MINI REVIEW

The Estrobolome and Gut Microbiome in Perimenopause: Bidirectional Interactions, Clinical Consequences, and Therapeutic Opportunities

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Abstract

Objective: To synthesize current evidence on gut microbiome alterations during perimenopause, focusing on the estrobolome's role in estrogen metabolism and its implications for women's health.

Materials and methods: Narrative review of peer-reviewed literature examining the estrogen–gut microbiome axis in perimenopause and early menopause.

Results: The estrobolome comprises gut microbial genes encoding β-glucuronidase and related enzymes that facilitate enterohepatic estrogen recycling. Hormonal volatility in perimenopause likely destabilizes microbial diversity, reduces short-chain fatty acid (SCFA) producers (e.g., *Roseburia*, *Faecalibacterium*), and increases pro-inflammatory taxa. These shifts impair estrogen recirculation, intestinal barrier function, and metabolic homeostasis, contributing to insulin resistance, visceral adiposity, bone loss, mood disturbances, and genitourinary symptoms. Bidirectional crosstalk exists: estrogen modulates gut immunity and barrier integrity, while dysbiosis exacerbates hormonal fluctuations. Longitudinal data remain limited, but preclinical and cross-sectional studies support causality in metabolic and skeletal phenotypes.

Conclusion: The gut microbiome, particularly the estrobolome, is a modifiable mediator of perimenopausal symptom burden and long-term cardiometabolic, skeletal, and neuropsychological risks. Dietary modulation and probiotics show promise, but rigorous interventional trials are needed. Integrating microbiome insights could refine preventive strategies and personalize care during the menopausal transition.

Keywords: Cardiometabolic health, Dysbiosis, Estrobolome, Estrogen metabolism, Gut microbiome, Perimenopause, Probiotics.

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Introduction

The menopausal transition is traditionally viewed through the lens of ovarian estrogen decline. Yet emerging evidence positions the gut microbiome as a critical modulator of estrogen homeostasis and midlife health. Perimenopause—characterized by erratic estradiol and progesterone levels—triggers vasomotor, psychological, metabolic, and genitourinary symptoms that vary widely among women.

The estrobolome refers to the aggregate of intestinal bacterial genes capable of metabolizing estrogens, chiefly through β-glucuronidase-mediated deconjugation of biliary estrogen conjugates, enabling reabsorption via enterohepatic circulation. Dysbiosis disrupts this process, potentially amplifying hormonal instability and systemic inflammation.

Bidirectional regulation defines the axis: Estrogen receptors (ERα, ERβ, GPER1) in the gastrointestinal tract influence epithelial integrity, mucus production, and immune tone, while microbial composition determines circulating estrogen bioavailability. Postmenopausal women frequently exhibit reduced microbial diversity and a microbiome profile resembling that of age-matched men, with fewer SCFA producers and lower β-glucuronidase activity. Perimenopause likely represents an earlier phase of instability driven by hormonal fluctuations rather than absolute deficiency.[1]

This narrative review examines the evidence linking perimenopausal gut dysbiosis to clinical outcomes and explores microbiome-targeted interventions as preventive tools.

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The Estrogen–Gut Microbiome Axis

Estrogen shapes the gut environment via receptor-mediated effects on barrier function and immune surveillance. Estrogen deficiency increases permeability ("leaky gut") and alters nutrient niches, favoring pro-inflammatory taxa.[2]

Conversely, the microbiome governs estrogen levels. β-Glucuronidase hydrolyzes estrogen-glucuronides, liberating active hormone for reabsorption. Metagenomic studies show reduced abundance of β-glucuronidase-producing taxa in postmenopausal samples, correlating with lower urinary estrogen metabolites.

This reciprocal relationship reframes menopause: Estrogen decline is partly microbiome-dependent, creating a reinforcing cycle of dysbiosis and hormonal insufficiency.

Gut Microbiome Alterations in Perimenopause: Taxonomic and Functional Shifts

Perimenopausal and postmenopausal microbiomes show decreased diversity, depleted *Lactobacillus*, *Bifidobacterium*, *Roseburia*, and *Faecalibacterium*, and enrichment of *Bacteroides* and certain Proteobacteria. Firmicutes/Bacteroidetes ratios often shift toward metabolic inflexibility.

Short-chain fatty acid production declines, compromising gut barrier integrity, appetite regulation, and anti-inflammatory effects. Metabolomic disturbances affect tryptophan (kynurenine pathway → mood dysregulation) and lipid metabolism.[3,4]

Temporal Aspects

Longitudinal observations suggest microbiome changes may precede overt symptoms, offering potential predictive biomarkers. FSH-stratified studies indicate greater dysbiosis with advancing endocrine transition.

Mechanistic Pathways[5]

- **Impaired estrogen recycling**—Reduced estrobolome activity exacerbates fluctuations.
- **Barrier dysfunction and endotoxemia**—Low estrogen weakens tight junctions; leaky gut elevates IL-6 and CRP.
- **Cardiometabolic effects**—Lower SCFAs and altered bile acids promote insulin resistance, dyslipidemia, and visceral fat. Animal models (ovariectomy + FMT) confirm microbiome causality.
- **Bone health**—Microbiota regulate osteoclast activity and calcium absorption; probiotics attenuate bone loss in preclinical studies. Microbiota regulate immune-mediated osteoclast activity and mineral absorption. Early bone loss during perimenopause may be partly microbiome-mediated. Probiotic interventions in ovariectomized rodent models attenuate bone loss, and preliminary human studies suggest similar potential.
- **Gut–brain axis**—Microbial metabolites and inflammation influence mood and cognition via vagal and cytokine pathways. Reduced microbial diversity correlates with elevated inflammatory markers, and peripheral inflammation reliably predicts depressive symptoms during the menopausal transition
- **Gut–vaginal crosstalk**—Gut dysbiosis may seed vaginal depletion of lactobacilli, worsening genitourinary syndrome of menopause (GSM).[6]

Clinical Implications

Dysbiosis likely accelerates cardiometabolic risk accumulation, contributes to "brain fog" and depression via inflammatory and kynurenine pathways, hastens early bone loss, and predisposes to recurrent UTIs and vaginal atrophy. Hormone therapy partially restores favorable microbial profiles (higher *Prevotella*, lower *Enterobacteriaceae*).

Therapeutic Horizons

Dietary strategies—High-fiber, Mediterranean, and polyphenol-rich patterns (soy isoflavones, berries) increase diversity and SCFA production, correlating with fewer vasomotor symptoms and better metabolic markers.

Probiotics—A recent meta-analysis (≈3,200 women) reported large effects on total symptom burden, vasomotor complaints, mood, and vaginal health with strains such as *Lactobacillus gasseri* CP2305, *L. brevis* KABP052, and *L. rhamnosus* GR-1. Heterogeneity and bias limit firm recommendations. Synbiotics warrant further study.

Menopausal hormone therapy—MHT modifies duodenal microbiota, potentially mediating benefits.

In low- and middle-income settings, traditional fermented and fiber-rich diets offer scalable protection, though nutrition transition threatens diversity.[7–9]

Limitations and Future Directions

Evidence relies heavily on cross-sectional designs and Western cohorts. Longitudinal multi-omics studies, diverse global populations, and large RCTs with mechanistic endpoints are urgently needed. Personalized (3 PM) approaches leveraging individual microbiome profiles hold promise.

Future Directions

Advancing this field requires methodological and conceptual shifts:

- Longitudinal cohort studies with repeated sampling across the perimenopausal transition are essential to establish temporal relationships between endocrine change, microbial succession, and symptom emergence.
- Multi-omics integration—metagenomics, metatranscriptomics, metabolomics, and hormonal profiling—must move beyond compositional description toward functional characterization.
- Personalized approaches acknowledging the profound inter-individual variation in gut microbial configuration are required. The predictive, preventive, and personalized medicine (3 PM/PPPM) framework, recently applied to vaginal microbiota in menopause, offers a template for gut-directed strategies.
- Global cohort studies including LMIC populations are urgently needed to ensure findings are generalizable.
- Rigorous randomized controlled trials of microbiome-targeted interventions, employing standardized formulations, objective outcome measures, and adequate follow-up duration, are urgently needed. Such trials must incorporate mechanistic endpoints—metabolomic profiling, metagenomic sequencing, barrier function assessment—to establish whether clinical improvements are microbiome-mediated.

Conclusion

The estrobolome emerges as a biologically plausible, modifiable mediator of perimenopausal physiology. Hormonal volatility disrupts microbial stability, perpetuating a cycle that influences metabolic, skeletal, neuropsychological, and genitourinary outcomes. Simple dietary changes offer immediate potential, while probiotics and refined hormone strategies await stronger validation. Recognizing the gut microbiome as an integral component of menopausal medicine opens new avenues for prevention and personalized care.

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