing a normal microbiota, highlighting the importance of microbes in regulating stress and mood physiology [21]. Furthermore, treatment with certain probiotics (live beneficial microbes) has been shown to alleviate anxiety- and depressive-like behaviors in rodent models, presumably by restoring healthy microbiota composition and function [22]. Taken together, these findings support a model in which the gut microbiota is an integral component of the pathophysiology of depression.

In the context of PPD, the gut–brain axis is of particular interest because the postpartum period involves unique biological changes that could interact with the microbiome. Pregnancy and childbirth lead to pronounced shifts in hormones (estrogen, progesterone, cortisol, oxytocin), immune activity, and metabolic processes – all factors that can influence or be influenced by gut microbes [9,10]. Conversely, the stress of childbirth and early childcare can activate neuroendocrine pathways (such as the HPA axis) that may alter gut function (e.g., changing gastrointestinal motility or permeability) and thereby affect microbial [23,24]. Thus, the postpartum period represents a convergence of potential risk factors for depression and for microbiota disruption. It is biologically plausible that an imbalance in the maternal gut microbiota could contribute to triggering or exacerbating PPD symptoms, via the mechanisms of the gut–brain axis described above. Research in this area is still in early stages, but it builds upon the broader depression literature.

Role of Gut Microbiota in PPD

Growing evidence suggests that the gut microbiota may play a contributing role in the development of postpartum depression. PPD does not arise in isolation; it presents with a constellation of alterations in immune, endocrine, and neural systems [25]. Interestingly, the gut microbiome lies at the intersection of these systems – it is both influenced by and capable of influencing immune responses, hormone levels, and neural signaling [26]. In the postpartum period, the maternal gut microbiota undergoes significant changes. During pregnancy, shifts in microbial composition occur naturally (often an increase in *Proteobacteria* and Actino*bacteria* in late pregnancy) and these changes can persist or further shift after delivery as the body transitions out of the pregnant state [16,27]. **The** postpartum gut microbiome is subject to "drastic changes after delivery," and if these changes become dysregulated or extreme, they could lead to microbiota imbalances that increase the risk of PPD [4,16]. In other words, while a certain degree of microbial change is normal postpartum, an *unhealthy* shift (for example, loss of beneficial microbes and overgrowth of opportunistic ones) might contribute to mood disturbances in susceptible mothers. Only recently have studies specifically examined the gut microbiota in women with PPD. In a pioneering study, Zhou et al. (2020) profiled the fecal microbiome of 28 patients with PPD compared to 16 healthy postpartum controls using 16S rRNA gene sequencing [19]. They found significant differences in the diversity and composition of the gut microbiota between the PPD group and controls [19]. Notably, certain bacterial taxa known to have beneficial roles were markedly reduced in PPD patients [19]. This provides direct clinical evidence linking gut dysbiosis with PPD. Meanwhile, animal model research offers complementary support. For instance, Zhang et al. reviewed several rodent models of PPD (such as high-fat diet–induced PPD in mice, chronic stress–induced PPD in mice, and a gestational diabetes–associated PPD model in rats) and observed that each model exhibited distinct alterations in gut microbiota composition concomitant with depressive-like behaviors [4]. While the specific bacteria involved varied by model, the common theme was that the microbiome was perturbed in these PPD analogs, strengthening the case that microbiota changes are linked to the PPD phenotype.

Moreover, there are hints that manipulating the gut microbiome might influence PPD outcomes. An intriguing randomized controlled trial by Slykerman et al. (2017) found that targeted probiotic supplementation in the perinatal period reduced postpartum depression and anxiety scores [28]. Although data on therapeutic interventions are discussed later, this finding already implies that the gut microbiota is not just a passive correlate but may have a functional role in PPD – since improving the microbiota (via probiotics) appeared to improve mental health

outcomes. Altogether, the available evidence – though limited in number of studies – consistently points toward an association between gut microbiota disturbances and postpartum depression. In the next section, we delve into what specific microbiotal changes have been observed in PPD, which provides insight into what a "dysbiotic" postpartum microbiome looks like in this condition.

Microbiota Composition Changes in PPD

Several characteristic gut microbiota alterations have been identified in women suffering from postpartum depression. The clearest data come from the human study by Zhou et al., which provides a snapshot of the PPD-associated microbiome. In that study, **PPD patients showed a lower abundance of the phylum Firmicutes and a higher relative abundance of Bacteroidetes and Actinobacteria** in their gut microbiota, compared to healthy postpartum women [19]. Firmicutes and Bacteroidetes are the two dominant bacterial phyla in the normal human gut; the balance between them (often measured as the Firmicutes/Bacteroidetes ratio) is an important indicator of microbiota structure. This balance was shifted in PPD. Specifically, the proportion of Firmicutes was significantly decreased in PPD (around 75% of sequences, vs. ~89% in controls), whereas Bacteroidetes (and to some extent Actinobacteria) were correspondingly increased [19]. One minor phylum, Patescibacteria, was detected only in the PPD group (absent in controls), though at very low levels [29,30]. These findings suggest a broad taxonomic shift in the PPD microbiome toward a state with fewer Firmicutes (many of which are beneficial fermenters) and more of other groups.

At finer taxonomic resolution, PPD is associated with reductions in several health-promoting gut bacteria. Table 1 summarizes key microbiota differences identified in PPD patients versus healthy controls [4,19]:

Taxa Decreased in PPD	Taxa Increased in PPD
Faecalibacterium (genus; a butyrate-producer)	*Bacteroidetes* (phylum)
Phascolarctobacterium (genus; produces SCFAs)	*Actinobacteria* (phylum)
Butyricicoccus (genus; butyrate-producer)	*Enterobacteriaceae* (family; Gram-negative)
Lachnospiraceae (family; includes butyrate-producers)	*Proteobacteria* (phylum)
Megasphaera (genus; lactic acid bacterium)	*Patescibacteria* (phylum)** † **

Table 1. Key microbiota differences identified in PPD. Notes: SCFAs = short-chain fatty acids. †Patescibacteria were found only in PPD samples at low levels

From Table 1, a notable pattern emerges: many of the taxa that decrease in PPD are ones known to produce SCFAs (like butyrate) and support gut health, whereas taxa that increase include groups with potential pro-inflammatory effects. For example, *Faecalibacterium* is one of the most abundant genera in a healthy gut and produces butyrate, a fatty acid that nourishes the gut lining and has anti-inflammatory properties. Zhou et al. reported that *Faecalibacterium* was the single most dominant genus in healthy postpartum women (~20% of the gut community on average), but its relative abundance dropped by over half in women with PPD (~9%) [19].
This decrease was statistically significant ($p = 0.003$) [19]. Similarly, *Phascolarctobacterium* and *Butyricicoccus* – both of which are genera in the Firmicutes phylum involved in fermentation and SCFA production – were significantly less abundant in PPD fecal samples (each with $p < 0.05$) [19]. On the other hand, the family *Enterobacteriaceae* (part of Proteobacteria, including *Escherichia* and other Gram-negative rods) was found at higher levels in PPD patients [19]. Members of *Enterobacteriaceae* can be opportunistic pathogens and are known to produce endotoxin (lipopolysaccharide, LPS), which can trigger inflammation. An increase in *Enterobacteriaceae* in PPD could thus indicate a more inflammatory gut microbiome.

Mechanisms Linking Dysbiosis to PPD

Gut microbes and their metabolites can affect systemic physiology in ways that ultimately influence brain function and mood. Gut dysbiosis in the postpartum period – characterized by a loss of beneficial microbes and overgrowth of pro-inflammatory species – can trigger a cascade of harmful effects. One consequence is mucosal barrier dysfunction in the gut: a less healthy microbiome may lead to a "leaky" intestinal lining. This allows bacterial products such as lipopolysaccharide (LPS) to translocate into the bloodstream, provoking systemic inflammation (elevated cytokines like IL-6, TNF-α, CRP) [31]. In turn, pro-inflammatory signals and LPS can penetrate the blood–brain barrier, activating immune cells in the brain (microglia and astrocytes) and causing neuroinflammation [17]. Neuroinflammation is thought to suppress neuronal plasticity and has been linked to depressive symptoms [31,32]. Concurrently, gut dysbiosis may lead to reduced production of beneficial metabolites such as **butyrate** (due to loss of butyrate-producing bacteria). Butyrate normally upregulates BDNF and supports hippocampal neurogenesis; its deficiency could result in **reduced neurogenesis** and impaired neural resilience to stress [33]. Gut dysbiosis can also exacerbate an **abnormal stress (HPA axis) response**: for example, germ-free animals with dysregulated microbiota show exaggerated HPA activation to stress [17]. All these factors – elevated

inflammation, neuroinflammation, diminished neurogenesis, and HPA axis hyperactivity – interact to contribute to depressive disorder. **Probiotics** (beneficial microbes) may counteract these processes by restoring the gut barrier, reducing systemic inflammation, producing metabolites like butyrate, and even directly signaling to the nervous [34].

1. Immune Activation and Inflammation: One of the most studied links between gut dysbiosis and depression is inflammation. Both clinical and preclinical evidence indicate that a chronic pro-inflammatory state can precipitate depressive symptoms [4,35]. In PPD, there is some evidence of immune system involvement – for instance, elevated levels of pro-inflammatory cytokines (IL-6, TNF-α) have been observed in depressed postpartum women in certain studies, similar to observations in non-postpartum depression [35]. Gut microbes are strong modulators of immune responses; a healthy microbiota promotes immune tolerance, whereas dysbiosis can promote inflammation. As described above, PPD microbiomes tend to have an overrepresentation of Gram-negative bacteria like Enterobacteriaceae, which shed LPS from their outer membranes. LPS is a potent endotoxin that, when it enters circulation, triggers the release of inflammatory cytokines. Normally, the intestinal barrier limits LPS translocation, but dysbiosis and stress can increase intestinal permeability (often termed "leaky gut") [17]. The result is higher circulating levels of microbial components that drive systemic inflammation. These inflammatory signals can cross into the brain or stimulate the vagus nerve, leading to activation of microglia (the brain's immune cells) and the production of neuroinflammatory mediators that alter neurotransmitter systems and neural plasticity [31-33]. In depression, elevated levels of inflammatory markers (e.g. IL-6, C-reactive protein) are commonly reported, and similar mechanisms may be at play in PPD. Thus, a gut microbiota skewed toward pro-inflammatory bacteria could promote a persistent inflammatory milieu postpartum, which in turn contributes to depressive mood and fatigue. This cytokine hypothesis of depression is supported by the observation that administering inflammatory cytokines can induce depressive symptoms, and anti-inflammatory treatments can alleviate them in some cases [4].

2. Neuroendocrine (HPA Axis) Dysregulation: The HPA axis, which controls the body's stress hormone (cortisol) response, undergoes significant changes during late pregnancy and postpartum. After delivery, cortisol levels – which are elevated in pregnancy – drop, but dysregulation in this system has been implicated in PPD risk (some women with PPD show an abnormal cortisol awakening response or blunted feedback inhibition) [36,37]. Gut microbiota can influence the HPA axis. Experiments in germ-free mice have demonstrated that absence of a normal microbiota leads to exaggerated HPA axis activity in response to stress (with elevated

corticosterone levels), an effect that can be reversed by colonizing the mice with a healthy microbiota or even with specific probiotic strains [4]. The presence of certain beneficial bacteria appears to regulate the set-point of HPA reactivity, possibly by impacting central glucocorticoid receptor expression or via microbial metabolites acting as signaling molecules. In postpartum women, hormonal fluctuations (the sudden withdrawal of estrogen and progesterone) can themselves activate stress pathways. There is evidence that women who develop PPD are biologically more sensitive to hormone withdrawal and show altered HPA axis responses postpartum [36,37]. Gut dysbiosis could exacerbate this by contributing to a hyper-activated HPA axis. Conversely, a balanced microbiome might help normalize cortisol dynamics. Indeed, a human study found that a probiotic (*Lactobacillus casei* strain Shirota) was able to dampen the rise of salivary cortisol in volunteers subjected to a stressful task [17]. This suggests that modifying the gut flora can directly affect stress hormone output. Thus, in PPD, an unhealthy microbiome might perpetuate stress-hormone imbalances that fuel anxiety and depression symptoms.

Another neuroendocrine aspect specific to PPD is the role of reproductive hormones. The postpartum drop in estrogen has been long suspected as a trigger for PPD (often referred to as the "estrogen withdrawal" hypothesis) [9,10]. How might gut microbes figure into this? One way is through the estrogen-gut microbiome axis. Certain gut bacteria produce an enzyme called β-glucuronidase which can deconjugate estrogens in the intestine, influencing the recirculation and excretion of estrogen in the body [38]. A dysbiotic microbiome might alter the levels of such enzymes, thereby affecting systemic estrogen levels.

3. Neurotransmitter and Neurotrophin Modulation: The gut microbiota can influence the availability of neurotransmitters and neurotrophic factors that are crucial for mood regulation. One pathway is via tryptophan metabolism. Tryptophan is an amino acid precursor to serotonin. In depression, a well-known phenomenon is the shift of tryptophan metabolism away from serotonin production toward the kynurenine pathway, leading to the accumulation of neurotoxic metabolites like quinolinic acid that can contribute to depressive symptoms [39]. Gut bacteria can affect this balance. Certain gut microbes consume tryptophan or convert it into other metabolites (such as indoles, which can have neuromodulatory effects via the aryl hydrocarbon receptor) [40]. Dysbiosis might reduce the pool of tryptophan available for serotonin synthesis or increase the production of metabolites that divert tryptophan from the serotonin pathway [17]. Additionally, germ-free mice have been shown to have lower levels of serotonin in the brain and altered expression of serotonin receptors [41]. In PPD, while direct data are scarce, it's conceivable that gut-driven changes in serotonin could occur. Many women with PPD

respond to SSRIs (which boost serotonin signaling), highlighting serotonin's importance; a microbiome that fails to support normal serotonin metabolism could therefore contribute to low mood.

Besides neurotransmitters, **neurotrophic factors** like BDNF are key to brain health and mood regulation. Depression is associated with reduced BDNF levels and impaired hippocampal neurogenesis [42]. Gut microbes, particularly SCFA producers, can influence BDNF. Butyrate produced by gut bacteria crosses into circulation and can cross the blood–brain barrier, where it has been shown to increase BDNF expression in the brain and promote the growth of new neurons [17]. When dysbiosis leads to a reduction in butyrate-producing bacteria (as seen in PPD with lower *Faecalibacterium* and *Butyricicoccus*), it may result in lower butyrate levels and consequently lower BDNF activity [17]. This could impair neurogenesis and synaptic plasticity, biological processes that are important for recovery from depression. Conversely, reintroducing butyrate-producing microbes or giving butyrate itself has antidepressant-like effects in animal models [43]. Therefore, the loss of beneficial microbes in PPD could directly translate into biochemical changes in the brain that foster a depressive state.

4. Other Contributing Factors: There are additional layers of interaction worth mentioning. The gut microbiome can produce vitamins (like B vitamins) and other cofactors that are important for neural function – dysbiosis could lead to deficiencies that affect mood. Gut bacteria also interact with the host's stress response via the vagus nerve; some studies suggest that certain probiotic strains can alter brain activity in emotion-processing regions even in human subjects, likely through vagal signaling rather than systemic effects [34]. In postpartum mothers, social and psychological stress is high, and a healthy microbiome might mitigate the physiological impact of stress, whereas a dysbiotic one might amplify it. Epigenetic factors have also been noted in PPD (e.g. DNA methylation changes) [4], and intriguingly, microbial metabolites like butyrate are known histone deacetylase inhibitors that can influence gene expression in the host. This raises the hypothesis that gut microbes could even shape the epigenetic landscape associated with PPD, although this remains to be researched.

Probiotic and Microbiota-Targeted Therapies

Given the emerging link between gut microbiota and PPD, there is growing interest in therapies that target the microbiome as a means to prevent or treat postpartum depression. These **microbiota-targeted interventions** include probiotics, prebiotics, dietary modulation, and even fecal microbiota transplantation. The appeal of such approaches is that they could correct the underlying dysbiosis and thereby address one root cause of PPD, potentially with

fewer side effects than systemic medications. Here, we review the current evidence and prospects for microbiota-based therapies in PPD.

Probiotics (Psychobiotics): Probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit to the host. When the benefit is related to mental health, the term "psychobiotic" has been used [34]. A number of clinical trials outside the postpartum setting have tested probiotics for mood and anxiety disorders. For example, administration of combinations of *Lactobacillus* and *Bifidobacterium* strains to otherwise healthy adults under stress improved their self-reported mental health and reduced stress hormone levels [44]. In patients with irritable bowel syndrome (who often have comorbid anxiety/depression), a probiotic (*Bifidobacterium longum* NCC3001) significantly reduced depression scores compared to placebo [44,45]. Another trial in adults with high depressive symptoms found that a fermented milk product containing *Lactobacillus casei* Shirota (LcS) improved mood and was associated with changes in gut microbiota (notably, an increase in Bifidobacteria) [46]. These studies, summarized by Suda and Matsuda (2022), demonstrate the potential of probiotics to positively influence mental health by modulating the gut–brain axis [44-46]. The mechanisms are thought to involve reducing inflammation, strengthening the gut barrier, producing neuroactive metabolites, and even direct neural communication via the vagus nerve [47].

In the specific context of PPD, direct evidence for probiotics is still limited but promising. The randomized controlled trial by Slykerman et al. (2017) is particularly noteworthy: in this study, perinatal women were given a probiotic supplement (containing *Lactobacillus hamnosus* HN001) or placebo, and the outcomes showed that the probiotic group had lower prevalence of postpartum anxiety and depression. This suggests that manipulating the maternal microbiome around the time of childbirth can have beneficial effects on mental health. Zhou et al. highlight this trial as supportive of a causative role of the microbiome in PPD and a potential therapeutic avenue. Beyond this, anecdotal or smaller studies have reported that probiotics may improve postpartum mood and bowel habits, although more rigorous research is needed. It is important to note which strains might be effective – current data in depression point to strains of *Lactobacillus* (such as *L. acidophilus*, *L. casei*) and *Bifidobacterium* (such as *B. lactis*, *B. longum*) as candidates [34,44,45]. These bacteria are common commensals often reduced in dysbiosis. By reintroducing them, probiotics could restore metabolic functions like SCFA production and reduce pathogenic bacteria through competition.

From a safety perspective, probiotics are generally considered safe for use in postpartum women, including those who are breastfeeding, since the strains used are typically normal

inhabitants of the gut and have no systemic absorption. In fact, improving the mother's gut health may also benefit the infant's microbiome (since maternal microbes transfer to the baby through breastfeeding and contact). Clinicians have begun to consider probiotic supplementation as an *adjunct* to standard PPD care, although it is not yet a mainstream recommendation. Ongoing clinical trials are examining whether multi-strain probiotics can reduce depressive symptoms in postpartum women with mild-to-moderate PPD, with results expected to further guide recommendations.

Prebiotics and Diet: Prebiotics are nondigestible food components (like certain fibers or oligosaccharides) that preferentially stimulate the growth of beneficial gut bacteria. A diet rich in plant fiber, for instance, promotes SCFA-producing commensals (e.g., *Faecalibacterium* and *Roseburia*). It stands to reason that dietary interventions could shape the postpartum microbiome in a favorable way. Although no specific trials on diet for PPD microbiota exist yet, general dietary studies show that a high-fiber, diverse diet is associated with a more diverse gut microbiome and better mental health outcomes, whereas a Western diet high in fat and sugar can induce dysbiosis and inflammation [48]. In fact, one of the animal models of PPD discussed earlier was a high-fat diet–induced PPD model, which demonstrated that an obesogenic diet in mice not only led to depressive-like behavior postpartum but also caused significant gut microbiota shifts (increases in *Actinobacteria* and *Proteobacteria* decreases in *Bacteroidetes*) [4]. This model underlines how diet and microbiota together can affect mood. Therefore, nutritional counseling for postpartum women – encouraging foods that support a healthy microbiome (fibers, fermented foods, omega-3 fatty acids) – could be a complementary strategy to bolster mood and reduce PPD risk. Though evidence is indirect, it aligns with broader maternal health guidelines.

Fecal Microbiota Transplantation (FMT): FMT is a procedure where stool from a healthy donor is transplanted into a patient's gastrointestinal tract to restore a balanced microbiome. FMT is well-established for treating *Clostridioides difficile* infection, and it's being explored for other conditions including inflammatory bowel disease and metabolic syndrome. Its application in psychiatric disorders is still experimental. However, preclinical studies provide a rationale: transferring microbiota from a healthy animal to a depressed animal can alleviate depressive behaviors [49]. Suda and Matsuda (2022) note that FMT from healthy donors improved both gut microbiota composition and depressive symptoms in rodent and primate models of depression [4,49]. In humans, a few case reports have suggested mood improvements in depressed patients after FMT given for other indications, and one small open-label trial found improvement in depression ratings following FMT in patients with irritable bowel syndrome.

For PPD specifically, there are not yet reports of FMT use. Nevertheless, one could imagine in the future, FMT or targeted microbiota therapy could be considered for severe PPD that is resistant to conventional treatment, especially if a clear gut dysbiosis is identified. Of course, FMT carries more risk (as it involves transfer of live microbes comprehensively) and unknowns, so it would likely be a last-resort or research-level intervention. More feasible in the near term is the development of **microbiome-derived therapies**– for example, using specific microbial metabolites (postbiotics) or designing *consortia* of beneficial bacteria as a treatment. One could isolate a mix of SCFA producers and administer them as a probiotic cocktail to replicate the effect of a fecal transplant in a more controlled manner.

Future Directions and Research Gaps

The study of gut microbiota in postpartum depression is a nascent field, and many questions remain to be answered. Identifying dysbiosis in PPD is just the first step; the next crucial step is demonstrating causation and clinical utility. Here we outline some key **future directions and research gaps:**

Longitudinal Cohort Studies: Most data so far are cross-sectional (comparing PPD patients to controls at one point in time). Longitudinal studies following women through pregnancy into the postpartum period are needed to track how the microbiome changes and whether those changes predict who will develop PPD. For example, enrolling pregnant women and sampling their gut microbiota in the third trimester, then again at 1 month, 3 months, 6 months postpartum while monitoring mood symptoms, could reveal microbial patterns that precede PPD onset. This would help answer if dysbiosis is a cause or a consequence of PPD. It could also identify microbial or metabolic **biomarkers** for early detection of PPD risk [4]. Zhang et al. suggested that specific changes in gut microbiota might serve as biomarkers of PPD risk or prognosis in the future, but robust longitudinal evidence is needed to validate such biomarkers.

Understanding Hormone-Microbiome Interaction: PPD is unique because of the dramatic endocrine changes postpartum. More research is needed on how exactly hormones like estrogen, progesterone, and prolactin interact with gut bacteria. For instance, do certain microbial shifts consistently follow the postpartum estrogen crash? Could the microbiome be manipulated to modulate hormone levels (e.g., increasing bacteria that produce estrogen-related enzymes to smooth out withdrawal)? Animal studies with hormone supplementation or depletion, combined with microbiome analysis, could shed light here. Also, research on **psychobiotics and breastfeeding** is important – since anything the mother ingests (including probiotics) could affect breast milk contents and infant microbiome. Studying the

triad of maternal microbiome, breast milk composition (some microbes and metabolites can transfer to milk), and infant outcomes would be valuable, especially because improving maternal mood also benefits the child's development [7,8].

Personalized Medicine Approach: The inter-individual variability in microbiomes means that a one-size-fits-all probiotic may not work for everyone. Future research might use each woman's baseline microbiome data to tailor interventions. For example, if a woman's microbiota sequencing shows she is low in a particular beneficial genus, a targeted probiotic containing that genus (or a prebiotic known to feed it) could be chosen. Machine learning models could be developed that combine microbiome, genomic, and clinical data to predict PPD risk and the best intervention. This level of personalized medicine is a way off, but the groundwork can be laid by accumulating large datasets of microbiome profiles linked to treatment outcomes in PPD.

Ensuring Diversity in Research: Much of the microbiome research to date has been in specific populations (for example, Zhou et al.'s study was in Chinese women). Microbiota compositions differ around the world due to diet, genetics, and environment. Future studies should include diverse populations to see if the same PPD-related dysbiosis patterns hold. They should also consider factors like mode of delivery (C-section vs vaginal can affect initial microbiome), antibiotic use around delivery, and diet, as these can confound results.

CONCLUSIONS

Postpartum depression is a complex disorder at the intersection of psychological, hormonal, and biological factors. This review has highlighted that the gut microbiota – long appreciated for its roles in digestion and immunity – also appears to be an important piece of the PPD puzzle. Women with PPD demonstrate alterations in their gut microbiome, notably a reduction in beneficial, metabolically important microbes and an increase in bacteria that could drive inflammation and other adverse effects. These microbial shifts may contribute to the development of depression after childbirth by promoting systemic inflammation, perturbing stress-response systems, altering neurotransmitter availability, and even modulating the drastic hormonal changes that occur postpartum. In essence, gut dysbiosis can create a biochemical environment that is conducive to depression, and in postpartum women already facing immense physiological stressors, this might tip the balance toward illness.

Understanding the role of gut microbes in PPD opens up novel avenues for intervention. Microbiota-targeted therapies, such as probiotic supplementation or dietary

adjustments, offer a promising complement to existing treatments. They come with the attractive possibility of improving not only mental health outcomes but also overall gastrointestinal and immune health, which is beneficial for postpartum women and their babies. Early clinical evidence indicates that such approaches are worth pursuing, though more rigorous trials are needed. Importantly, microbiome interventions are generally safe and well-tolerated – a critical consideration for new mothers.

That said, the integration of microbiome science into PPD care is still in its infancy. In the coming years, research will clarify whether gut dysbiosis is a consistent marker or mediator of PPD across different populations, and whether fixing the dysbiosis can reliably improve outcomes. If the answers are affirmative, we could see a paradigm shift in how we manage postpartum mental health – moving toward a more holistic model that includes the gut–brain axis as a target for diagnosis, prevention, and therapy.

In conclusion, the current evidence, derived from both human studies and animal models, supports the notion that the gut microbiota is an influential player in the pathogenesis of postpartum depression. PPD exemplifies how intricately the mind and body are connected – the brain, the endocrine system, the immune system, and the gut microbiome all communicate in this condition. By advancing our understanding of these connections, we stand to improve the lives of many mothers. Future research and clinical innovation grounded in the gut–brain axis perspective hold the potential to reduce the burden of PPD, fostering healthier mothers, infants, and families.

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