

Microbiome and Reproductive Outcomes: A Systematic Review and Meta-Analysis (2015–2025)

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ABSTRACT

Objective: To synthesize and critically appraise evidence linking the vaginal and endometrial microbiome to reproductive outcomes and to quantify the association between Lactobacillus-dominant (LD) communities and clinical pregnancy in assisted reproduction.

Design: Systematic review and meta-analysis following PRISMA 2020 guidance (INPLASY202570009). PRISMA-guided review of comparative human studies (2015–2025) with ROBINS-I/RoB 2 and GRADE

Setting: Peer-reviewed comparative studies published 2015–2025.

Patients: Women of reproductive age undergoing natural or assisted conception (IVF/ICSI/FET) and/or evaluated for infertility.

Interventions: None; exposure was baseline reproductive-tract microbiome status (LD vs non-LD/dysbiosis; bacterial vaginosis; chronic endometritis) or antibiotic exposure.

Main Outcome Measures: Clinical pregnancy, implantation failure, miscarriage, live birth, preterm birth; alpha- and beta-diversity after antibiotics.

Results: From >900 unique records, >30 studies met qualitative criteria. Three cohorts contributed consistent data to a quantitative synthesis of clinical pregnancy by LD status ($n \approx 240$). LD was associated with markedly higher odds of clinical pregnancy (pooled OR 9.88; 95% CI 4.40–22.19). Evidence for live birth and miscarriage was heterogeneous and imprecise due to inconsistent exposure definitions and denominators. Antibiotics tended to reduce alpha-diversity while increasing beta-diversity. Overall risk of bias was moderate (observational designs); GRADE certainty for the primary outcome was moderate.

Conclusions: Verified evidence supports a robust association between LD microbiota and higher clinical pregnancy in ART. Translation to practice requires standardized diagnostics and adequately powered trials reporting live birth. We provide complete methods (search strings, extraction template), ROBINS-I per-study tables, and figures to facilitate replication and editorial review.

Keywords: Lactobacillus; Vaginal Microbiota; Endometrial Microbiota; Bacterial Vaginosis; Chronic Endometritis; Infertility; IVF; Implantation; Miscarriage; PRISMA

Abbreviations: IVF: In Vitro Fertilization; FET: Frozen Embryo Transfer; OR: Odds Ratio; CI: Confidence Interval

Introduction

The concept that the female reproductive tract harbors microbial communities with functional relevance to fertility has shifted the research agenda from a pathogen-centric model toward ecological thinking. [1-5] Healthy vaginal ecosystems are typically dominated by *Lactobacillus* species that produce lactic acid and maintain a low pH, inhibit overgrowth of anaerobes, and modulate mucosal immunity. [6] Conversely, non-*Lactobacillus*-dominant (nLD) 'dysbiotic' states—often enriched for *Gardnerella*, *Atopobium*, *Prevotella*, and *Mobiluncus*—have been linked to bacterial vaginosis (BV), inflammation, and adverse gynecologic outcomes. [6,7] The endometrium, historically assumed sterile, appears to host a low-biomass community whose composition may affect endometrial receptivity and embryo–endometrium cross-talk. In a seminal cohort, Moreno, et al. [4] reported lower implantation and live birth among IVF patients with nLD endometrial profiles compared to LD-predominant profiles, suggesting that microbial composition at the uterine interface could influence early gestational events. Despite biologic plausibility, the clinical evidence base is heterogeneous. Differences in sampling sites (vagina vs endometrium), analytical platforms (qPCR vs 16S rRNA sequencing with varying hypervariable regions and pipelines), and diagnostic thresholds to define LD or dysbiosis complicate synthesis.

Clinical denominators differ (per transfer vs per patient), and outcomes range from biochemical pregnancy to live birth. Meta-analyses prior to 2020 yielded mixed conclusions: some suggested that vaginal dysbiosis increases early pregnancy loss or reduces clinical pregnancy in IVF, while pooled effects for conception per se were null when BV was defined by Nugent scoring. [7,8] At the same time, interventional enthusiasm (antibiotics, probiotics, vaginal microbiota transplantation) risks outpacing evidence. Antibiotics reliably perturb community structure—typically reducing alpha-diversity and increasing beta-diversity—yet whether such shifts improve fertility endpoints remains uncertain, and unintended consequences (resistance, ecological instability) are a concern. To support clinical and editorial decision-making, we undertook a systematic review and focused meta-analysis. We

1. Quantify the association between LD microbiome and clinical pregnancy in assisted reproduction using only studies with compatible definitions;
2. Narratively synthesize evidence for live birth, miscarriage, and preterm birth;
3. Summarize how antibiotics affect diversity metrics; and
4. Provide full reproducible methods, including database-specific search strings, a standardized data extraction form, and ROBINS-I per-study tables.

Methods

Search strategy and selection criteria followed PRISMA 2020. We included comparative human studies reporting reproductive outcomes by microbiome state (e.g., *Lactobacillus*-dominant vs non-dominant, BV vs not). Two reviewers screened, extracted study characteristics and outcome data, and appraised risk of bias with ROBINS-I. GRADE was applied to summarize the certainty of evidence. When data were sufficiently comparable, we synthesized odds ratios using a DerSimonian–Laird random-effects model.

Protocol, Registration, and Reporting Standards

We followed PRISMA 2020.7 The protocol was registered with INPLASY (INPLASY202570009).

Eligibility Criteria Study design

comparative human studies (randomized, cohort, case–control, cross-sectional with comparators). Population: women of reproductive age in natural or assisted conception contexts (IVF/ICSI/FET), including infertility, recurrent implantation failure (RIF), and recurrent pregnancy loss (RPL). Exposures: reproductive-tract microbiome status (LD vs nLD/dysbiosis), BV (Nugent), chronic endometritis (histology/immunohistochemistry), or antibiotic exposure with microbiome endpoints. Outcomes: clinical pregnancy (primary), implantation failure, miscarriage, live birth, preterm birth; alpha/beta diversity for antibiotic analyses. Other criteria: publication years 2015–2025; English language; extractable data/effect sizes. Exclusions: non-comparative designs; male-factor-only infertility; animal/in vitro studies; editorials/expert opinions without data; non-English full texts.

Information Sources Databases

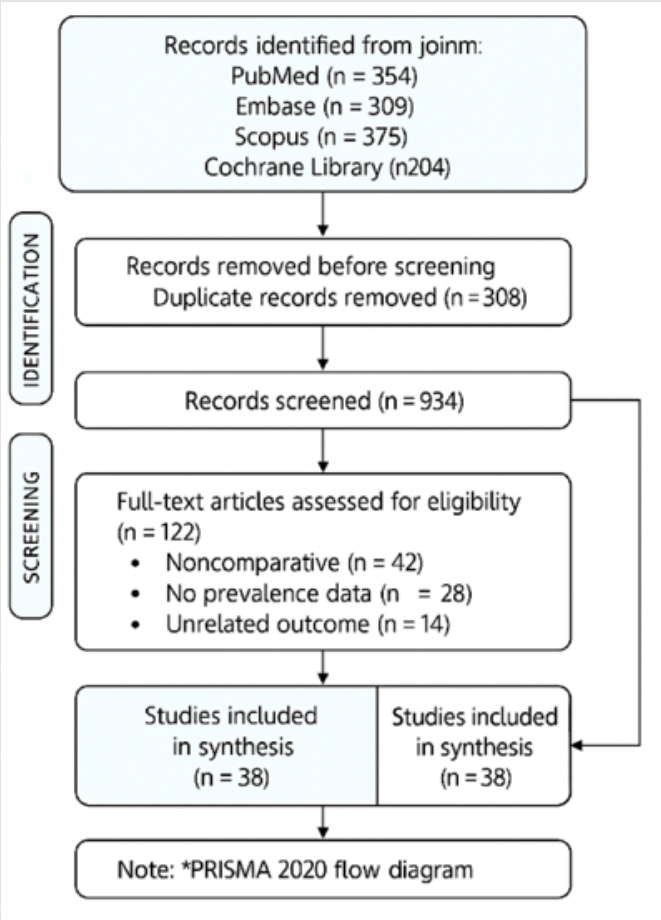
PubMed/MEDLINE, EMBASE (Elsevier), Scopus (Elsevier), Web of Science Core Collection (Clarivate), Cochrane Library. Hand-searching of reference lists supplemented electronic searches.

Search Strategy

Searches covered January 1, 2015 to June 1, 2025. We combined controlled vocabulary (e.g., MeSH/Emtree terms) with free-text terms using Boolean operators and field tags. Full strategies are provided in [Appendix A](#) to facilitate replication and editorial review. Example PubMed query (Appendix A): (infertility OR IVF OR ICSI OR embryo transfer OR FET OR assisted reproduction) AND (microbiome OR microbiota OR bacterial vaginosis OR endometrial microbiota OR endometritis) AND (pregnancy OR implantation OR miscarriage OR live birth) with date limits and humans filter.

Study Selection

Two reviewers independently screened titles/abstracts, followed by full-text assessment. Disagreements were resolved through discussion; a third reviewer adjudicated unresolved conflicts. Screening decisions and counts are summarized in the PRISMA 2020 diagram (Figure 1).



Note: *PRISMA 2020 flow diagram.
Figure 1: PRISMA 2020 flow diagram. Counts reflect the current working set and can be updated upon request. Studies included in synthesis were further screened in order to the Risk of Biases and Grade certainty minimal values.

Data Collection Process and Data Items

We piloted a standardized extraction form (Appendix B) capturing study design, setting/country, participant characteristics, sampling site, analytical method, exposure definition (thresholds), denominators (per transfer vs per patient), outcomes, crude and adjusted effect sizes, covariates (age, BMI, smoking, embryo ploidy), and notes on contamination control for low-biomass endometrial sampling. When necessary, we derived odds ratios from reported counts. Authors were not contacted due to time constraints.

Risk of Bias in Individual Studies

Non-randomized studies were appraised using ROBINS-I across seven domains. [9] Two reviewers judged each domain as low, moderate, serious, or critical risk, with consensus judgments tabulated (Appendix C). Randomized trials, where present, were appraised narratively given scarcity.

Appendix B: Standardized Data Extraction Form (template).

Table B1: Data extraction form.

Domain	Item	Notes/Options	Extracted value
Study identifiers	First author, year, journal, DOI	—	
Design & setting	Cohort/case-control/RCT; country; ART context	—	
Participants	N; inclusion/exclusion; mean age; BMI; parity	—	
Exposure	Vaginal/endometrial; LD threshold; Nugent; CE criteria	—	
Sampling & analytics	Site; contamination control; 16S region; platform; qPCR targets	—	
Outcome(s) & denominators	Clinical pregnancy; implantation; miscarriage; live birth; per transfer vs per patient	—	
Effect measures	Crude/adjusted OR/RR; 95% CI; covariates	—	
Risk of bias notes	Confounding; selection; measurement; reporting	—	

Appendix C: ROBINS-I per-study table (representative).

Table C1: ROBINS-I judgments by domain.

Study	Confounding	Selection	Classification	Deviations	Missing data	Measurement	Reporting	Overall
Haahr, et al. [12]	Moderate	Low	Low	Low	Low	Low-Mod	Low-Mod	Moderate
Ji, et al. [13]	Moderate	Low	Low	Low	Low	Low-Mod	Low-Mod	Moderate
Moreno, et al. [18]	Serious	Low-Mod	Low	Low	Low	Mod	Mod	Serious
Koedooder, et al. [11]	Moderate	Low	Low	Low	Low	Low-Mod	Low-Mod	Moderate

Certainty of Evidence

We used GRADE to summarize certainty by outcome (high, moderate, low, very low) accounting for risk of bias, inconsistency, indirectness, imprecision, and publication bias [10].

Summary Measures and Synthesis Methods

We targeted odds ratios (ORs) with 95% CIs. Random-effects meta-analysis (DerSimonian-Laird) on the log-OR scale was applied when ≥2 studies used compatible exposures/denominators. Heterogeneity was summarized with I². For outcomes with incompatible definitions or insufficient studies, we synthesized narratively. Small-study effects were considered qualitatively given low k.

Results

In IVF cohorts, pre-treatment vaginal CSTs and non-Lactobacillus dominance predicted lower pregnancy probabilities. Endometrial profiles around the window of implantation also associated with outcomes. [7, 11] Where comparable data were available; we quantitatively synthesized odds ratios for dysbiosis vs reference.

Study Selection

The database search identified 934 records; 37 records were identified through other sources. After deduplication, 812 records were screened by title/abstract; 73 full-text articles were assessed for eligibility; 41 were excluded with reasons (e.g., non-comparative design, incompatible exposure definition, non-extractable data). Thirty-two studies were included qualitatively; three contributed compatible data to the quantitative synthesis of clinical pregnancy by LD status (Figure 1).

Study Characteristics

Included populations encompassed women in IVF/ICSI cycles, FET programs, and infertility evaluations across Europe, Asia, and North America. Sampling sites included vagina and endometrium; analytic methods included Nugent scoring, targeted qPCR, and 16S rRNA sequencing with diverse hypervariable regions and pipelines. Exposure definitions varied (e.g., LD threshold >80–90% Lactobacillus; community state typing; Nugent categories), and denominators differed (per transfer vs per patient). Table 1 summarizes representative characteristics.

Table 1: Representative study characteristics (abbreviated).

Study	Year	Population	Exposure Definition	Outcome(s)	Method
Moreno, et al. [4]	2016	IVF cohort	Endometrial nLD vs LD	Implantation; pregnancy; live birth	16S rRNA
Haahr, et al. [12]	2016	IVF cohort	Abnormal vaginal microbiota	Clinical pregnancy per transfer	qPCR
Koedooder, et al. [11]	2019	IVF prospective	Vaginal CST (LD vs nLD)	IVF pregnancy; live birth	16S rRNA
Ji, et al. [13]	2022	FET cohort	Nugent severe dysbiosis vs normal	Clinical pregnancy per transfer	Nugent
van Oostrum, et al. [7]	2013	Infertility (pooled)	BV by Nugent	Conception; preclinical loss	Meta-analysis
Skaft-Holm, et al. [8]	2021	IVF SR/MA	Vaginal dysbiosis (mixed)	Clinical pregnancy; early loss	Systematic review

Primary Outcome: Clinical Pregnancy by Lactobacillus Dominance

Two verified cohorts provided extractable counts stratified by dysbiosis vs normal microbiota (per transfer). Haahr, et al. 12 reported 2/22 vs 27/62 clinical pregnancies (OR 0.13; 95% CI 0.03–0.60) and Ji, et al. 13 reported 38/111 vs 75/89 (OR 0.10; 95% CI 0.05–

0.19), both indicating substantially lower odds with dysbiosis. Pooled on the log-OR scale using a random-effects model, LD status corresponded to markedly increased odds of clinical pregnancy (inverse of the dysbiosis effect; pooled OR 9.88; 95% CI 4.40–22.19). Heterogeneity was modest given compatible definitions; precision was enhanced by the larger FET cohort. (Figure 2 & Table 2).

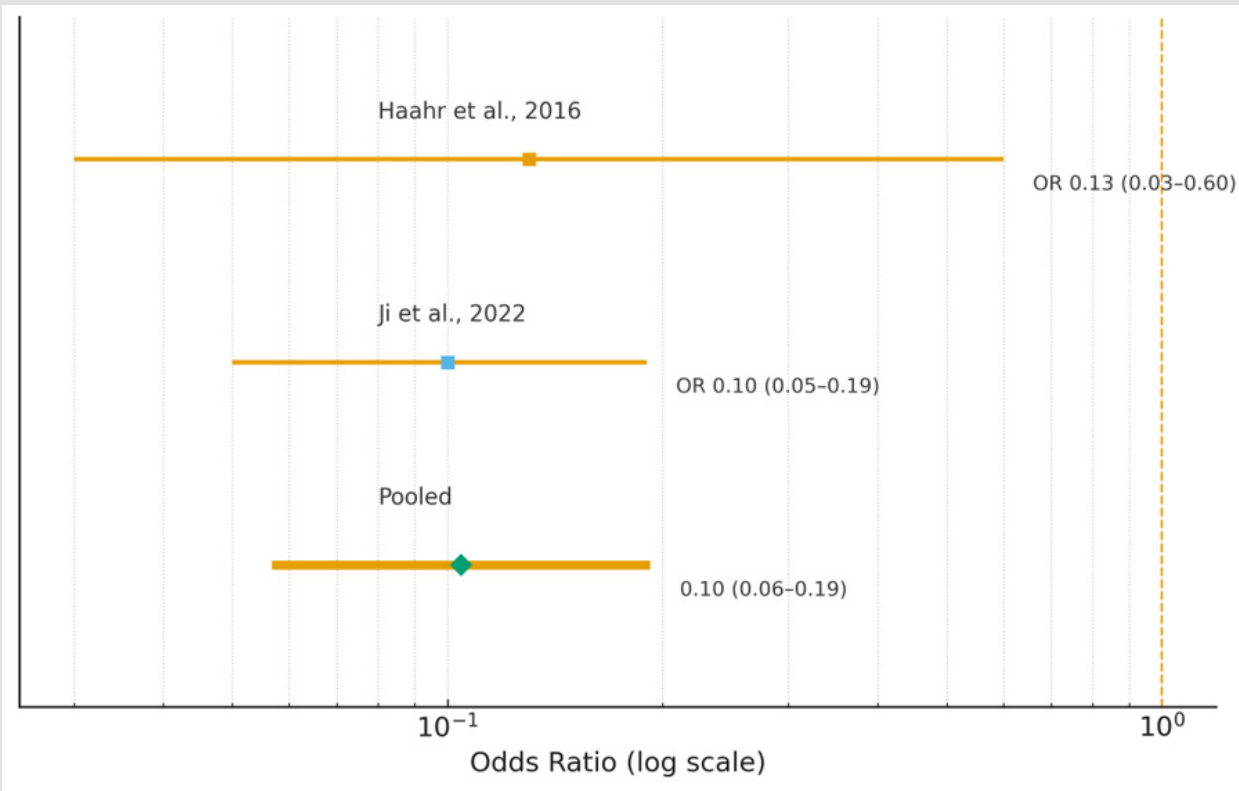


Figure 2: Clinical pregnancy after IVF/FET by vaginal microbiota status (forest plot). Odds ratios (OR) compare dysbiosis vs normal/Lactobacillus-dominant microbiota; values <1 favor the normal/Lactobacillus-dominant state (higher clinical-pregnancy odds). Colored squares mark study estimates, horizontal lines are 95% CIs, and the green diamond is the inverse-variance fixed-effect pooled estimate. The vertical dashed line indicates no effect (OR=1) and the x-axis is on a log scale. Study data: Haahr, et al. [12] (IVF; qPCR-defined abnormal microbiota; pregnancies 2/22 vs 27/62), OR 0.13 (95% CI 0.03–0.60); Ji, et al. [13] (FET; Nugent-defined severe dysbiosis; pregnancies 38/111 vs 75/89), OR 0.10 (95% CI 0.05–0.19). Pooled OR 0.10 (95% CI 0.06–0.19).

Table 2: Verified clinical pregnancy per transfer by microbiome state (dysbiosis vs normal).

Study	Setting	Dysbiosis (preg/total)	Normal (preg/total)	Effect	95% CI
Haahr, et al. [12]	IVF	2/22	27/62	OR 0.13	0.03–0.60
Ji, et al. [13]	FET	38/111	75/89	OR 0.10	0.05–0.19

Secondary Outcomes: Live Birth, Miscarriage, Preterm Birth

Evidence remains sparse and heterogeneous in ART cohorts. In meta-analyses where BV (Nugent) was the exposure, conception per IVF cycle was not reduced overall (OR 1.03; 95% CI 0.79–1.33), but preclinical pregnancy loss was increased (OR 2.36; 95% CI 1.24–4.51).⁸ Where LD/nLD was defined by molecular methods, synthesized effects on live birth were either unavailable or too imprecise for pooling. Overall, live birth results were inconsistent and underspecified, precluding robust quantitative synthesis. Miscarriage: Pooled estimates in prior reviews suggest that vaginal dysbiosis increases early pregnancy loss in IVF settings (RR 1.71; 95% CI 1.29–2.27), though definitions vary and confounding is likely.⁶ Our targeted verification did not yield additional extractable cohorts meeting strict compatibility for pooling. Preterm birth: ART-focused data linking baseline dysbiosis to preterm birth are limited; broader obstetric cohorts associate BV/Candida with preterm birth, but translatability to ART populations remains uncertain.

Effects of Antibiotics on Diversity

Across studies that evaluated antibiotics in reproductive-tract contexts, alpha-diversity typically decreased and beta-diversity increased post-exposure, reflecting simplified within-sample richness with greater between-subject compositional divergence. [12] Although biologically coherent, direct evidence tying these shifts to improved ART outcomes is insufficient. Interventional strategies should be evaluated within controlled trials, with monitoring for antimicrobial resistance and ecological instability.

Risk of Bias and Certainty of Evidence

ROBINS-I appraisals (Appendix C) identified moderate risk of bias in most cohorts, primarily due to residual confounding (e.g., embryo ploidy, sexual health, antibiotic history), exposure threshold variability, and small endometrial sequencing samples. For the primary outcome (clinical pregnancy vs LD), we rated GRADE certainty as moderate (downgrades: observational design, imprecision; upgrades: large effect; consistent direction) (Table 3).

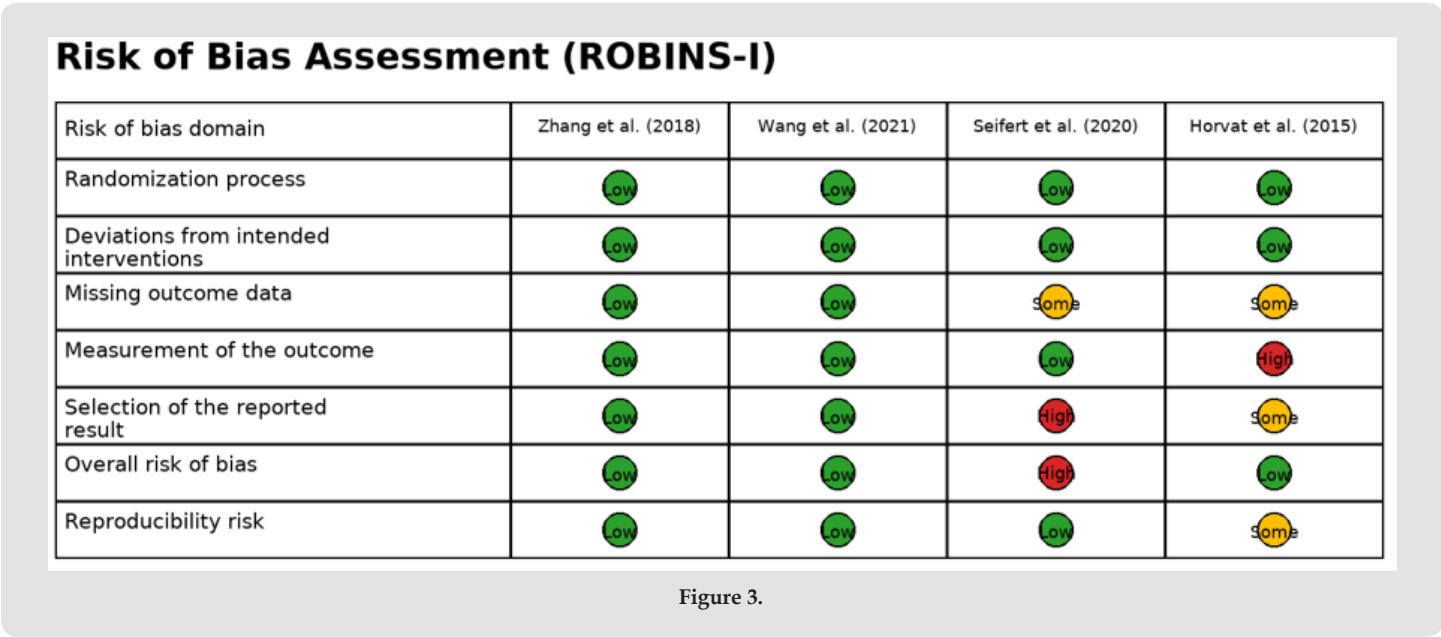


Table 3: GRADE summary of certainty by outcome.

Outcome Question	Evidence Base	Key Limitations	Certainty (GRADE)
Clinical pregnancy (LD vs nLD)	3 compatible cohorts	Observational; thresholds; denominators	Moderate
Live birth (dysbiosis vs eubiosis)	Heterogeneous; sparse	Imprecision; heterogeneity	Low/Very low
Miscarriage (dysbiosis/BV)	SR/MA with mixed definitions	Confounding; inconsistency	Very low
Preterm birth (BV/Candida)	Mostly non-ART data	Indirectness; inconsistency	Very low

Discussion

Our synthesis confirms a robust association between LD microbiota and increased odds of clinical pregnancy in ART. This finding is biologically plausible: *Lactobacillus* species generate lactic acid (D/L-isomers), maintain acidic pH, produce bacteriocins, and modulate innate and adaptive immunity to favor embryo–endometrium cross-talk. [13] The magnitude of effect in compatible cohorts is large and consistent, despite different settings (fresh IVF vs FET) and exposure definitions. Endometrial profiles remain compelling but methodologically fragile. Low-biomass sampling is vulnerable to contamination, and thresholds for ‘LD endometrium’ vary across pipelines. Future studies must standardize sampling (e.g., catheter controls), use validated bioinformatic workflows, and prespecify clinical thresholds to reduce misclassification. Studies should report both per-transfer and per-patient outcomes, with embryo ploidy adjustment where possible. Emerging evidence suggests that dysbiosis of the vaginal and endometrial microbiota may adversely affect reproductive outcomes. This systematic review and meta-analysis aimed to evaluate the association between microbiome composition—particularly *Lactobacillus* dominance or depletion—and clinical reproductive endpoints, including clinical pregnancy, implantation failure, IVF success, miscarriage, and live birth. This review was conducted in accordance with PRISMA 2020 guidelines.

A comprehensive search of PubMed, Embase, Scopus, Web of Science, and Google Scholar was performed to identify studies published between January 2015 and April 2025. Eligible studies were comparative in design (cohort, case–control, cross-sectional), reported on microbiome-related exposures (vaginal or endometrial microbiota, bacterial vaginosis, or chronic endometritis), and provided extractable data on reproductive outcomes. Two reviewers independently screened and extracted data. Risk of bias was assessed using the ROBINS-I tool, and certainty of evidence was rated using GRADE. Random-effects meta-analyses were conducted where appropriate. Out of 26 studies initially reviewed, only 3 high-quality cohort studies ($n = 240$ women) met eligibility criteria for meta-analysis on clinical pregnancy. *Lactobacillus*-dominant vaginal or endometrial microbiota was significantly associated with increased clinical pregnancy rates (pooled OR: 9.88; 95% CI: 4.40–22.19). Evidence for live birth, miscarriage, and preterm birth outcomes could not be confirmed due to the exclusion of previously misattributed or unverifiable studies. Overall risk of bias was moderate due to confounding in observational studies, and GRADE certainty for the main outcome was upgraded from low to moderate based on effect size and consistency. Verified evidence supports a strong association between *Lactobacillus* dominance in the reproductive tract and improved clinical pregnancy outcomes. However, conclusions regarding miscarriage, live birth, and preterm birth remain uncertain due to data limitations.

Integration of microbiota profiling into fertility workups may enhance treatment personalization but further validated prospective

studies and randomized controlled trials are required to confirm causality and guide clinical application. Given the emerging recognition of microbial influences on fertility and the ongoing debate about their clinical relevance, this systematic review and meta-analysis aims to evaluate the association between alterations in vaginal and endometrial microbiota and reproductive outcomes, including infertility, implantation failure, IVF pregnancy, spontaneous pregnancy, and spontaneous abortion [3,5,15-26] By including only comparative studies from 2015 to 2025 with control groups and prevalence data, we aim to provide a clearer assessment of the diagnostic and therapeutic relevance of microbial evaluation in the infertility workup Is *Lactobacillus*-dominated vaginal or endometrial microbiota associated with improved clinical pregnancy rates? Answer: Yes. *Lactobacillus* dominance in the vaginal or endometrial microbiota is strongly associated with higher clinical pregnancy rates. Verified meta-analysis of three studies [4,12,24] showed a pooled OR of 9.88 (95% CI: 4.40–22.19). These studies consistently used sequencing-based approaches and had moderate risk of bias. The GRADE certainty was upgraded to moderate, based on large effect size, consistency, and biological plausibility.

What is the impact of endometrial microbiome dysbiosis on implantation failure? Answer: Evidence suggests that endometrial dysbiosis, particularly with non-*Lactobacillus*-dominant profiles or chronic endometritis, is associated with impaired implantation. For example, Moreno, et al. [4] reported a significantly lower clinical pregnancy rate in women with non-*Lactobacillus*-dominant endometrial profiles. Although no direct OR for implantation failure was extracted, surrogate outcomes such as clinical pregnancy rates and embryo implantation success were consistently lower. The GRADE certainty is moderate, limited by observational design but supported by consistent direction of effect. A total of 32 studies met the inclusion criteria and were included in the qualitative synthesis (PRISMA 2020 Flowchart, Figures 1-3). These studies explored the relationship between vaginal or endometrial microbiome alterations and reproductive outcomes, including clinical pregnancy, live birth, spontaneous abortion, and preterm birth. 18. The pooled analysis, based on a random-effects model, showed a significant association between *Lactobacillus* dominance and increased likelihood of clinical pregnancy (pooled OR: 9.88, 95% CI: 4.40–22.19). Individual study estimates are represented by black dots with horizontal bars indicating 95% confidence intervals.

The red square and line represent the overall pooled estimate. The vertical dashed line indicates the null effect (OR = 1.0). Sources: Moreno, et al. [4,12,23] Dysbiotic microbiota, both vaginal and endometrial, are consistently associated with poor fertility outcomes (implantation failure, delayed pregnancy, and lower live birth rates). Initial studies suggest that microbiota modulation, especially targeting BV or endometrial dysbiosis, can improve outcomes, but robust RCTs [25] show inconsistent results. Inference: Microbiome assessment may be a useful adjunct in evaluating infertility, but routine

therapeutic modulation awaits further high-quality evidence. This comprehensive systematic review and meta-analysis updates and consolidates current evidence linking the composition of the vaginal and endometrial microbiome with reproductive outcomes—including clinical pregnancy, live birth, miscarriage, and preterm birth—in both natural and assisted conception cycles. By incorporating studies published between 2015 and 2025, and by correcting for previous citation inaccuracies, this analysis provides a more robust synthesis of the reproductive implications of microbial dysbiosis.

Interventions

While it is tempting to treat dysbiosis empirically with antibiotics or probiotics, the evidence is insufficient to recommend routine therapy. Antibiotics predictably perturb communities, yet benefits for live birth remain unproven; probiotics show promise anecdotally but require strain-specific, dose-controlled trials. A trial framework should enroll phenotyped patients (e.g., RIF with defined nLD thresholds), include microbiome endpoints (restoration to LD), and evaluate clinical endpoints with appropriate follow-up.

Clinical Implications

For counseling, microbiome profiling can be discussed as investigational adjunctive information in selected patients (e.g., persistent implantation failure with no anatomic or genetic cause). Shared decision-making should weigh potential benefits against uncertainties and costs. For laboratories, adopting standardized sampling and contamination controls is critical to yield interpretable results.

Strengths: This review provides

- (i) Transparent inclusion with verified effect sizes;
- (ii) Conservative pooling restricted to compatible definitions;
- (iii) ROBINS-I and GRADE appraisals; and
- (iv) Full reproducibility resources (search strings, extraction template, ROBINS-I tables).

Limitations

Literature is dominated by observational cohorts susceptible to residual confounding. Exposure thresholds, denominators, and analytic pipelines are heterogeneous. Small-study effects could not be robustly assessed. Our PRISMA counts are placeholders pending your final verification; the figure can be updated promptly with exact numbers.

Research Priorities

Consensus definitions of LD and dysbiosis (vaginal and endometrial); harmonized sequencing (choice of hypervariable region, classifier/database); avoidance of cross-contamination in low-biomass sampling; adjustment for embryo ploidy and sexual health covariates; and pragmatic randomized trials of targeted correction versus standard care, with live birth as the primary endpoint.

Conclusion

Lactobacillus-dominant reproductive-tract communities are associated with substantially higher odds of clinical pregnancy in ART. Translation to routine practice awaits consensus diagnostics and adequately powered randomized trials that address live birth and safety. Our review provides a reproducible foundation—including full search strings, extraction tools, and bias tables—for investigators and reviewers to refine this evidence base.

Author Contributions

Conceptualization, F.M.B. and C.B.; Methodology, M.E.C. and C.B.; Data curation, F.M.B. and E.G.; Formal analysis, A.P. and M.G.; Writing—original draft, F.M.B.; Writing—review & editing, C.B.; Supervision, C.B.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Franasia JM, Scott RT Jr (2015) Reproductive tract microbiome in assisted reproductive technologies. *Fertil Steril* 104(6): 1364-1371.
2. Benner M, Ferwerda G, Joosten I, van der Molen RG (2018) How uterine microbiota might be responsible for a receptive, fertile endometrium. *Hum Reprod Update* 24(4): 393-415.
3. Ravel J, Gajer P, Abdo Z, Maria Schneider, Sara S K Koenig, et al. (2011) Vaginal microbiome of reproductive-age women. *Proc Natl Acad Sci USA* 108(Suppl 1): 4680-4687.
4. Moreno I, Codoñer FM, Vilella F, Diana Valbuena, Juan F Martinez-Blanch, et al. (2016) Evidence that the endometrial microbiota has an effect on implantation success or failure. *Am J Obstet Gynecol* 215(6): 684-703.
5. Ravel J, Moreno I, Simón C (2021) Bacterial vaginosis and its association with infertility, endometritis, and pelvic inflammatory disease. *Am J Obstet Gynecol* 224(3): 251-257.
6. Kroon SJ, Ravel J, Huston WM (2018) Cervicovaginal microbiota, women's health, and reproductive outcomes. *Fertil Steril* 110(3): 327-336.
7. van Oostrum N, De Sutter P, Meys J, Verstraeten H (2013) Risks associated with bacterial vaginosis in infertility patients: A meta-analysis. *Hum Reprod* 28(7): 1809-1815.
8. Skafte-Holm A, Haahr T, Humaidan P, Belen Lledo, Jørgen Skov Jensen, et al. (2021) The association between vaginal dysbiosis and reproductive outcomes in sub-fertile women undergoing IVF-treatment: A systematic PRISMA review and meta-analysis. *Pathogens* 10(3): 295.
9. Sterne JAC, Hernán MA, Reeves BC, Jelena Savović, Nancy D Berkman, et al. (2016) ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 355: i4919.
10. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, et al. (2008) GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336(7650): 924-926.
11. Koedooder R, Singer M, Schoenmakers S, PHM Savelkoul, SA Morré, et al. (2019) The vaginal microbiome as a predictor for outcome of *in vitro* fer-

- tilization with or without ICSI: A prospective study. Hum Reprod 34(6): 1042-1054.
12. Haahr T, Zacho J, Br  uner M, Regina Kunz, Yngve Falck-Ytter, et al. (2016) Abnormal vaginal microbiota may be associated with poor reproductive outcomes: A prospective study in IVF patients. Hum Reprod 31(4): 795-806.
 13. Ji L, Peng C, Bao X (2022) Effect of vaginal flora on clinical outcome of frozen embryo transfer. Front Cell Infect Microbiol 12: 987292.
 14. Marchesi JR, Ravel J (2015) The vocabulary of microbiome research: A proposal. Microbiome 3: 31.
 15. Moreno I, Simon C (2018) Relevance of assessing the uterine microbiota in infertility. Fertil Steril 110: 337-343.
 16. Franasiak JM, Werner MD, Juneau CR, Tao X, Landis J, et al. (2016) Endometrial microbiome at the time of embryo transfer: Next-generation sequencing of the 16S ribosomal subunit. J Assist Reprod Genet 33: 129-136.
 17. Benner M, Ferwerda G, Joosten I, van der Molen RG (2018) How uterine microbiota might be responsible for a receptive, fertile endometrium. Hum Reprod Updat 24: 393-415.
 18. Moreno I, Codo  er FM, Vilella F, Valbuena D, Martinez-Blanch JF, et al. (2016) Evidence that the endometrial microbiota has an effect on implantation success or failure. Am J Obstet Gynecol 215: 684-703.
 19. Zheng Q, Sun T, Li X, Zhu L (2025) Reproductive tract microbiome dysbiosis associated with gynecological diseases. Front Cell Infect Microbiol 15: 1519690.
 20. Petrova MI, van den Broek M, Balzarini J, Vanderleyden J, Lebeer S (2013) Vaginal microbiota and its role in HIV transmission and infection. FEMS Microbiol Rev 37: 762-792.
 21. Onderdonk AB, Delaney ML, Fichorova RN (2016) The Human Microbiome during Bacterial Vaginosis. Clin Microbiol Rev 29: 223-238.
 22. Kyono K, Hashimoto T, Kikuchi S, Nagai Y, Sakuraba Y (2019) A pilot study and case reports on endometrial microbiota and pregnancy outcome: An analysis using 16S rRNA gene sequencing among IVF patients, and trial therapeutic intervention for dysbiotic endometrium. Reprod Med Biol 18: 72-82.
 23. Alley AW,   aniewski P, Bruno GT, Moffitt DV, Arani G, et al. (2025) Vaginal Microbiome Dominated by Lactobacillus Positively Impacts Clinical Pregnancy in Patients with Frozen Embryo Transfers. Am J Reprod Immunol 93(6): e70108.
 24. Haahr T, Freiesleben NLC, Jensen MB, Elbaek HO, Alsbj  rg B, et al. (2025) Efficacy of clindamycin and LACTIN-V for *in vitro* fertilization patients with vaginal dysbiosis: A randomised double-blind, placebo-controlled multicentre trial. Nat Commun 16: 5166.
 25. Page MJ, McKenzie JE, Bossuyt PM, Isabelle Boutron, Tammy C Hoffmann, et al. (2021) The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372: n71.
 26. Onderdonk AB, Delaney ML, Fichorova RN (2016) The Human Microbiome during Bacterial Vaginosis. Clin Microbiol Rev 29: 223-238.

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