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Vaginal and Endometrial Microbiome: The Next Frontier in Infertility and Gynecological Disorders

Dr. Sumana Talakokkula

DA, DGO, Fellowship in Gynae Laparoscopy (OBGYN), Apollo Hospital, Kondapur, Hyderabad, India

ABSTRACT

The female reproductive tract microbiome particularly Lactobacillus-dominant (LD) vaginal communities has emerged as a key determinant of reproductive outcomes. Evidence links vaginal dysbiosis and non-Lactobacillus–dominant endometrial communities with infertility, Recurrent Implantation Failure (RIF), and adverse In-vitro Fertilization (IVF) outcomes, while highlighting substantial methodological pitfalls in low-biomass endometrial sampling. This narrative, evidence-based review synthesizes contemporary data on (1) physiology and measurement of the vaginal/endometrial microbiome, (2) associations with infertility, RIF, recurrent pregnancy loss (RPL), endometriosis, and gynecologic pathology, (3) interventional options (antibiotics, probiotics, vaginal microbiota transplantation), and (4) a pragmatic clinical framework for ART programs. While LD vaginal states especially L. crispatus consistently correlate with improved implantation and live birth, the existence and clinical significance of a stable, distinct "endometrial microbiome" remains debated due to contamination risks. High-quality, contamination-controlled, prospective trials are urgently needed before routine microbiome-directed therapy is adopted in ART pathways.

***Corresponding author**

Dr. Sumana Talakokkula, DA, DGO, Fellowship in Gynae Laparoscopy (OBGYN), Apollo Hospital, Kondapur, Hyderabad, India.

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Background and Rationale

The lower genital tract microbiome is typically LD, producing lactic acid that maintains acidic pH, inhibits pathogens, modulates mucosal immunity, and supports epithelial barrier integrity. Non-LD states (e.g., Gardnerella, Atopobium, anaerobes) are linked to Bacterial Vaginosis (BV), inflammation, altered cervical mucus, and biofilm formation factors plausibly detrimental to gametes, embryos, and endometrium. In ART cohorts, LD vaginal communities and particularly L. crispatus associate with higher implantation and ongoing pregnancy rates.

Emerging studies propose that the endometrium may harbor a low-biomass microbial signal, with early reports linking non-LD endometrial profiles to poorer IVF outcomes. However, subsequent work emphasizes contamination control and questions whether many signals reflect carryover from the vagina/cervix or laboratory reagents. This controversy is central to interpretation and translation to practice.

Methods (Scope of Review)

We conducted a targeted review of peer-reviewed primary studies, systematic reviews, and consensus-style appraisals (2016–2025) focusing on: microbiome sampling/analytics, infertility and ART outcomes, RIF/RPL, endometriosis, and interventional studies (antibiotics, probiotics, VMT). Priority was given to contamination-controlled designs, prospective ART cohorts, and recent meta-analyses where available. Representative citations are provided throughout.

Measurement and Methodological Pitfalls

Sampling the Endometrium: A Low-Biomass Problem

- **Contamination Risk is the Dominant Bias:** Transcervical passage, device lumens, skin, air, kits ("kitome"), and PCR reagents may seed false positives.
- Best practices include double-lumen catheters, paired vaginal/cervical controls, reagent blanks, and quantitative assessments (qPCR) to benchmark biomass; sequencing negative controls must be processed identically.

Community State Types and Metrics

Vaginal "community state types" (CST I–V) map to dominance by L. crispatus (CST I), L. gasseri (II), L. iners (III), L. jensenii (V), or diverse anaerobes (IV). LD profiles especially L. crispatus associate with favorable ART outcomes. L. iners dominance can be transitional and less protective.

Associations with Reproductive Outcomes

IVF, Implantation, and Clinical Pregnancy

Multiple cohort studies, including recent machine-learning analyses integrating vaginal microbiome with clinical covariates, show that LD vaginal communities predict higher implantation/ongoing pregnancy rates; non-LD or higher diversity states associate with reduced success. Signals are strongest for L. crispatus.

Early work reported that non-LD endometrial profiles reduce implantation and live birth; however, subsequent contamination-

controlled studies observed that implantation can occur even with very low bacterial biomass, casting doubt on a strict requirement for endometrial LD status. The balance of evidence supports vaginal LD status as the robust biomarker; the endometrial signal remains uncertain.

Recurrent Implantation Failure and Chronic Endometritis (CE)

RIF often coexists with CE and dysbiosis. Studies describe altered endometrial communities and elevated inflammatory markers in RIF+CE; treatment of CE (antibiotics ± probiotics) may improve outcomes, though high-quality randomized data remain limited and definitions of CE vary.

Recurrent Pregnancy Loss (RPL)

Scoping reviews suggest plausible links between dysbiosis (vaginal and possibly endometrial) and early pregnancy loss, mediated by inflammation and impaired receptivity. Yet, low biomass, inconsistent diagnostic criteria, and confounding by CE limit causal inference.

Endometriosis and Gynecologic Pathology

Microbiome alterations and microbial metabolites (e.g., lactic acid isomers) are implicated in endometriosis pathophysiology (immune modulation, angiogenesis, pain sensitization), but findings are heterogeneous; causality is unproven. In endometrial cancer, several studies warn that prior reports may overestimate biomass without rigorous controls.

Mechanistic Pathways

- **pH and Metabolites:** Lactic acid (D/L) from lactobacilli lowers vaginal pH, inhibits pathogens, and modulates cytokines; bacteriocins and H_2O_2 may add protection.
- **Immune Crosstalk:** Dysbiosis may promote mucosal inflammation (elevated IL-1β, IL-6, TNF-α), impairing sperm motility, embryo development, and endometrial receptivity.
- **Biofilms and Proteases:** Gardnerella biofilms and sialidases degrade mucus barriers, aiding ascending infection and implantation failure risk.

Interventions: What Should Clinicians Do Now?

Screening and Optimization before ART

- **Who to Screen:** Prior BV, RIF/RPL, CE, prior culture-proven infections, symptomatic patients.
- **What to Use:** Vaginal NAAT panels or 16S rRNA sequencing (if available) to characterize CST; consider Nugent scoring when resources constrain. Evidence supports targeting a vaginal LD state prior to embryo transfer.

Antibiotics

Metronidazole or clindamycin for BV; doxycycline/azithromycin for CE, tailored to local resistance and pathogens. Overuse risks collateral damage to protective lactobacilli and resistance; combine with strategies to re-establish LD communities. High-quality ART-specific RCTs are still scarce.

Probiotics and Adjuncts

Oral/intravaginal Lactobacillus preparations (preferentially L. crispatus where available) show promise in restoring LD states and may improve ART outcomes, but strains, dosing, and timing vary across studies; robust, strain-resolved RCTs are needed.

Vaginal Microbiota Transplantation (VMT)

A landmark feasibility study demonstrated donor VMT can durably resolve intractable, recurrent BV nonresponsive to antibiotics establishing proof-of-concept for microbiome replacement therapies. Multiple trials are underway; standardization, donor screening, and long-term safety frameworks are essential before ART-specific application.

Practice Pearl: Optimize the vaginal milieu first. Treat symptomatic dysbiosis/CE, then (re)check vaginal CST shortly before embryo transfer. Reserve endometrial sampling for research protocols or well-defined CE evaluation with contamination controls [1-7].

The Endometrial Microbiome: Signal or Noise?

- **Pro-signal:** Early IVF cohorts reported that non-LD endometrial profiles correlated with lower implantation/ongoing pregnancy; some recent datasets echo this association.
- **Skepticism:** Contamination-controlled studies show successful implantation despite negligible endometrial bacterial biomass, challenging the concept of a robust, stable "core endometrial microbiome." Methodology likely explains divergent conclusions.
- **Implication:** Until standardized, contamination-controlled protocols and prospective validation exist, endometrial microbiome testing should not be routine in ART decision-making outside of research or carefully selected RIF/CE contexts.

Gynecological Disorders Beyond Infertility

- **Endometriosis:** Correlative shifts in cervical/vaginal/endometrial taxa and metabolomes have been observed, with hypothesized roles in lesion biology and pain, but intervention trials are lacking.
- **Endometrial Cancer:** Recent high-quality appraisals emphasize strict contamination controls and caution against over-interpretation of microbial signals.

A Pragmatic Clinical Framework (for ART Programs)

1. **Pre-ART Screening:** Take a targeted history (prior BV/CE/RIF/RPL), evaluate symptoms; consider vaginal CST assessment in at-risk or prior-failure patients.
2. **Correct Dysbiosis:** Treat BV/CE per guidelines; consider probiotic add-back to favor LD re-colonization; re-assess CST prior to transfer.
3. **Lifestyle and Co-factors:** Address douching, smoking, poorly controlled diabetes, and unnecessary intravaginal products which disrupt LD communities. (Consensus across reviews.)
4. Avoid routine endometrial microbiome tests until standardized; if performed (e.g., RIF+CE), use double-lumen sampling with matched controls and reagent blanks.
5. **Research/Innovation:** Consider well-designed trials on probiotic strain selection and timing, antibiotic-then-probiotic protocols, and controlled VMT in recalcitrant dysbiosis pre-ART.

Research Gaps and Agenda for 2025–2030

- Standardized endometrial sampling with rigorous negative controls and reporting checklists.
- Strain-resolved trials of L. crispatus and other candidate lactobacilli with ART endpoints (implantation, live birth).
- Mechanistic studies linking metabolites (lactate isomers, bacteriocins) and mucosal immune signatures to embryo-endometrium cross-talk.
- Microbiome-aware ART algorithms integrating CST with clinical/embryology features; early ML models are promising but require external validation.
- VMT safety/efficacy in ART candidates with recurrent, antibiotic-refractory dysbiosis, under robust donor screening and long-term follow-up.

Conclusion

Among microbiome signals relevant to reproduction, the vaginal microbiome is currently the most actionable: LD particularly L. crispatus is consistently associated with improved IVF outcomes, whereas dysbiosis correlates with implantation failure and possibly loss. The endometrial microbiome remains a frontier with active debate; credible progress hinges on contamination-controlled sampling and prospective validation. For now, ART programs should prioritize vaginal ecosystem optimization and address CE when present, while participating in high-quality trials that can transform associative insights into evidence-based care pathways.

Clinical Impact Statement

Optimizing the vaginal microbiome toward a Lactobacillus-dominant state is a practical, near-term lever to improve ART outcomes. Adoption of contamination-controlled endometrial microbiome protocols and participation in prospective trials will be crucial to move the field from correlation to causation and from promise to practice.

Author Contributions and Conflicts of Interest

The author conceptualized, curated literature, and drafted the manuscript. No conflicts of interest to declare.

References

1. Moreno I, Francisco M Codoner, Felipe Vilella, Diana Valbuena, Juan F Martinez Blanch, et al. (2016) Evidence that the Endometrial Microbiota has an Effect on Implantation Success or Failure. AJOG: PubMed, ajog.org, Europe IVF 215: 684-703.
2. Koedooder R, M Singer, S Schoenmakers, PHM Savelkoul, SA Morre, et al. (2019) The Vaginal Microbiome as a Predictor for Outcome of in Vitro Fertilization with or without Intracytoplasmic Sperm Injection: A Prospective Study. PMC 34: 1042-1054.
3. Ofri Bar, Stylianos Vagios, Omer Barkai, Joseph Elshirbini, Irene Souter, et al. (2025) Harnessing Vaginal Inflammation and Microbiome: A Machine Learning Model for Predicting IVF Success. NPJ Digital Medicine 11: 95.
4. Marco Reschini, Laura Benaglia, Ferruccio Ceriotti, Raffaella Borroni, Stefania Ferrari, et al. (2022) Endometrial Microbiome: Sampling, Assessment, and Possible Impact on Embryo Implantation. Nature Sci Rep 12.
5. Joshua Odendaal, Naomi Black, Phillip R Bennett, Jan Brosens, Siobhan Quenby, et al. (2024) The Endometrial Microbiota and Early Pregnancy Loss. Human Reproduction: Oxford Academic 39: 638-646.
6. Ahinoam Lev Sagie, Debra Goldman Wohl, Yotam Cohen, Mally Dori Bachash, Avner Leshem, et al. (2019) Vaginal Microbiome Transplantation in Women with Intractable Bacterial Vaginosis. Nat Med, PubMed, Nature, ClinicalTrials.gov 25: 1500-1504.
7. Anthi Papakonstantinou, Efthalia Moustakli, Anastasios Potiri, Athanasios Zikopoulos, Ermioni Tsarna, et al. (2025) Behind-the-Scenes Actors in Fertility: A Comprehensive Review of the Female Reproductive Tract Microbiome and Its Clinical Relevance. PMC, MDPI 5: 916.