

EDITORIAL

Beyond microbial composition: Toward mechanism-based postbiotics for endometrial aging

Da Li^{1,2,*}¹Center of Reproductive Medicine, Shengjing Hospital of China Medical University, Shenyang 110022, Liaoning Province, China²NHC Key Laboratory of Advanced Reproductive Medicine and Fertility (China Medical University), National Health Commission, Shenyang 110022, Liaoning Province, China

Age-associated reproductive decline has long been viewed predominantly through the lens of ovarian reserve and oocyte quality. Increasing evidence, however, indicates that aging also alters the uterine environment and compromises the capacity of the endometrium to support implantation.^[1,2] This shift in perspective has created growing interest in identifying modifiable factors that contribute to endometrial dysfunction.

The recent study by Li *et al.* adds the reproductive tract microbiome to this framework.^[3] The authors reported an age-related reduction in endometrial *Lactobacillus* and subsequently screened several reproductive tract isolates for functional properties relevant to host protection. *Lactobacillus gasseri* (*L. gasseri*) emerged as a leading candidate because of its favorable adhesive, antioxidative, anti-inflammatory, and antimicrobial characteristics. More importantly, the study moved beyond strain-level observations by identifying bacterial exopolysaccharide (EPS) as functional mediators. Genetic disruption of EPS production weakened the protective effects of *L. gasseri*, whereas manipulation of Hippo-Yes-associated protein (YAP) signaling demonstrated that the beneficial effects on endometrial senescence and receptivity depend substantially on Hippo-YAP activity.^[3]

This progression from microbial profiling to microbial effector biology is particularly important. It raises a broader question for the field: is restoration of a “favorable” microbial community itself the optimal therapeutic goal, or should greater emphasis be placed on the bacterial molecules that directly modify host physiology?

The distinction is clinically relevant. Several studies have associated *Lactobacillus*-enriched reproductive tract communities with better implantation and pregnancy outcomes.^[4,5] Nevertheless, such associations have not consistently translated into therapeutic benefit when the microbiome itself is targeted. A recent randomized, double-blind, placebo-controlled multicenter study evaluating antimicrobial treatment followed by *Lactobacillus crispatus* CTV-05 (LACTIN-V) in women with vaginal dysbiosis undergoing in vitro fertilization (IVF) did not show a clear improvement in IVF outcomes.^[6] These findings illustrate the complexity of live-bacterial interventions, which depend on successful colonization, competition with existing microbial communities, hormonal conditions, host immunity, and interindividual ecological differences.

A postbiotic approach may therefore offer several advantages. Rather than requiring persistence of a living organism, a defined microbial product could potentially be standardized, dosed, and pharmacologically characterized. In this regard, the identification of EPS may ultimately have greater translational value than the prioritization of *L. gasseri* itself. However, converting this concept into a therapeutic strategy will require several key uncertainties to be addressed.

One concerns anatomical delivery. In the mouse experiments, *L. gasseri* was administered intravaginally, whereas the primary readouts were obtained from uterine tissue. The route by which the intervention influences the endometrium remains uncertain. The bacteria might ascend transiently into the uterus, EPS could diffuse or

***Corresponding Author:**

Da Li, Center of Reproductive Medicine, Shengjing Hospital of China Medical University, No.39, Huaxiang Road, Shenyang 110022, Liaoning Province, China.

E-mail: leeda@ymail.com; <https://orcid.org/0000-0002-4895-1185>.

Received: 27 July 2026; Revised: 29 August 2026; Accepted: 15 September 2026

<https://doi.org/10.54844/prm.2026.1351>

be transported across reproductive tract compartments, or local vaginal changes could indirectly affect the uterus through immunological or metabolic signaling. This distinction is particularly important because the endometrium is a low-biomass microbial environment in which contamination and signal redistribution remain major methodological concerns.^[7] Future studies using strain-specific tracing, spatial microbial detection, and direct measurement of EPS within uterine tissue would help determine whether the observed uterine effects arise from direct exposure or inter-compartment communication.

A second unresolved issue is the direction of causality between microbial remodeling and endometrial aging. Reproductive aging involves major changes in endocrine signaling, chromatin regulation, oxidative balance, stromal function, and tissue architecture. Recent work has shown that endometrial aging is accompanied by loss of H3K27 acetylation and progesterone receptor activity,^[8] while ovarian stimulation and progesterone supplementation can themselves reshape the reproductive tract microbiota.^[9] Thus, a reduction in beneficial *Lactobacillus* may participate in endometrial aging, but it may also reflect a tissue environment already altered by aging and hormonal change. Longitudinal sampling, hormone-controlled experiments, and preventive interventions initiated before overt endometrial dysfunction would provide stronger evidence for temporal and causal relationships.

The third major question concerns the molecular interface between EPS and Hippo-YAP signaling. The study convincingly demonstrates that YAP activity is necessary for much of the observed protective phenotype, but the upstream connection remains undefined. Hippo-YAP signaling is highly context-dependent in the uterus, and YAP1 together with WW domain-containing transcription regulator 1 (WWTR1) is required for normal pregnancy initiation in mice.^[10] Therefore, the biological relevance lies not simply in increasing or decreasing YAP activity, but in restoring its appropriate spatial and temporal regulation.

Li *et al.* observed that EPS treatment reduced oxidative stress,^[3] decreased large tumor suppressor kinase 1 (LATS1) and YAP phosphorylation, and promoted nuclear YAP accumulation. Several mechanisms could account for this relationship. EPS may interact with a cell-surface receptor, modify membrane-associated signaling, influence redox-sensitive components upstream of Hippo signaling, or alter cellular metabolism and mechanics. Establishing pathway hierarchy through receptor identification, LATS1/2 perturbation, reactive oxygen species (ROS) manipulation, and YAP rescue experiments would substantially strengthen the mechanistic model.

The chemical heterogeneity of bacterial EPS also deserves greater attention. EPS activity can vary according to molecular weight, monosaccharide composition, glycosidic linkage, branching pattern, and higher-order structure. Consequently, the biological effects observed with *L. gasseri*-derived EPS should not necessarily be generalized to all *Lactobacillus* EPS. Comparative structure-function analyses involving *L. gasseri*, *L. crispatus*, and other reproductive tract strains may help identify the structural features responsible for anti-senescent activity. Such work could ultimately permit development of standardized postbiotic molecules rather than biologically variable bacterial preparations.

Taken together, the study by Li *et al.* points toward a potentially important transition in reproductive microbiome research.^[3] The next stage should move beyond cataloguing microbial composition and attempting ecological replacement toward defining the specific microbial signals that alter endometrial biology. Establishing where these molecules act, how they reach the uterus, which host proteins they engage, and which structural features determine their activity will be critical. A mechanism-based postbiotic strategy may ultimately offer a more controllable and reproducible route for translating reproductive microbiome biology into therapies for age-related endometrial dysfunction.

DECLARATIONS

Acknowledgments

Not applicable.

Author contributions

Li D contributed solely to this Editorial.

Source of funding

None.

Ethical approval

Not applicable.

Informed consent

Not applicable.

Use of large language models, AI and machine learning tools

None declared.

Data availability statement

None declared.

Conflict of interest

Li D is the Editor-in-Chief of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of the editor and his

research group.

REFERENCES

1. Pathare ADS, Loid M, Saare M, *et al.* Endometrial receptivity in women of advanced age: an underrated factor in infertility. *Hum Reprod Update.* 2023;29:773–793.
2. Marti-Garcia D, Martinez-Martinez A, Sanz FJ, *et al.* Age-related uterine changes and its association with poor reproductive outcomes: a systematic review and meta-analysis. *Reprod Biol Endocrinol.* 2024;22:152.
3. Li M, Li S, Zheng D, *et al.* Lactobacillus gasseri postbiotics ameliorate age-related decline in endometrial receptivity. *Cell Host Microbe.* 2026;34(9):1779–1794.e6.
4. Moreno I, Codoñer FM, Vilella F, *et al.* Evidence that the endometrial microbiota has an effect on implantation success or failure. *Am J Obstet Gynecol.* 2016;215:684–703.
5. Moreno I, Garcia-Grau I, Perez-Villaroya D, *et al.* Endometrial microbiota composition is associated with reproductive outcome in infertile patients. *Microbiome.* 2022;10:1.
6. Haahr T, Freiesleben NLC, Jensen MB, *et al.* Efficacy of clindamycin and LACTIN-V for in vitro fertilization patients with vaginal dysbiosis: a randomised double-blind, placebo-controlled multicentre trial. *Nat Commun.* 2025;16:5166.
7. Molina NM, Sola-Leyva A, Haahr T, *et al.* Analysing endometrial microbiome: methodological considerations and recommendations for good practice. *Hum Reprod.* 2021;36:859–879.
8. Wang Y, Zhou P, Shan H, *et al.* Endometrial aging is accompanied by H3K27ac and PGR loss. *Nat Aging.* 2025;5:816–830.
9. Carosso A, Revelli A, Gennarelli G, *et al.* Controlled ovarian stimulation and progesterone supplementation affect vaginal and endometrial microbiota in IVF cycles: a pilot study. *J Assist Reprod Genet.* 2020;37:2315–2326.
10. Moldovan GE, Massri N, Vegter EL, *et al.* YAP1 and WWTR1 are required for murine pregnancy initiation. *Reproduction.* 2025;169.(1):e240355