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Endometrial Microbiome Dysbiosis and IVF Outcomes: From Association to Clinical Utility: A Narrative Literature Review

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Abstract

Background: The female reproductive tract, once assumed to be sterile above the cervix, is now recognised to harbour a distinct, low-biomass microbial community. Molecular studies over the past decade have proposed that the composition of this endometrial microbiota particularly the relative dominance of Lactobacillus species is associated with embryo implantation and pregnancy outcomes following in vitro fertilisation (IVF). However, the field remains divided between researchers who view endometrial dysbiosis as a clinically actionable biomarker and others who question whether a genuine endometrial microbiome exists at all, given the confounding effect of low-biomass contamination.

Objective: This review synthesises the current evidence on endometrial microbiome dysbiosis and IVF outcomes, tracing the field from its foundational association studies to the emerging, but still contested, question of clinical utility.

Methods: A narrative synthesis of peer-reviewed literature (2016–2026) was performed, drawing on studies indexed in PubMed, Scopus and related repositories that examined endometrial or genital-tract microbiota composition, chronic endometritis, and reproductive outcomes in women undergoing IVF or intracytoplasmic sperm injection (ICSI).

Results: A Lactobacillus-dominated endometrial microbiota (generally defined as >90% relative abundance) is repeatedly associated with higher implantation, clinical pregnancy and live birth rates compared with a non-Lactobacillus-dominated, dysbiotic profile. Dysbiosis correlates with local pro-inflammatory cytokine activity and frequently co-occurs with, but is not identical to, histologically defined chronic endometritis. Commercial next-generation-sequencing panels (e.g. EMMA/ALICE) and small prospective cohorts report improved pregnancy rates after antibiotic and/or probiotic correction of dysbiosis, yet larger and better-controlled studies have failed to reproduce a benefit, and methodological concerns, sampling contamination, absence of validated normative thresholds, and heterogeneous outcome definitions, temper confidence in causality.

Conclusion: Endometrial dysbiosis is a reproducible association with adverse IVF outcomes, but current evidence does not yet establish it as a validated, actionable clinical biomarker. Routine endometrial microbiome testing and empirical treatment are not yet justified outside of research settings or, arguably, recurrent implantation failure (RIF) work-ups; adequately powered randomised controlled trials (RCTs) with standardised sequencing methodology and contamination controls are required before the transition from association to clinical utility can be considered complete.

Keywords: endometrial microbiome; dysbiosis; in vitro fertilisation; implantation failure; chronic endometritis; Lactobacillus; reproductive outcome

Introduction

Infertility affects a substantial proportion of reproductive-age couples worldwide, and assisted reproductive technologies, particularly IVF, remain the mainstay of treatment for many aetiologies (Cox et al., 2022). Despite continuous refinement of ovarian stimulation protocols, laboratory culture systems and embryo selection tools, live birth rates per embryo transfer have plateaued at well below 50% in most programmes, focusing renewed attention on the receiving environment of the embryo, the endometrium, rather than the embryo itself. For much of the twentieth century, the uterine cavity was considered sterile in health, with bacterial presence equated with infection. This paradigm has been challenged by culture-independent, sequencing-based studies demonstrating that the endometrium, like the gut and vagina, hosts a distinct, low-biomass microbial community that differs in composition from the vaginal microbiota (Moreno et al., 2016). This community appears to be dominated in fertile, reproductively healthy women by Lactobacillus species, mirroring the protective, lactic-acid-producing ecology long described in the vagina. Deviation from this Lactobacillus-dominated state — termed endometrial dysbiosis — has been proposed as

a novel, modifiable factor in implantation failure, recurrent pregnancy loss and IVF failure.

The clinical appeal of this hypothesis is considerable: unlike embryo aneuploidy or age-related oocyte decline, a dysbiotic endometrial microbiome is, in theory, correctable with antibiotics or probiotics, offering a tractable target for improving IVF success. This has driven the rapid commercialisation of endometrial microbiome sequencing panels, most notably the Endometrial Microbiome Metagenomic Analysis (EMMA) and Analysis of Infectious Chronic Endometritis (ALICE) tests, which are now marketed directly to IVF patients, particularly those with recurrent implantation failure (RIF) (Moreno et al., 2022). However, the endometrial microbiome field is also one of the more contested areas of reproductive microbiology. Because the endometrial bacterial load is extremely low, close to or indistinguishable from background reagent and extraction-kit contamination (the 'kitome'), some investigators using stringent contamination controls and transabdominal sampling have questioned whether a genuine resident endometrial microbiota exists at all, and have suggested that earlier Lactobacillus-dominance findings may reflect vaginal or cervical contamination during transcervical sampling (Winters et al., 2019). This tension between a clinically attractive, commercially available biomarker and a still-unsettled basic science question — motivates the present review.

This review aims to: (i) summarise the evidence linking endometrial microbiome composition to IVF outcomes; (ii) examine the relationship between endometrial dysbiosis and the overlapping but distinct entity of chronic endometritis; (iii) appraise the evidence for microbiota-targeted interventions (antibiotics, probiotics) in improving reproductive outcomes; and (iv) critically evaluate whether the field has moved convincingly from association to genuine clinical utility.

Methods

This is a narrative, rather than systematic, literature review, reflecting the aim of providing a critical, integrative synthesis across a methodologically heterogeneous and rapidly evolving field rather than a quantitative pooled estimate of effect.

Search strategy

A structured literature search was conducted across PubMed/MEDLINE, Scopus and related full-text repositories for articles published between 2016 (the year of the first major endometrial microbiota–IVF outcome study) and 2026. Search terms combined the concepts of 'endometrial microbiome' OR 'endometrial microbiota' OR 'uterine microbiome' with 'dysbiosis', 'in vitro fertilisation' OR 'IVF' OR 'assisted reproduction', 'implantation', 'chronic endometritis', and 'pregnancy outcome' OR 'live birth'. Reference lists of identified systematic reviews and meta-analyses were hand-searched for additional primary studies.

Eligibility criteria

Original research articles (prospective and retrospective cohorts, case-control studies, pilot studies and randomised trials), together with systematic reviews, meta-analyses and narrative reviews, were eligible if they reported endometrial or genital-tract microbiota composition (by culture, quantitative PCR or next-generation sequencing) in relation to IVF/ICSI outcomes, chronic endometritis, or microbiota-targeted therapeutic interventions in infertile women. Studies restricted purely to vaginal microbiota without an endometrial or intrauterine component were included selectively where they provided relevant mechanistic or ascending-infection context.

Data synthesis

Given the marked heterogeneity in sampling technique (transcervical catheter, endometrial biopsy, hysterectomy specimen), sequencing methodology (16S rRNA gene sequencing, shotgun metagenomics, culturomics, quantitative PCR), dysbiosis definitions (most commonly <90% relative Lactobacillus abundance, but not uniformly applied), and outcome definitions (implantation rate, clinical pregnancy rate, ongoing pregnancy rate, live birth rate), a formal meta-analysis was not undertaken for the review as a whole; where meta-analytic data already exist in the literature (e.g. for vaginal dysbiosis and IVF outcome), these pooled estimates are reported and cited directly.

Results

A total of 14 studies and reviews forming the core evidence base of this review are summarised in Table 1, spanning foundational cohort studies, diagnostic comparison studies, systematic reviews/meta-analyses, and mechanistic/interventional work published between 2011 and 2025. Detailed narrative synthesis by theme follows in Sections 3.1-3.6.

Table 1: Characteristics of included studies

Study (Author, Year)	Design	Population / Sample	Microbiota / Diagnostic Method	Key Finding Relevant to IVF Outcome
Moreno et al. (2016)	Prospective cohort	35 infertile women undergoing IVF (41 endometrial fluid samples)	16S pyrosequencing of paired endometrial fluid & vaginal aspirates	Non-Lactobacillus-dominated (NLD) endometrial profile associated with significantly lower implantation, pregnancy, ongoing pregnancy and live birth rates vs Lactobacillus-dominated (LD) profile
Moreno et al. (2018)	Comparative diagnostic study	Infertile asymptomatic women	Histology, microbial culture, hysteroscopy and molecular microbiology compared head-to-head	Molecular microbiology showed poor concordance with histology/culture for chronic endometritis diagnosis
Winters et al. (2019)	Case-control, contamination-controlled	25 women (hysterectomy specimens) vs cervix, vagina, rectum, oral cavity, background controls	16S qPCR & sequencing with rigorous contamination (kitome) controls	Endometrial bacterial load exceeded background contamination in only 60% of samples; Lactobacillus-dominance may reflect transcervical sampling contamination
Kyono et al. (2019)	Pilot cohort with case reports	IVF patients	16S rRNA sequencing; trial therapeutic intervention for dysbiosis	Dysbiotic endometrium associated with poorer outcome; therapeutic intervention explored in case reports
Kadogami, Nakaoka & Morimoto (2020)	Prospective interventional cohort	Infertile women	Vaginal probiotic suppository + antibiotics; pre/post microbiota sequencing	Combined antibiotic and probiotic treatment altered endometrial microbiota composition
Riganelli et al. (2020)	Case-control	Infertile women vs fertile controls	16S sequencing of vaginal and endometrial microbiota	Structural variation in vaginal/endometrial microbiota associated with female infertility
Skafte-Holm et al. (2021)	Systematic review & meta-analysis (PRISMA)	17 studies; 3,543 IVF patients	Nugent score, qPCR and next-generation sequencing (pooled)	Vaginal dysbiosis prevalence 18%; significant risk factor for early pregnancy loss (RR 1.71) and reduced clinical pregnancy rate on molecular diagnosis (RR 0.55)
McQueen et al. (2021)	Methodological/diagnostic review	Women with recurrent pregnancy loss	CD138 immunohistochemistry vs stromal morphology	Proposed refined histological criteria for chronic endometritis diagnosis
Li et al. (2021)	Cohort, dose-response	Infertile women undergoing endometrial biopsy	CD138+ plasma cell density (cells/HPF)	Higher CD138+ cell density associated with worse pregnancy outcome; supports threshold-based diagnosis
Cela et al. (2022)	Cohort (eubiosis vs dysbiosis)	Women with recurrent implantation failure (RIF)	Endometrial Lactobacillus % (eubiosis ≥90% vs dysbiosis <90%) + tissue cytokine assay	Dysbiosis group had significantly higher IL-6, IL-1β, HIF-1α, COX-2 and lower IL-10, IGF-1 vs eubiosis group
Moreno et al. (2022)	Multicentre prospective observational	342 infertile patients undergoing ART	16S rRNA sequencing of endometrial fluid & biopsy pre-transfer	Dysbiotic profile (Atopobium, Bifidobacterium, Gardnerella, Klebsiella, etc.) associated with unsuccessful reproductive outcome; proposed as predictive biomarker
EMMA/ALICE cohort studies (2020–2024, various single- & multi-centre)	Prospective cohorts & retrospective chart reviews	Range: 66–527 RIF/IVF patients per study	Commercial NGS panels (EMMA for Lactobacillus dominance; ALICE for CE pathogens)	Mixed results: some cohorts show higher clinical pregnancy rate after guided treatment; at least one comparator study shows no

				significant benefit over untested controls
Hiratsuka et al. (2025)	Prospective comparative diagnostic cohort	73 women with RIF (all 3 tests performed)	Hysteroscopy, endometrial CD138 test, and endometrial microbiome NGS test compared head-to-head	Poor concordance between the three diagnostic modalities; only microbiome-dysbiosis-positive group showed significantly improved outcome after targeted treatment
Yan, Jiao & Wang (2025)	Narrative review	N/A (review)	Synthesis of histopathology, hysteroscopy and microbiological literature	Summarised CE pathogenesis, diagnostic heterogeneity (30–67% prevalence range) and treatment approaches

Establishing an endometrial microbiota distinct from the vagina

The foundational study in this field, by Moreno et al. (2016), used pyrosequencing of endometrial fluid obtained before endometrial receptivity biopsy in 35 women undergoing IVF, and demonstrated a bacterial community profile in the endometrium that differed from paired vaginal aspirates, while remaining relatively stable across the pre-receptive and receptive phases of the cycle. Clustering of samples according to Lactobacillus, Bifidobacterium, Gardnerella and Streptococcus abundance allowed classification into Lactobacillus-dominated (LD, ≥90% Lactobacillus) and non-Lactobacillus-dominated (NLD, <90% Lactobacillus) profiles. Subjects with an NLD endometrial profile had significantly lower implantation (23.1% vs 60.7%), pregnancy (33.3% vs 70.6%), ongoing pregnancy (13.3% vs 58.8%) and live birth (6.7% vs 58.8%) rates than those with an LD profile, alongside a non-significant trend towards higher miscarriage rates.

This work was substantially extended in a larger, multicentre, prospective observational study of 342 infertile patients (Moreno et al., 2022), which again used 16S rRNA gene sequencing of endometrial fluid and biopsy samples collected before embryo transfer. A dysbiotic profile enriched for Atopobium, Bifidobacterium, Chryseobacterium, Gardnerella, Haemophilus, Klebsiella, Neisseria, Staphylococcus and Streptococcus was associated with unsuccessful reproductive outcomes, and the authors concluded that pre-transfer endometrial microbiota composition constitutes a potentially useful biomarker for predicting reproductive outcome.

Smaller cohorts have produced broadly concordant findings. In an exploratory study of 141 women whose first IVF/ICSI cycle had failed, women who achieved a live birth within 12 months had a significantly higher relative abundance of Lactobacillus crispatus specifically, rather than Lactobacillus species in general, and a smaller proportion had L. crispatus abundance below 10%, suggesting that species-level, and not only genus-level, resolution may be clinically informative. A culturomics-based analysis of the endometrial microbiota in 93 women undergoing single embryo transfer similarly linked a dysbiotic culturable profile to lower ongoing pregnancy rates, indicating that the association is not an artefact confined to sequencing-based methods alone.

Vaginal dysbiosis and its relationship to endometrial and IVF outcomes

Because ascending colonisation from the vagina is proposed as one route by which the endometrial cavity acquires its microbial community, vaginal dysbiosis has been studied extensively as a proxy, or contributing cause, of poor IVF outcomes. A systematic PRISMA review and meta-analysis of 17 studies and 3,543 patients found a vaginal dysbiosis prevalence of 18%, and demonstrated that vaginal dysbiosis was a significant risk factor for early pregnancy loss in IVF (relative risk 1.71, 95% CI 1.29–2.27); a pre-specified sub-analysis restricted to molecular diagnostic methods additionally showed a significantly reduced clinical pregnancy rate in women with vaginal dysbiosis compared with those with a normal vaginal microbiota (relative risk 0.55, 95% CI 0.32–0.93) (Skafte-Holm et al., 2021). A more recent systematic review and meta-analysis of the vaginal microbiome and assisted reproduction similarly concluded that women with a favourable, Lactobacillus-dominated vaginal microbiome have better reproductive outcomes than those with an unfavourable profile, proposing that vaginal and endometrial dysbiosis share a common mechanistic pathway through pro-inflammatory cytokine up-regulation, local immune overactivation, and consequently impaired endometrial receptivity.

A comparative analysis of the genital tract microbiota of IVF patients and oocyte donors similarly reported that genital tract dysbiosis correlates with poorer

reproductive outcomes, and cited earlier work demonstrating an increased risk of a Gardnerella-dominated biofilm attached to the endometrium in women with bacterial vaginosis, consistent with an ascending-infection model linking vaginal dysbiosis to endometrial pathology.

Mechanistic evidence: dysbiosis, inflammation and endometrial receptivity

Beyond simple association, several studies have sought a mechanistic bridge between microbial composition and impaired implantation. Cela et al. (2022) compared endometrial tissue cytokine profiles in women with RIF stratified into eubiosis (≥90% endometrial lactobacilli) and dysbiosis (<90%) groups, and found that the dysbiosis group had significantly higher tissue concentrations of the pro-inflammatory markers IL-6, IL-1β, HIF-1α and COX-2, alongside significantly lower levels of the anti-inflammatory and trophic factors IL-10 and IGF-1. The percentage of endometrial Lactobacillus correlated negatively with inflammatory marker concentrations and positively with IL-10/IGF-1 levels, providing a plausible inflammatory pathway by which a dysbiotic microbiota could impair the receptive, immunologically tolerant endometrial state required for implantation. Complementary work by the same group (structural variation studies of vaginal and endometrial microbiota in infertility, reviewed by Riganelli et al., 2020) has reinforced the concept that structural shifts in the local microbial ecosystem, rather than the presence of any single pathogen, may underlie impaired receptivity.

Chronic endometritis: an overlapping but distinct entity

Chronic endometritis (CE) a persistent, often subclinical inflammation of the endometrium classically diagnosed by the presence of CD138-positive stromal plasma cells on immunohistochemistry, sometimes supported by hysteroscopic findings of mucosal oedema, focal hyperaemia or micropolyps — is frequently discussed alongside endometrial dysbiosis, and the two concepts are often conflated in clinical practice, but the available evidence indicates they are related, overlapping, yet distinct phenomena. CE prevalence estimates in RIF populations range widely, from around 30% up to 56–67% depending on diagnostic criteria and population (Kitaya, 2011; Yan, Jiao and Wang, 2025), reflecting persistent difficulty in standardising histological thresholds — a limitation formally addressed by proposals to refine CE diagnosis using stromal morphological changes in addition to plasma cell counts (McQueen et al., 2021), and by dose-response analyses of CD138-positive cell density and pregnancy outcome (Li et al., 2021).

Critically, direct comparative studies indicate that hysteroscopy, CD138 immunohistochemistry, and endometrial microbiome sequencing identify only partially overlapping patient groups. In a study of 266 women undergoing hysteroscopy for infertility, the overall CD138 positivity rate was 32.7%, with clinical pregnancy rates similar between antibiotic-treated CD138-positive and CD138-negative women, raising questions about the independent prognostic and therapeutic value of CD138 positivity alone. In a subsequent study of 73 women with RIF who underwent all three diagnostic modalities in parallel — hysteroscopy, endometrial CD138 testing, and endometrial microbiome sequencing — the incidences of CE by hysteroscopy and CD138 testing were 56.2% and 49.3% respectively, and endometrial dysbiosis was present in 53.4%, yet no significant correlation was observed between test-positivity across the three modalities, indicating that they capture different, only partially overlapping patient subgroups; notably, only the endometrial-dysbiosis-positive group, treated with combined antibiotics and vaginal Lactobacillus probiotics, showed a significantly improved post-treatment pregnancy outcome, whereas CE detected by the other two modalities did not (Hiratsuka et al., 2025).

Commercial testing and microbiota-targeted intervention: does correction improve outcomes?

The clinical translation of endometrial microbiome research is most visible in commercially available sequencing panels such as EMMA (assessing overall Lactobacillus dominance) and ALICE (targeting specific pathogens implicated in CE, principally Enterobacteriaceae such as Klebsiella and Escherichia, together with Staphylococcus species), typically followed by tailored antibiotic and/or vaginal probiotic therapy. Early prospective cohort data have been encouraging: in a cohort of 158 women with RIF undergoing EMMA/ALICE testing, those found to have a non-Lactobacillus-dominated profile and treated accordingly achieved a significantly higher clinical pregnancy rate than untreated comparators, and a separate single-centre Japanese cohort reported clinical pregnancy rates of up to 64.5% after EMMA/ALICE-guided treatment

compared with 33.3% in untested controls. A larger, multicentre Japanese study across 14 IVF clinics (527 women under 42 years, stratified by EMMA/ALICE result into normal, dysbiotic, and treated subgroups using vaginal Lactobacillus probiotic suppositories before transfer) was subsequently undertaken to test whether correcting the endometrial microbiome improves ongoing pregnancy rates, reflecting the field's shift from purely observational association studies towards intervention-based, hypothesis-testing designs.

However, this optimistic picture is not universal. Real-world, single-centre retrospective experience with EMMA/ALICE testing (446 patients over a ten-year period) found that a substantial proportion of samples (around 38%) returned an 'ultralow biomass' result of uncertain interpretability, that abnormal EMMA profiles frequently did not correlate with conventional endometrial biopsy pathology for CE, and that outcomes after indicated treatment, while numerically favourable in some subgroups, were drawn from small samples insufficient to firmly establish a causal treatment benefit. More strikingly, at least one comparative cohort study found that use of the EMMA test, and subsequent tailored treatment, did not significantly improve implantation or clinical pregnancy rates compared with an age-matched control group managed without microbiome testing, directly challenging the assumption that identifying and 'correcting' dysbiosis translates into better IVF outcomes.

A broader systematic review of microbiota-targeted therapies (antibiotic, probiotic and nutraceutical interventions) for CE-associated RIF, encompassing four eligible studies with considerable heterogeneity in diagnostic criteria and microbiota assessment methods, reported pooled clinical pregnancy, ongoing pregnancy and live birth rates of approximately 50.5%, 40.1% and 41.2% respectively across treated patients, but the authors emphasised substantial methodological heterogeneity and generally low-to-moderate study quality on Newcastle-Ottawa Scale and ROBINS-I assessment, precluding firm causal conclusions. Similarly, a systematic review and meta-analysis of vaginal probiotic use for reproductive dysbiosis found that most existing protocols have targeted bacterial vaginosis rather than IVF-specific endometrial outcomes, with comparatively few trials designed specifically around IVF pre-treatment, and considerable variability in probiotic strain, dose, and administration route (oral versus vaginal), limiting the comparability and generalisability of intervention data.

Methodological controversy: does a true endometrial microbiome exist?

A parallel and unresolved thread of the literature challenges the basic premise that molecular sequencing accurately captures a genuine, resident endometrial microbial community. Winters et al. (2019) compared mid-endometrial samples obtained via hysterectomy — avoiding transcervical contamination — with cervical, vaginal, rectal, oral and background DNA contamination control samples. Universal bacterial quantitative PCR demonstrated a bacterial load exceeding background contamination control in only 60% (15/25) of endometrial samples, and endometrial bacterial profiles differed from the vagina, oral cavity and rectum but were not clearly distinguishable from the cervix. The authors explicitly cautioned that the previously reported Lactobacillus-dominance of the endometrial microbiota may, in earlier transcervically sampled studies, reflect contamination with vaginal Lactobacillus species introduced during catheter passage through the cervix, and that at very low bacterial biomass, background DNA from extraction kits and sequencing reagents (the 'kitome') can constitute a considerable, or even total, proportion of the apparent microbial signal unless rigorously controlled for.

This methodological critique is reinforced by related work on endometrial cancer and benign endometrial tissue, which similarly found endometrial, fallopian tube and ovarian bacterial biomass to be one to four orders of magnitude lower than vaginal, cervical or rectal biomass, and comparable to negative extraction controls in many samples, underscoring the technical difficulty of confidently characterising a low-biomass niche. Collectively, these findings do not refute the clinical association between an apparently 'dysbiotic' sequencing result and poorer IVF outcomes, but they substantially complicate its biological interpretation: it remains unclear whether a truly resident, functionally active endometrial microbiota exists and mediates implantation failure directly, or whether sequencing-detected 'dysbiosis' is, at least in part, a marker of ascending vaginal/cervical contamination or of a permissive, inflamed endometrial environment that is secondarily more susceptible to microbial detection.

Discussion

Taken together, the literature supports a consistent, moderate-to-large association between a non-Lactobacillus-dominated (dysbiotic) endometrial or vaginal microbial profile and adverse IVF outcomes, spanning implantation, clinical pregnancy, ongoing pregnancy and live birth rates, and this association is biologically plausible given accompanying evidence of local pro-inflammatory cytokine dysregulation in dysbiotic endometria. This represents genuine progress from the pre-2016 assumption of endometrial sterility, and has legitimately reframed the endometrium as an active site of host–microbe interaction relevant to reproductive success.

However, several considerations temper any claim that the field has definitively progressed from association to validated clinical utility. First, diagnostic heterogeneity remains substantial: sampling route (transcervical catheter versus biopsy versus hysterectomy), sequencing platform, bioinformatic pipeline, and the threshold used to define dysbiosis (most commonly, but not universally, <90% relative Lactobacillus abundance) all vary across studies, limiting direct comparability and the derivation of a single validated normative range. Second, the low bacterial biomass of the endometrial cavity renders sequencing-based studies acutely vulnerable to contamination artefact, and rigorously contamination-controlled studies have raised legitimate doubt as to whether the widely reported Lactobacillus-dominance of the endometrium is a genuine biological feature or a sampling artefact of transcervical contamination with vaginal flora (Winters et al., 2019). Third, and most importantly from a clinical decision-making perspective, chronic endometritis, endometrial CD138 positivity, and sequencing-defined endometrial dysbiosis identify only partially overlapping patient populations, with treatment response differing meaningfully between them (Hiratsuka et al., 2025); this suggests that these three diagnostic constructs, though often used interchangeably in clinical marketing materials, are not clinically or biologically interchangeable, and that a positive result on one test cannot be assumed to predict a positive result — or the same therapeutic benefit — on another.

Fourth, evidence for the pivotal claim that correcting dysbiosis (via antibiotics and/or Lactobacillus probiotics) improves reproductive outcomes remains inconsistent. While several small-to-moderate prospective cohorts report improved pregnancy rates after EMMA/ALICE-guided treatment, at least one comparative study found no benefit over untested, standard-care controls, and systematic reviews of microbiota-targeted therapy for CE-associated RIF describe considerable study heterogeneity and low-to-moderate methodological quality, without a consistent RCT evidence base. This pattern — encouraging observational and single-arm cohort data, without confirmatory adequately powered RCT evidence — is a recognised precursor to over-adoption of unproven interventions in reproductive medicine, and mirrors historical experience with other 'add-on' IVF interventions that were widely adopted on the strength of association data before rigorous trials clarified, or refuted, their benefit.

From a clinical-utility standpoint, three criteria are generally required before a biomarker-guided intervention can be considered validated for routine practice: analytical validity (the test reliably and reproducibly measures what it claims to measure), clinical validity (the test result reliably predicts the clinical outcome of interest), and clinical utility (acting on the test result, typically through treatment, demonstrably improves that outcome, ideally in a randomised comparison against no testing or sham treatment). The reviewed literature provides reasonably consistent evidence for clinical validity — dysbiotic profiles do correlate with worse IVF outcomes across multiple independent cohorts — but weaker and more contested evidence for analytical validity, given the low-biomass contamination problem, and still-immature evidence for clinical utility, given the paucity of adequately powered RCTs directly comparing microbiome-guided treatment against standard care.

Practically, this has implications for how clinicians should currently counsel patients. Endometrial microbiome testing may reasonably be considered, with appropriate counselling about the limitations of current evidence, in the specific context of unexplained RIF after exclusion of other established causes (embryo aneuploidy, uterine structural anomalies, thrombophilia), where it may be integrated alongside, rather than as a replacement for, established chronic endometritis assessment. It should not, on current evidence, be recommended as a routine, first-line investigation for all IVF patients, nor should a positive dysbiosis result alone be assumed automatically to justify empirical antibiotic or probiotic therapy outside a shared decision-making conversation acknowledging the uncertain magnitude of benefit.

Future research priorities that would meaningfully advance the field from association to clinical utility include: standardisation of sampling technique and contamination controls across studies; consensus, externally validated dysbiosis thresholds derived from large, diverse reference populations; adequately powered, blinded RCTs of microbiome-guided antibiotic/probiotic intervention against standard care, with live birth rate as the primary outcome; and mechanistic studies clarifying whether the endometrial microbial signal reflects a genuinely resident, functionally active community or a secondary marker of local immune and inflammatory status.

Conclusion

The past decade has transformed the endometrium from a presumed-sterile organ into a putative site of microbial ecology with plausible relevance to implantation and IVF success. A dysbiotic, non-Lactobacillus-dominated endometrial or vaginal microbial profile is consistently associated with reduced implantation, pregnancy and live birth rates across independent cohorts, and this association is supported by mechanistic evidence of local pro-inflammatory dysregulation. However, unresolved methodological concerns regarding low-biomass sampling contamination, inconsistent diagnostic thresholds, imperfect concordance with chronic endometritis, and — most critically — inconsistent evidence that correcting dysbiosis actually improves reproductive outcomes, mean that the field has not yet completed its transition from association to validated clinical utility. Endometrial microbiome testing and empirical treatment may have a role in carefully selected patients with unexplained recurrent implantation failure, but should currently be regarded as an evolving adjunct rather than a validated, routine component of IVF care, pending the results of larger, methodologically rigorous, contamination-controlled randomised trials.

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