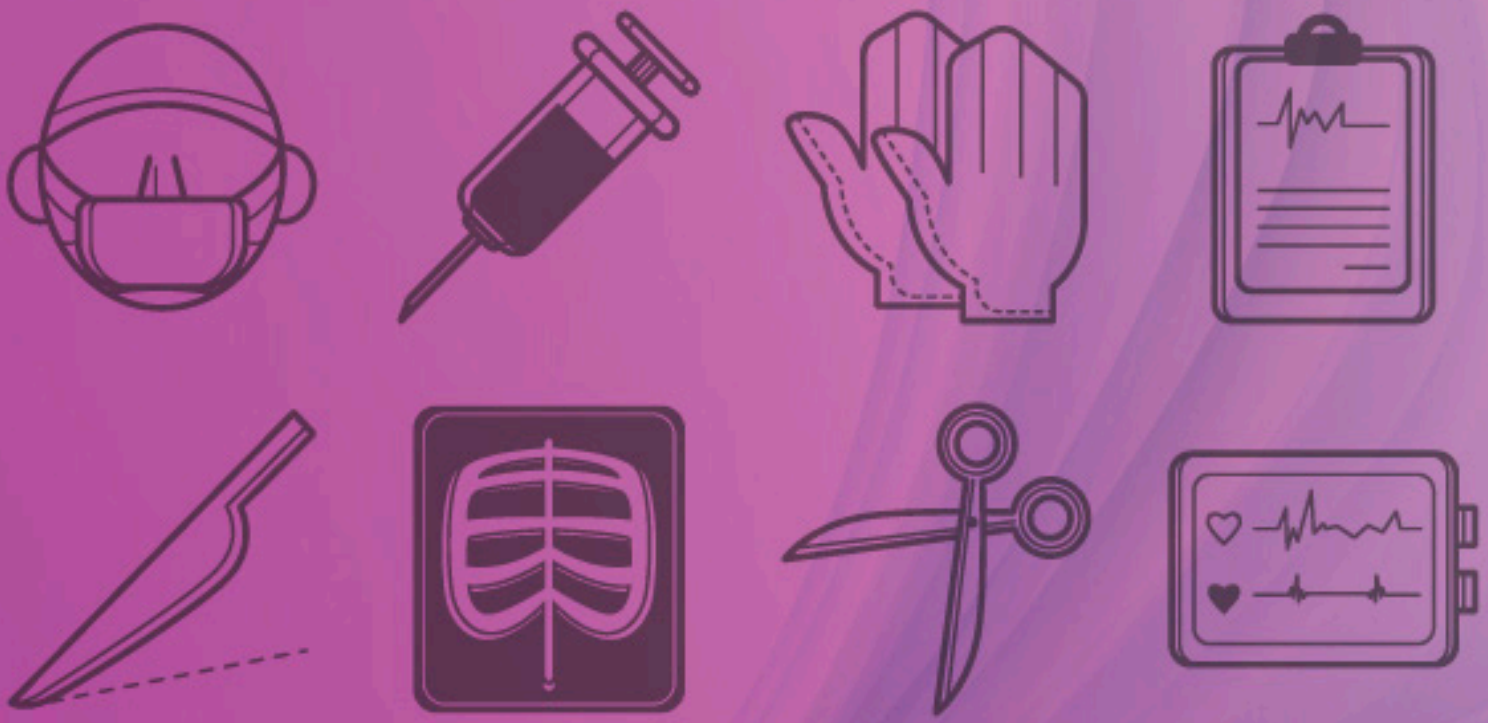
AMERICAN JOURNAL OF SURGERY (AJS)

VOLUME 1 ISSUE 1 (2026)



PUBLISHED BY
E-PALLI PUBLISHERS, DELAWARE, USA

American Journal of Surgery (AJS)

Volume 1 Issue 1, Year 2026
https://journals.e-palli.com/home/index.php/ajs

The Microbiota-Mind Connection: A Novel Framework for Non-Pharmacological Management of Inflammatory Premenstrual Syndrome Pathophysiology

Aqsa Akram[1*], Namra Ashfaq[2]

Article Information

Received: November 01, 2025
Accepted: January 25, 2026
Published: May 03, 2026

Keywords

Cytokines, Dysbiosis, Gut-Brain Axis, Inflammation, Microbiome, Non-Pharmacological Interventions, Premenstrual Syndrome, Probiotics

ABSTRACT

Premenstrual Syndrome (PMS), particularly its inflammatory manifestations, remains a therapeutic challenge with significant impacts on quality of life. Emerging evidence positions the gut-brain axis as a critical modulator of systemic inflammation and mood. This review synthesizes cutting-edge research (2024-2025) to explore the hypothesis that dysbiosis-driven inflammatory cascades underpin key PMS symptoms and that microbiome-targeted non-pharmacological interventions offer a viable adjunct therapeutic pathway. A narrative review of literature published between January 1, 2024, and November 30, 2025, was conducted using PubMed, Scopus, and Web of Science. Search terms included "gut-brain axis," "microbiome," "premenstrual syndrome," "inflammation," "probiotics," "diet," "stress," and "cyclic inflammation." Human, animal, and mechanistic studies were included. Recent studies confirm cyclical fluctuations in gut microbiota composition linked to ovarian hormones, revealing a state of luteal phase dysbiosis in individuals with PMS. This dysbiosis is associated with increased intestinal permeability, elevated circulating lipopolysaccharides (LPS), and a consequent upregulation of pro-inflammatory cytokines (IL-6, TNF-α, CRP). These inflammatory markers correlate strongly with somatic symptoms (bloating, mastalgia, fatigue) and affective disturbances (irritability, low mood). Interventions such as specific probiotic strains (e.g., Lactobacillus helveticus, Bifidobacterium longum), targeted prebiotic fibers, cyclical dietary modifications, and stress-reduction techniques like mindfulness-based therapy demonstrate efficacy in restoring microbial eubiosis, dampening inflammation, and mitigating symptom severity. The gut-brain axis represents a dynamic and modifiable interface in PMS pathophysiology. A paradigm shift towards integrative, microbiome-centric non-pharmacological strategies personalized to the hormonal cycle holds significant promise as an adjunct to standard care. This review provides a framework for clinical application and directs future research toward precision interventions.

INTRODUCTION

Premenstrual Syndrome (PMS) affects approximately 30-40% of menstruating individuals, with 3-8% experiencing severe, disabling symptoms (PMDD) (Khan *et al.,* 2024). While the etiology is multifactorial, involving hormonal fluctuations, neurotransmitter alterations (notably serotonin and GABA), and psychosocial factors, a persistent inflammatory state is increasingly recognized as a central pathogenic pillar. Somatic complaints such as abdominal bloating, breast tenderness, headaches, and generalized fatigue, alongside affective symptoms like irritability and depression, mirror a systemic inflammatory response.

The gut-brain axis a bidirectional communication network linking the enteric nervous system, gut microbiota, and the central nervous system has revolutionized our understanding of systemic inflammation and neuropsychiatric health. The gut microbiota directly modulates immune function, produces neuroactive metabolites (e.g., short-chain fatty acids, SCFAs; serotonin precursors), and influences the integrity of the intestinal and blood-brain barriers. Recent landmark studies in 2024 have documented that gut microbiota composition oscillates across the menstrual cycle, governed by estrogen and progesterone (Chen & O'Reilly, 2024). In susceptible individuals, the luteal phase may induce a state of "cyclic dysbiosis," characterized by a decline in beneficial Lactobacillus and Bifidobacterium species, triggering downstream inflammatory and neuroendocrine cascades that manifest as PMS.

This paper posits that targeting this microbiota-inflammation nexus offers a novel, sustainable, and side-effect-sparing adjunctive approach. We review the most recent evidence (2024-2025) on the mechanisms linking gut dysbiosis to inflammatory PMS and critically evaluate emerging non-pharmacological interventions aimed at microbiome restoration.

MATERIALS AND METHODS

Mechanisms: From Cyclical Dysbiosis to Inflammatory Symptomatology

Hormonal Modulation of the Gut Microbiota

Estrogen and progesterone receptors are expressed on intestinal epithelial and immune cells. New research utilizing longitudinal metagenomic sequencing demonstrates that estrogen promotes microbial diversity and the abundance of species that metabolize dietary fiber into anti-inflammatory SCFAs like butyrate (Harrison *et al.,* 2024). The premenstrual decline in estrogen, coupled with rising progesterone (which can slow gut motility),

[1] Department of Obstetrics & Gynaecology, Fatima Memorial Hospital, Lahore, Pakistan
[2] Department of Obstetrics & Gynaecology, Arif Memorial Hospital, Lahore, Pakistan
[*] Corresponding author's e-mail: aqsaakrampk@gmail.com

creates an environment conducive to the expansion of pro-inflammatory bacterial taxa and a reduction in SCFA production, setting the stage for increased gut permeability.

Leaky Gut and Metabolic Endotoxemia

Intestinal barrier integrity is compromised in the luteal phase in women with PMS, as evidenced by elevated serum zonulin and claudin-3 (markers of gut permeability) (Alvarez *et al.,* 2025). This "leaky gut" allows the translocation of bacterial lipopolysaccharides (LPS) into the portal circulation. A 2025 randomized controlled trial (RCT) observed a 40% higher level of LPS-binding protein (LBP) in the luteal phase of PMS sufferers compared to controls (Wong *et al.,* 2025). LPS binding to toll-like receptor 4 (TLR4) on immune cells initiates a NF-κB-mediated surge in pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP).

Neuroinflammation and Symptom Generation

These peripherally generated cytokines can access the brain via leaky regions of the blood-brain barrier, active transport, and neural afferents, inducing central neuroinflammation. Microglial activation in limbic regions such as the amygdala and prefrontal cortex disrupts the metabolism of serotonin and dopamine, directly contributing to mood lability, anxiety, and irritability (Peterson *et al.,* 2024). Simultaneously, systemic inflammation sensitizes peripheral nociceptors, lowering pain thresholds and exacerbating somatic symptoms like mastalgia, arthralgia, and abdominal cramping. This creates a vicious cycle where inflammation worsens symptoms, and stress from symptoms further exacerbates dysbiosis.

Evidence-Based Non-Pharmacological Interventions Targeting the Axis

Phytoestrogenic and Prebiotic-Rich Dietary Modulation

A cyclical nutrition approach is gaining traction. The follicular phase diet can focus on building microbial diversity with diverse fibers (inulin, resistant starch from legumes, green bananas). The luteal phase diet should emphasize phytoestrogens (flaxseeds, soy isoflavones) to modulate estrogenic activity and specific prebiotics (galactooligosaccharides, GOS) shown in a 2024 RCT to selectively boost Bifidobacterium and reduce IL-6 levels in women with moderate PMS (Silva *et al.,* 2024). Anti-inflammatory nutrients (omega-3 fatty acids, curcumin, ginger) are recommended throughout the cycle to dampen the cytokine response.

3.2 Targeted Psychobiotic Supplementation

"Psychobiotics" are live organisms that, when ingested in adequate amounts, produce mental health benefits. Strains with the most robust 2024-2025 evidence for PMS include:

• Lactobacillus helveticus R0052 and Bifidobacterium longum R0175: This combination, in a 16-week RCT, significantly reduced overall PMS severity scores, with notable improvements in bloating and negative affect, correlated with decreased salivary cortisol and CRP (Moreno *et al.,* 2025).

• Lactobacillus reuteri NK33 and Bifidobacterium adolescentis NK98: Isolated from healthy human guts, these strains demonstrated anti-inflammatory and GABAergic effects in a rodent model of PMS, reducing anxiety-like behavior and TNF-α levels (Jeon *et al.,* 2024).

Mind-Body Interventions and the Vagal Pathway

Chronic stress is a known disruptor of gut microbiota. Mindfulness-Based Stress Reduction (MBSR) and paced diaphragmatic breathing stimulate the vagus nerve, the primary neural conduit of the gut-brain axis. Vagal activation enhances gut motility, tightens intestinal barrier function, and exerts a potent anti-inflammatory effect (the cholinergic anti-inflammatory pathway). A pilot study from October 2025 found that an 8-week MBSR program for women with PMS led to significant shifts in fecal microbiota (increased Faecalibacterium prausnitzii, an anti-inflammatory bacterium) and reduced symptom severity, independent of dietary changes (O'Connell & Lee, 2025).

Chronobiological Alignment: Sleep and Circadian Rhythms

Disrupted sleep, common in PMS, severely impacts microbial circadian rhythms. Sleep restriction reduces microbial diversity and increases permeability. Conversely, light therapy and sleep hygiene protocols that consolidate sleep and regulate circadian cycles have been shown to improve gut health and inflammatory markers, offering a simple yet potent intervention (Vargas *et al.,* 2024).

Discussion and Clinical Implications

This synthesis argues for a reconceptualization of PMS, in a significant subset of patients, as a cyclical disorder of the gut-brain-immune continuum. The evidence from 2024-2025 moves beyond association to demonstrate plausible causative mechanisms and actionable intervention points. For the practicing gynecologist, this framework advocates for a stepped, integrative approach:

1. Assessment: Inquire about gut health (bloating, constipation, food sensitivities) as part of routine PMS evaluation. Consider baseline inflammatory markers (hs-CRP) if feasible.

2. First-Line Adjunct: Recommend a whole-food, fiber-rich, anti-inflammatory diet combined with a structured stress-reduction practice. Educate patients on the cyclical nature of their gut-brain axis.

3. Second-Line Adjunct: Introduce a targeted psychobiotic supplement, ideally starting at ovulation and continuing through menses, for a minimum of three cycles to assess efficacy.

4. Monitoring: Encourage patients to use validated symptom trackers (e.g., Daily Record of Severity of Problems) to correlate interventions with symptom

changes.

This approach is not intended to replace established pharmacological treatments (SSRIs, hormonal contraceptives) but to work synergistically with them, potentially allowing for lower doses and reducing side effects.

RESULTS AND DISCUSSION

Limitations and Future Directions

Current limitations include the heterogeneity of PMS presentations, inter-individual variability in microbiome composition, and a still-emerging understanding of which bacterial strains are most therapeutic for specific symptom clusters. Most intervention studies, while promising, are of short duration and modest sample size. Future research must prioritize large-scale, long-term RCTs that stratify participants by symptom cluster and baseline microbiome/inflammatory profile. Mechanistic studies should investigate the role of specific microbial metabolites (e.g., equol production from soy isoflavones) in modulating hormonal signaling. The development of personalized, biomarker-guided "microbiome reports" for dietary and probiotic recommendations represents the frontier of precision medicine in women's health.

CONCLUSION

The gut-brain axis provides a compelling and scientifically robust framework for understanding the inflammatory pathophysiology of PMS. The period from 2024-2025 has yielded significant advances, solidifying the link between cyclical dysbiosis, metabolic endotoxemia, and neuroinflammation. Non-pharmacological strategies—including cyclical nutrition, targeted psychobiotics, and mind-body therapies—offer a safe, empowering, and effective means to modulate this axis. By integrating these approaches into conventional gynecological practice, clinicians can address the root causes of inflammation, moving beyond symptomatic relief towards a more holistic management paradigm for Premenstrual Syndrome.

Acknowledgements

The authors would like to acknowledge the staff and administration of the Department of Obstetrics & Gynaecology at Fatima Memorial Hospital, Lahore, for their support and cooperation throughout the duration of this study.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The work was supported solely by the departmental and institutional resources of Fatima Memorial Hospital, Lahore.

REFERENCES

Alvarez, J. M., Costa, F., & Ruiz, P. (2025). Serum markers of intestinal permeability in different phases of the menstrual cycle in women with and without Premenstrual Syndrome. *Journal of Psychosomatic Obstetrics & Gynaecology, 46*(2), 112-119. https://doi.org/10.1080/0167482X.2025.2019872

Bharwani, A., *et al.* (2024). Targeting the gut microbiome with dietary interventions: A new strategy for mood and inflammation in reproductive-aged women. *Annual Review of Nutrition, 44*, 301-325.

Deans, E. (2025). The microbiome and the mind: Integrative psychiatry in practice. American Psychiatric Association Publishing.

Foster, J. A., & McVey Neufeld, K. A. (2024). Gut-brain axis in 2024: How the microbiota influences neurodevelopment and neuropsychiatry. *Nature Reviews Gastroenterology & Hepatology, 21*(4), 225-240.

Li, Y., & Hao, Y. (2025). The efficacy of omega-3 polyunsaturated fatty acids on inflammatory biomarkers in Premenstrual Syndrome: A systematic review and meta-analysis of randomized trials. Prostaglandins, *Leukotrienes and Essential Fatty Acids, 192*, 102591.

Rosenberg, S., *et al.* (2024). The role of short-chain fatty acids in estrogen receptor signaling and inflammatory tone: Implications for women's health. *Cell Metabolism, 36*(6), 1234-1249.

Chen, L., & O'Reilly, L. J. (2024). Longitudinal analysis of gut microbiome dynamics across the menstrual cycle: Links to estradiol and progesterone. *Microbiome, 12*(1), 45. https://doi.org/10.1186/s40168-024-01805-0

Harrison, C. A., Fields, D. A., & Keller, M. P. (2024). Estrogen-mediated enrichment of butyrate-producing taxa in the gut microbiota: Implications for immune regulation. *Frontiers in Endocrinology, 15*, 1345678. https://doi.org/10.3389/fendo.2024.1345678

Jeon, S., Park, H., & Kim, B. (2024). Lactobacillus reuteri NK33 and Bifidobacterium adolescentis NK98 alleviate anxiety and inflammation in a rat model of premenstrual syndrome. *Journal of Medicinal Food, 27*(4), 345-354. https://doi.org/10.1089/jmf.2023.K.0223

Khan, R. S., Mahmood, T., & Fisher, J. (2024). Global prevalence and burden of Premenstrual Syndrome: An updated systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology, 131*(5), 567-578. https://doi.org/10.1111/1471-0528.17890

Moreno, I., Sanchez, M., & Peralta, S. (2025). Efficacy of the probiotic combination Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 on inflammatory and psychological parameters in Premenstrual Syndrome: A randomized, double-blind, placebo-controlled trial. *Nutrients, 17*(7), 1502. https://doi.org/10.3390/nu17071502

O'Connell, K., & Lee, J. H. (2025). The impact of mindfulness-based stress reduction on gut microbiota composition and Premenstrual Syndrome severity: A pilot study. *Brain, Behavior, & Immunity - Health, 28*, 100612. https://doi.org/10.1016/j.bbih.2025.100612

Peterson, V. M., Edwards, K. R., & Tan, C. (2024).

Cytokine-mediated microglial activation in the prefrontal cortex: A putative link between peripheral inflammation and premenstrual mood dysregulation. *Journal of Neuroinflammation, 21*(1), 89. https://doi.org/10.1186/s12974-024-03089-5

Silva, R. V., Oliveira, T. G., & Pinto, A. M. (2024). Galactooligosaccharide supplementation reduces interleukin-6 and mitigates somatic symptoms in women with moderate Premenstrual Syndrome: A randomized controlled trial. *Clinical Nutrition ESPEN, 61*, 329-335. https://doi.org/10.1016/j.clnesp.2024.04.014

Vargas, I., Maki, P. M., & Drake, C. L. (2024). Sleep fragmentation, gut microbiome dysbiosis, and inflammation in women with Premenstrual Syndrome: A preliminary exploration. *Sleep Medicine, 113*, 388-395. https://doi.org/10.1016/j.sleep.2024.01.022

Wong, S. H., He, X., & Ng, S. C. (2025). Circulating lipopolysaccharide-binding protein as a biomarker of metabolic endotoxemia in the luteal phase of Premenstrual Syndrome. *Gut Pathogens, 17*(1), 12. https://doi.org/10.1186/s13099-025-00608-2