REVIEW ARTICLE

Nurturing the Mind from Within: Exploring the Role of Gut–Microbiota–Brain Axis in Postpartum Depression

Srinidhi Rai[1], Priya Alva[2], Sriram Naresh[3]

Received on: 02 April 2023; *Accepted on:* 05 March 2024; *Published on:* 29 April 2024

Abstract

The pathophysiology of postpartum depression (PPD) mostly involves disruptions of the immunological system, gut microbiota, neurotransmitters, hormone production, and neuroendocrine regulation. This review explores the reciprocal exchange of signals along the gut–brain axis, with a particular emphasis on the role that gut microorganisms play in neurotransmitter synthesis, precursor generation, and the secretion of vital metabolites, thus unravelling the complex interactions of the microbiota–gut–brain axis to pave a better understanding of microbiota-mediated pathogenesis, avenues for therapeutic possibilities leveraging microbiota–gut–brain axis modulations.

Keywords: Postpartum depression, Psychology, Screening.

Journal of South Asian Federation of Obstetrics and Gynaecology (2024): 10.5005/jp-journals-10006-2411

Introduction

One of the happiest moments in a woman's life might be welcoming a new born home, it is not always a happy experience for many. The baby blues, also known as postpartum blues, affect most new mothers, are essentially a mild, transient form of depression that ends when hormone levels stabilize. Approximately, 85% of new mothers will encounter the postpartum blues. It is possible to have moments of happiness followed by overwhelming and crying the next. Postpartum depression (PPD) is defined as periods of depression that starts within 6 months of birth as defined by "The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5)."[1] Global estimates place the prevalence of PPD between 10 and 30%. About 22% of mothers in India experience PPD.[2] Postpartum depression or PPD, affects about 13% of women who have the pregnancy blues.[3] Perinatal anxiety, mental health issues, life stress, social isolation, low self-esteem, low socioeconomic position, history of physical abuse, postpartum medical complications, and a family history of PPD are among the factors that are associated with PPD. Furthermore, PPD causes family conflicts in addition to being a significant financial and medical burden on society and its members. Child of a mother with PPD may suffer with decreased feeding, lack of socializing skills and emotional bonding. The PPD-related suicide is known to be the second most common cause of death in postpartum women.[4] A meta-analysis has revealed that 8.4% of men had PPD, demonstrating that the disorder is not just a problem for women.[5] The postpartum period is a critical phase marked by significant hormonal fluctuations and psychosocial stressors, making women vulnerable to mental health disorders, including PPD. Since pregnant and postpartum women are highly sensitive for medications, there is still a dearth of effective and safe therapeutic options. The gut microbiome has been shown to have an impact on mental health outcomes in recent study, providing new insights into and strategies for treating PPD. The goal of this review is to compile the state-of-knowledge regarding the gut–brain axis and its connection to PPD.

[1–3]Department of Biochemistry, K S Hegde Medical Academy, Nitte (Deemed to be University), Mangaluru, Karnataka, India

Corresponding Author: Srinidhi Rai, Department of Biochemistry, K S Hegde Medical Academy, Nitte (Deemed to be University), Mangaluru, Karnataka, India, Phone: +91 9591247186, e-mail: srinidhirai@nitte.edu.in

How to cite this article: Rai S, Alva P, Naresh S. Nurturing the Mind from Within: Exploring the Role of Gut–Microbiota–Brain Axis in Postpartum Depression. J South Asian Feder Obst Gynae 2024;16(3):285–288.

Source of support: Nil

Conflict of interest: None

The Microbiota–Gut–Brain Axis: A Brief Overview

In order to better understand human biology, the human genome project was completed in 2003 which decoded the human genome. The "second human genome project" was recently conceived to explore the importance of trillions of gut microbial species. The human intestine harbors 500–1000 distinct bacterial species and 100 trillion (10^{14}) bacteria that coexist peacefully with the human body.[6] More than 75% of the intestinal bacteria in the human gut belong to the two most common phyla, Firmicutes and Bacteroidetes.[7] There is growing evidence that gut microbiota may impact behavior and brain activity through neuronal and humoral pathways and may have practical uses in the management of neuropsychiatric disorders.[8–11] Through the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, the brain regulates the gut function. Gut influences the central nervous system (CNS) functions via microbiota derived products, neuroactive compounds, and various gut hormones that travel through the enteric nervous system, vagus nerve, circulatory system, or immune system to reach the brain. Indeed, new research has linked the vagus nerve to mood and behavior by affecting CNS reward neurons.[12]

Healthy Gut Microbiome

Short-chain fatty acids (SCFA), catecholamines, histamines, gamma-aminobutyric acid (GABA), and other microbial neuromolecules are produced by microbial metabolism and may have a direct or indirect impact on brain metabolism and function.[13,14] Gut microbiota influences the synthesis of neurotransmitters and its precursors such as GABA, serotonin, and tryptophan. Secretion of metabolites like neuropeptides, brain derived neurotrophic factor and SCFA is also regulated by gut microbes.[15,16]

Alterations in Gut Microbiota Composition and Associated Metabolic Changes in PPD

Molecules connected to pathophysiological pathways in PPD are closely linked to gut microorganisms. Studies on PPD-affected humans and rats have shown alterations in their gut microbiota (Table 1).[17,18] These modifications to the gut microbiota in the depressed individuals offer concrete proof of the connection between gut microbiota and PPD, indicating that gut microbiota changes may be a significant factor in the development of PPD in both animal models and individuals.

Mechanistic Insights into the Involvement of Gut Microbiota in the Pathogenesis of Postpartum Depression (PPD)

Estrogen, Progesterone, and their derivatives

Postpartum depression incidence is influenced by the significant changes in ovarian hormones that occur during pregnancy and the postpartum phase.[19] Levels of estrogen and progesterone are significantly increased during pregnancy; hormones decrease rapidly after childbirth.[20] Decrease in the levels of these hormones is a crucial factor which may lead to decrease in the levels of serotonin, thus contributing to PPD.[21] It is interesting to note that some gut microbiota is linked to the release of β-glucuronidase, an enzyme that converts estrogen into its most physiologically active form. This suggests that systemic levels of progesterone and estrogen may be linked with gut microbiota.[22] Hence, disruption of the gut flora during delivery may result in rapid drop in the levels of progesterone and estrogens by altering the levels of β-glucuronidase, thereby contributing to the pathogenesis of PPD.[4]

Hypothalamic–Pituitary–Adrenal Axis (HPA Axis)

The HPA axis is activated in depressed individuals in response to both internal and external stressors, increasing cortisol levels. Cortisol influences gut motility, intestinal integrity, and mucus production and may also contribute to changes in the gut microbiota composition. Pathway is upregulated during depression leading to disruption of gut microbiota.[23]

Serotonin (5-HT)

Abnormal neurotransmitter functions have been implicated as one of the physiological reasons for depression, mainly serotonin levels.[24] Gut microbiota plays a significant role in the metabolism of serotonin and tryptophan. Native spore-forming bacteria (Sp) from the human and mouse microbiota stimulate colonic enterochromaffin cells (ECs) to produce 5-HT, which in turn supplies 5-HT to lumen, mucosa, and platelets. Spore forming bacteria significantly modulates the host 5-HT levels and plays a major role in controlling 5-HT-related biological processes.[25] Tryptophan metabolism in the host was found to be regulated by Fecal Microbiota Transplantation (FMT) on the early gut microbiota of neonatal piglets offering a novel avenue for the gut microbiota to control depression-like phenotypes through tryptophan metabolism modulation.[26]

Short-chain Fatty Acids (SCFA)

Serotonin metabolism and HPA axis modulation are related to the generation of gut-associated microbial metabolites, such as tryptophan and SCFA, in depression patients.[27,28]

Bacterial end products like acetate, propionate, and butyrate stimulate the production of tyrosine and tryptophan hydroxylase, which are essential for neurotransmission processes as they have a vital role in the synthesis of dopamine, norepinephrine, and serotonin.[29–31]

Gut microbiota has been shown to control levels of kynurenic acid by influencing tryptophan synthesis, as well as steroid and glucocorticoid levels through SCFA-mediated promotion of serotonin synthesis in the intestinal endothelium.[4] Gut microbes, like *Ruminococcus obeum* and *Akkermansia muciniphila*, can break down fibers into SCFA like butyric, propionic, and acetic acids, this could account for the beneficial effects of a high dietary fiber intake in HFD-induced PPD in mice.[32] It has been shown that sodium butyrate reduces aversive memory impairment, depression-like behaviors, and activates hippocampus microglia by blocking histone deacetylase and elevating the expression of BDNF, 5-HT, and Ten-Eleven Translocation 1 (TET1).[33–35]

Amino Acids

Patients with depression were found to have lower blood levels of the amino acid like serine, methionine, asparagine, glutamine, and tryptophan, but higher plasma levels of phenylalanine,

Table 1: Study on distribution of Gut microbiota in PPD patients and animal models

Authors	*Study design*	*Participants*	*Results*
Zhou et al.[17]	Case control study	28 patients with PPD and 16 healthy controls	The relative abundance of *Firmicutes* phyla was lower in PPD patients. The PPD patients experienced reduced levels of *Faecalibacterium, Phascolarctobacterium, Butyricicoccus*, and *Lachnospiraceae*, as well as increased levels of *Enterobacteriaceae* family. A correlation was observed between levels of *Phascolarctobacterium, Lachnospiraceae, Faecalibacterium*, and *Tyzzerella.3* and the severity of depressive symptoms.
Zhao et al.[18]	Rat model study	Gestational Diabetes Mellitus (GDM) rat model	The ratio of Firmicutes to Bacteroidetes decreased. Lactobacillus and Bacteroides were negatively correlated with 5-HT level and positively correlated with Kynurenine (Kyn) level, whereas Clostridium XlVa and Ruminococcus were positively correlated with 5-HT level.

aspartate, serine, and γ-glutamyl amino acids.[36,37] Significantly, these investigations showed that variations in plasma AA levels are correlated with variations in AAs linked to gut microbial metabolism which may be related as the pathological basis for gut microbial-induced depression.[38]

Implications for Intervention

Because PPD patients report their condition infrequently and are reluctant to seek medical attention, outside support, or pharmaceutical intervention, current preventive, diagnostic, and treatment approaches for PPD are woefully inadequate. Early identification and diagnosis of PPD depend on screening following delivery, using a screening tool such as the Edinburgh Postpartum Depression Scale (EPDS).[39] Psychotherapy is preferred over medications.[40] Serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin–norepinephrine reuptake inhibitors (SNRIs) are the primary medications utilized in therapeutic practice.[41] Being non-invasive, gut microbiota therapy is a more promising treatment technique that offers a desirable model for the clinical treatment of PPD patients in the future. In animal models, probiotics, prebiotics, nutrition, and fecal microbial transplantation can all help to restore the natural microbiota.[42–45] These interventions may positively impact gut microbial composition and, consequently, mental health outcomes in the postpartum period.

Conclusion

Exploration of the gut–brain axis in the context of PPD has revealed a complex interplay between gut microbiota and psychological well-being. The complex interactions among various gut microorganisms that impact the synthesis of neurotransmitters, precursors, and essential metabolite release highlight the possible role of the gut microbiota in the pathophysiology of PPD. The results point to a possible direction for deciphering the biological basis of PPD and the influence of gut microbiota on mental health outcomes in the postpartum period.

The unraveling of these mechanisms highlights the complexity of PPD and emphasizes the need for a holistic approach that considers the bidirectional communication between the gut and the brain. This information is essential for creating focused interventions that go beyond conventional psychiatric methods and may open up new therapy and preventative options.

Orcid

Srinidhi Rai https://orcid.org/0000-0002-4769-9002
Priya Alva https://orcid.org/0000-0002-4439-4270

References

1. Pearlstein T, Howard M, Salisbury A, et al. Postpartum depression. Am J Obstet Gynecol 2009;200(4):357–364. DOI: 10.1016/j.ajog.2008.11.033.
2. Lanjewar S, Nimkar S, Jungari S. Depressed motherhood: Prevalence and covariates of maternal postpartum depression among urban mothers in India. Asian J Psychiatr 2021;57(102567):1–6. DOI: 10.1016/j.ajp.2021.102567.
3. Ghosh A, Goswami S. Evaluation of post-partum depression in a tertiary hospital. J Obstet Gynaecol India 2011;61(5):528–530. DOI: 10.1007/s13224-011-0077-9.
4. Zhang S, Lu B, Wang G. The role of gut microbiota in the pathogenesis and treatment of postpartum depression. Ann Gen Psychiatry 2023;22(36):1–13. DOI: 10.1186/s12991-023-00469-8.
5. Cameron EE, Sedov ID, Tomfohr-Madsen LM. Prevalence of paternal depression in pregnancy and the postpartum: An updated meta-analysis. J Afect Disord 2016;206:189–203. DOI: 10.1016/j.jad.2016.07.044.
6. Rai S, Sreelatha S, Devang N, et al. The microbiota–gut–brain axis and diabetic cognitive impairment: A memorable journey. Clinical Diabetology 2023;12(4):261–271. DOI: 10.5603/DK.a2023.0025.
7. Diamant M, Blaak EE, de Vos WM. Do nutrient-gut-microbiota interactions play a role in human obesity, insulin resistance and type 2 diabetes? Obes Rev 2011;12(4):272–281. DOI: 10.1111/j.1467-789X.2010.00797.x.
8. Cryan JF, Dinan TG. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci 2012;13(10):701–712. DOI: 10.1038/nrn3346.
9. Dinan TG, Cryan JF. Melancholic microbes: A link between gut microbiota and depression? Neurogastroenterol Motil 2013;25(9):713–719. DOI: 10.1111/nmo.12198.
10. Cryan JF, Dinan TG. Microbiota and neuroimmune signalling—Metchnikoff to microglia. Nat Rev Gastroenterol Amp; Hepatol 2015;12(9),494–496. DOI: 10.1038/nrgastro.2015.127.
11. Desbonnet L, Clarke G, Shanahan F, et al. Microbiota is essential for social development in the mouse. Mol Psychiatry 2014;19(2):146–148. DOI: 10.1038/mp.2013.65.
12. Liu L, Huh JR, Shah K. Microbiota and gut brain axis. Implications for new therapeutic design in the CNS. eBiomedicine 2022;77:1–11. DOI: 10.1016/j.ebiom.2022.103908.
13. Cheung SG, Goldenthal AR, Uhlemann AC, et al. Systematic review of gut microbiota and major depression. Front Psychiatry 2019;10(34):1–17. DOI: 10.3389/fpsyt.2019.00034.
14. Dalile B, Van Oudenhove L, Vervliet B, et al. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat Rev Gastroenterol Hepatol 2019;16(8):461–478. DOI: 10.1038/s41575-019-0157-3.
15. Bercik P, Verdu EF, Foster JA, et al. Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. Gastroenterology 2010;139(6):2102–2112. DOI: 10.1053/j.gastro.2010.06.063.
16. O'Sullivan E, Barrett E, Grenham S, et al. BDNF expression in the hippocampus of maternally separated rats: Does bifidobacterium breve 6330 alter BDNF levels? Benef Microbes 2011;2(3):199–207. DOI: 10.3920/BM2011.0015.
17. Zhou Y, Chen C, Yu H, et al. Fecal microbiota changes in patients with postpartum depressive disorder. Front Cell Infect Microbiol 2020;10:567268. DOI: 10.3389/fcimb.2020.567268.
18. Zhao R, Zhou Y, Shi H, et al. Effect of gestational diabetes on postpartum depression-like behavior in rats and its mechanism. Nutrients 2022;14(6):1229. DOI: 10.3390/nu14061229.
19. Aoyagi SS, Tsuchiya KJ. Does maternal postpartum depression affect children's developmental outcomes? J Obstet Gynaecol Res 2019;45(9):1809–1820. DOI: 10.1111/jog.14064.
20. Brett M, Baxendale S. Motherhood and memory: A review. Psychoneuroendocrinol 2001;26(4):339–362. DOI: 10.1016/s0306-4530(01)00003-8.
21. Rupanagunta GP, Nandave M, Rawat D, et al. Postpartum depression: Aetiology, pathogenesis and the role of nutrients and dietary supplements in prevention and management. Saudi Pharm J 2023;31(7):1274–1293. DOI: 10.1016/j.jsps.2023.05.008.
22. Baker JM, Al-Nakkash L, Herbst-Kralovetz MM. Estrogen-gut microbiome axis: Physiological and clinical implications. Maturitas 2017;103:45–53. DOI: 10.1016/j.maturitas.2017.06.025.
23. Mayer SE, Lopez-Duran NL, Sen S, et al. Chronic stress, hair cortisol and depression: A prospective and longitudinal study of medical internship. Psychoneuroendocrinology 2018;92:57–65. DOI: 10.1016/j.psyneuen.2018.03.020.
24. Daut RA, Fonken LK. Circadian regulation of depression: A role for serotonin. Front Neuroendocrinol 2019;54:1–37. DOI: 10.1016/j.yfrne.2019.04.003.

25. Yano JM, Yu K, Donaldson GP, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell 2015;161(2):264–276. DOI: 10.1016/j.cell.2015.02.047
26. Geng S, Cheng S, Li Y, et al. Faecal microbiota transplantation reduces susceptibility to epithelial injury and modulates tryptophan metabolism of the microbial community in a Piglet model. J Crohns Colitis 2018;12(11):1359–1374. DOI: 10.1093/ecco-jcc/jjy103.
27. Dinan TG, Cryan JF. Regulation of the stress response by the gut microbiota: Implications for psychoneuroendocrinology. Psychoneuroendocrinology 2012;37(9):1369–1378. DOI: 10.1016/j.psyneuen.2012.03.007.
28. Dinan TG, Cryan JF. Microbes, immunity, and behavior: Psychoneuroimmunology meets the microbiome. Neuropsychopharmacology 2017;42(1):178–192. DOI: 10.1038/npp.2016.103.
29. Christiansen CB, Gabe MBN, Svendsen B, et al. The impact of short-chain fatty acids on GLP-1 and PYY secretion from the isolated perfused rat colon. Am J Physiol Gastrointest Liver Physiol 2018;315(1):G53–G65. DOI: 10.1152/ajpgi.00346.2017.
30. Nankova BB, Agarwal R, MacFabe DF, et al. Enteric bacterial metabolites propionic and butyric acid modulate gene expression, including CREB-dependent catecholaminergic neurotransmission, in PC12 cells–possible relevance to autism spectrum disorders. PLoS ONE 2014;9(8):1–16. DOI: 10.1371/journal.pone.0103740.
31. Pascale A, Marchesi N, Marelli C, et al. Microbiota and metabolic diseases. Endocrine 2018;61:357–371. DOI: 10.1007/s12020-018-1605-5.
32. Koh A, De Vadder F, Kovatcheva-Datchary P, et al. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. Cell 2016;165(6):1332–1345. DOI: 10.1016/j.cell.2016.05.041.
33. Steckert AV, Comim CM, Igna DM, et al. Effects of sodium butyrate on aversive memory in rats submitted to sepsis. Neurosci Lett 2015;595:134–138. DOI: 10.1016/j.neulet.2015.04.019.
34. Yamawaki Y, Yoshioka N, Nozaki K, et al. Sodium butyrate abolishes lipopolysaccharide-induced depression-like behaviors and hippocampal microglial activation in mice. Brain Res 2018;1680:13–38. DOI: 10.1016/j.brainres.2017.12.004.
35. Wei Y, Melas PA, Wegener G, et al. Antidepressant-like effect of sodium butyrate is associated with an increase in TET1 and in 5-hydroxymethylation levels in the Bdnf gene. Int J Neuropsychopharmacol 2014;18(2):pyu032. DOI: 10.1093/ijnp/pyu032.
36. Hashimoto K, Bruno D, Nierenberg J, et al. Abnormality in glutamine-glutamate cycle in the cerebrospinal fluid of cognitively intact elderly individuals with major depressive disorder: A 3-year follow-up study. Transl Psychiatry 2016;6(3):e744. DOI: 10.1038/tp.2016.8.
37. Pu J, Liu Y, Zhang H, et al. An integrated meta-analysis of peripheral blood metabolites and biological functions in major depressive disorder. Mol Psychiatry 2021;26(8):4265–4276. DOI: 10.1038/s41380-020-0645-4.
38. Domin H, Szewczyk B, Woźniak M, et al. Antidepressant-like effect of the mGluR5 antagonist MTEP in an astroglial degeneration model of depression. Behav Brain Res 2014;273:23–33. DOI: 10.1016/j.bbr.2014.07.019.
39. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150:782–786. DOI: 10.1192/bjp.150.6.782.
40. Walton GD, Ross LE, Stewart DE, et al. Decisional conflict among women considering antidepressant medication use in pregnancy. Arch Womens Ment Health 2014;17(6):493–501. DOI: 10.1007/s00737-014-0448-1.
41. Leucht S, Hierl S, Kissling W, et al. Putting the efficacy of psychiatric and general medicine medication into perspective: Review of meta-analyses. Br J Psychiatry 2012;200(2):97–106. DOI: 10.1192/bjp.bp.111.096594.
42. Cammarota G, Ianiro G, Bibbò S, et al. Gut microbiota modulation: Probiotics, antibiotics or fecal microbiota transplantation? Intern Emerg Med 2014;9(4):365–373. DOI: 10.1007/s11739-014-1069-4.
43. Liu X, Cao S, Zhang X. Modulation of gut–microbiota–brain axis by probiotics, prebiotics, and diet. J Agric Food Chem 2015;63(36):7885–7895. DOI: 10.1021/acs.jafc.5b02404.
44. Sandhu KV, Sherwin E, Schellekens H, et al. Feeding the microbiota-gut-brain axis: Diet, microbiome, and neuropsy chiatry. Transl Res 2017;179:223–244. DOI: 10.1016/j.trsl.2016.10.002.
45. Garg R, Chauhan V, Agrawal P, et al. Polycystic ovary syndrome till date and possibilities in coming years. J South Asian Feder Obs Gynae 2024; 16(2):169–173. DOI: 10.5005/jp-journals-10006-2371.