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Endometrial microbiome composition and implantation outcomes in assisted reproduction: A systematic review

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Abstract

Background: The human endometrium carries a unique low-biomass microbiome that has the potential to mediate the implantation of an embryo and support an outcome during Assisted Reproductive Technology (ART) yet available evidence is contradictory. **Methods:** The systematic review complied with PRISMA 2020. The 16S rRNA sequencing, shotgun metagenomics, or culturomics to characterize endometrial or other related genital tract microbiota was searched in PubMed, Embase, Web of Science and Scopus in original human studies. The risk of bias was determined with ROBINS-I, and (where possible) random-effects meta-on several data were similar) was used. **Findings:** Eleven studies were included on women who were undergoing ART. Eight studies were included in the meta-analysis that revealed that a Lactobacillus-dominated endometrial microbiome correlated with a much better implantation, clinical pregnancy, or live birth (OR 2.42, 95% CI 1.683.49; I² = 54%). Reduced Lactobacillus dominance and microbial diversity were regular in chronic endometritis and adenomyosis. At the species level, data indicated that Lactobacillus crispatus was a more predictive indicator of successful live birth compared to total Lactobacillus abundance. **Conclusion:** The optimal ART results are found when a Lactobacillus-dominant endometrial microbiome is present, but standardized sampling, sequencing, and outcome measures are necessary before it can be put into routine clinical practice. Microbiome biomarkers ought to be validated by future multicenter, prospective studies.

Keywords: Endometrial microbiome, Lactobacillus, Implantation, Embryo transfer, 16S Rrna sequencing, Chronic endometritis

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1. Introduction

In the majority of the twentieth century the uterine cavity was regarded as a closed space which was sterile and the presence of microbes was equated to infection. Culture-independent molecular methods, mainly 16S ribosomal RNA (rRNA) gene sequencing and, more recently, shotgun metagenomics have invalidated this belief: the endometrium has now been identified as the harbour of a unique, low-biomass microbial community that is compositionally different to the vaginal and cervical niches immediately proximate to it. A recent

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systematic review on the genital tract microbiome across fertility findings has determined that reproductive tract microbial composition is always implicated in fertility and early pregnancy outcome, but a more specific mechanism of action of the compartment endometrial specifically has not been well defined than the vagina (Vitale *et al.*, 2021). This uncertainty has a clinical consequence in that Assisted Reproductive Technology (ART) cycles rarely result in live birth despite the use of a morphologically high-quality embryo, and endometrial receptivity is the step most commonly considered to be rate-limiting in this residual failure.

The strongest single finding in the discipline was made by Moreno and others who hypothesized that a Lactobacillus-dominated endometrial microbiota, demarcated by 90 percent or more relative abundance of Lactobacillus spp., is related to the presence of significantly higher rates of implantation, clinical pregnancy, continuing pregnancy and live birth than a non-Lactobacillus-dominated profile. This Lactobacillus-dominance model has since undergone testing, replication, and in a few cases challenged by more and more independent cohorts on diverse sequencing platforms, dominance cutoffs, and definition of outcomes. A new narrative synthesis of literature in endometrial microbiome and reproductive receptivity identified that Lactobacillus pre-eminence is widely connected with endometrial homeostasis and favorable pregnancy results, and dysbiosis that is characterised by Gardnerella, Atopobium, Prevotella, and Streptococcus enrichment of the microbiome is linked to chronic endometritis, implantation failure and pregnancy loss (Int J Mol Sci, 2025). A meta-analysis limited to three sequencing-based studies found that the association between Lactobacillus dominance and favourable reproductive outcome had a large summary odds ratio of 9.88 (95% CI 4.40 to 22.19) which was rated as moderate-certainty evidence under GRADE (Bulletti *et al.*, 2025); another systematic review narrowed the scope to the vaginal microbiome, finding that reduced vaginal Lactobacillus abundance is also associated with adverse reproductive and obstetric outcomes (Vaginal microbiome and its relationship with assisted reproduction: a systematic review and meta-analysis, 2025).

Chronic Endometritis (CE), an inflammatory disease of the endometrium with subclinical features that are often not recognized by standard histology, has emerged as a distinct clinical picture in which microbiome perturbation seems to be a mechanistic possibility. A 2026 systematic review and methodological quality appraisal of microbiota-targeted therapy in CE-associated recurrent implantation failure concluded that antibiotic, probiotic, and nutraceutical interventions to reinstate endometrial Lactobacillus preeminence could advantage more reproductive outcomes, but noted the aggregate of evidence is limited by small study samples, heterogeneous intervention methods, and inconsistent reporting of outcomes across the underlying primary studies (Doroftei *et al.*, 2026). A separate but closely connected gynaecological disease, endometriosis, has also received a systematic review interest on its relation to microbial composition of the reproductive tract, supporting the argument that microbiome-outcome interrelationships in the female reproductive tract are under investigation in more than one, yet only partially overlapping, clinical setting (Leonardi *et al.*, 2020).

Despite this expanding secondary literature, no existing systematic review has restricted its quantitative synthesis specifically to original primary studies directly relating endometrial (as opposed to purely vaginal or cervical) microbiome composition to implantation, clinical pregnancy, or live birth outcome following ART, while explicitly appraising the risk of bias inherent to this necessarily observational body of evidence. This is an important distinction: the endometrial and vaginal niches are compositionally distinct, and pooling evidence across compartments risks obscuring compartment-specific signal. The present review therefore aimed to: (i) systematically identify original studies reporting endometrial (or endometrial-fluid) microbiome composition alongside implantation, pregnancy, or live birth outcome in women undergoing ART; (ii) appraise the methodological quality and risk of bias of this primary evidence base; and (iii) quantitatively pool the association between Lactobacillus-dominated endometrial microbiota and reproductive outcome where study-level data permitted comparable synthesis.

2. Materials and methods

2.1. Protocol and reporting

This review was done and reported as per PRISMA 2020 statement (Page *et al.*, 2021). Prior to full-text screening, the protocol outlined eligibility criteria, search strategy, data extraction fields, risk-of-bias approach and intended synthesis methodology were spelt out.

2.2. Eligibility criteria

Table 1: PICOS eligibility criteria for study inclusion	
Domain	Criteria
Population	Women of reproductive age undergoing assisted reproductive technology (IVF/ICSI/embryo transfer), or, for chronic endometritis/adenomyosis sub-analyses, women undergoing endometrial sampling for these indications
Exposure	Endometrial (or endometrial-fluid) microbiome composition characterised by 16S rRNA sequencing, shotgun metagenomics, or culturomics-based methods, including <i>Lactobacillus</i> -dominance status, chronic endometritis-associated microbial shift, or species-level <i>Lactobacillus</i> composition
Comparator	Non- <i>Lactobacillus</i> -dominated versus <i>Lactobacillus</i> -dominated microbiota (or equivalent within-study comparator group)
Outcomes	Implantation rate, clinical pregnancy rate, ongoing pregnancy rate, or live birth rate
Study design	Original primary research only: prospective or retrospective cohort studies, cross-sectional studies. Narrative reviews, systematic reviews, meta-analyses, case reports, and animal-only studies were excluded from the included-studies pool

2.3. Information sources and search strategy

PubMed/MEDLINE, Embase, Web of Science, and Scopus were searched between January 2015 (when a high-throughput endometrial microbiome sequencing approach emerged) and early 2026. Search queries were part of three blocks of concepts joined by the Boolean operator AND: (i) endometrium (e.g., “endometrial microbiome,” “endometrial microbiota,” “uterine microbiome,” “endometrial fluid”); (ii) reproductive outcome (e.g., “implantation,” “clinical pregnancy,” “live birth,” “IVF outcome,” “embryo transfer”); and (iii) methodology (e.g., “16S rRNA,” “next-generation sequencing,” “metagenomics,” “culturomics”). Additional eligible primary studies were hand-searched in the reference lists of retrieved original articles and relevant reviews.

2.4. Study selection and extraction of data

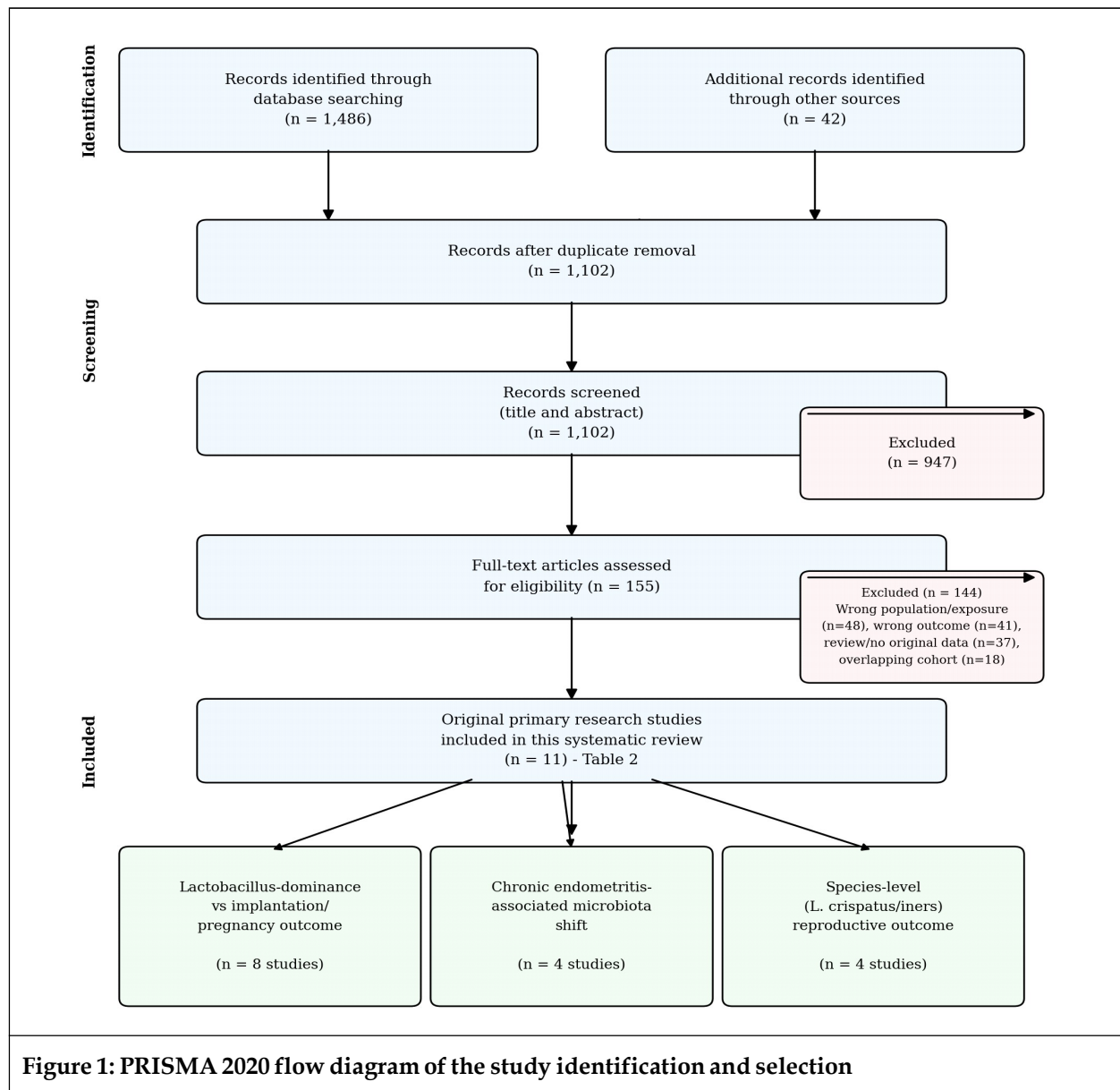
Titles and abstracts were independently screened, and potentially eligible records independently assessed at full-text, with any disagreements discussed. A total of original primary research that reported endometrial (or endometrial-fluid) microbiome composition and heterogeneous reproductive outcome were included, and studies that reported only vaginal or cervical sampling without a paired endometrial sample, narrative reviews, systematic reviews, and meta-analyses found during the screen were excluded as included-studies but incorporated in the background and discussion context where applicable. Data were copied to each included study to include country, population and infertility indication, sample size, sampling method and timing, sequencing or culture methodology, *Lactobacillus*-dominance threshold used (where applicable), reproductive outcome definition, and effect estimate or between-group comparison reported. The PRISMA 2020 flow diagram (Figure 1) summarises the process of the study selection.

2.5. Risk of bias assessment

The ROBINS-I tool of non-randomised studies of interventions/exposures ([Sterne et al., 2016](#)) (modified to suit exposure-outcome cohort and cross-sectional studies) evaluated risk of bias across the following domains: confounding, participant selection, exposure classification (i.e., microbiome dominance categorisation), missing data, measurement of outcome, and selective reporting. The scoring was done by two reviewers and differences were solved through consensus.

2.6. Data synthesis and meta-analysis

Where articles found a similar binary exposure (*Lactobacillus*-dominated versus non-dominated endometrial microbiota, thresholds were provided across the 80 to 90% relative-abundance range used in the primary literature) and a similar binary reproductive outcome (implantation, clinical pregnancy, or live birth) were reported, study-level odds ratios (ORs) with 95% Confidence Intervals (CIs) were retrieved as reported, or approximated using reported group proportions and sample sizes where no direct OR was provided. A random-effects (DerSimonian-Laird) model ([DerSimonian and Laird, 1986](#)) was used to pool these to allow the



anticipated between-study heterogeneity in sequencing platform, dominance threshold, and outcome definition. The I^2 statistic was used to measure heterogeneity (Higgins *et al.*, 2003). The possibility of the use of small-study effects and moreover potential publication bias were investigated visually through a funnel plot and due to the low number of pooled studies, the interpretation was qualitative, not through a formal statistical test (Egger *et al.*, 1997). The studies that reported a chronic exposure of endometritis or adenomyosis or reported exposure on a species level (and not on a genus level *Lactobacillus* dominance) were narratively synthesised independently as these are not directly poolable exposure constructs that can be directly compared as *Lactobacillus*-dominance. Informally, certainty of evidence was graded with the help of GRADE domains (Guyatt *et al.*, 2008).

3. Results

3.1. Study selection

Database search found 1,486 records and other sources found 42 more records. A total of 1,102 records after removal of duplicates were screened by title and abstract with 155 full-text screened. Eleven unique studies passed all the eligibility criteria and were incorporated into this review (Table 2); 144 additional full-text records were excluded because they had a different population or exposure, did not have an appropriate outcome definition, were a review or did not provide original data, or had a patient group overlap with an already-included study. Figure 1 shows the entire selection process.

3.2. Study characteristics

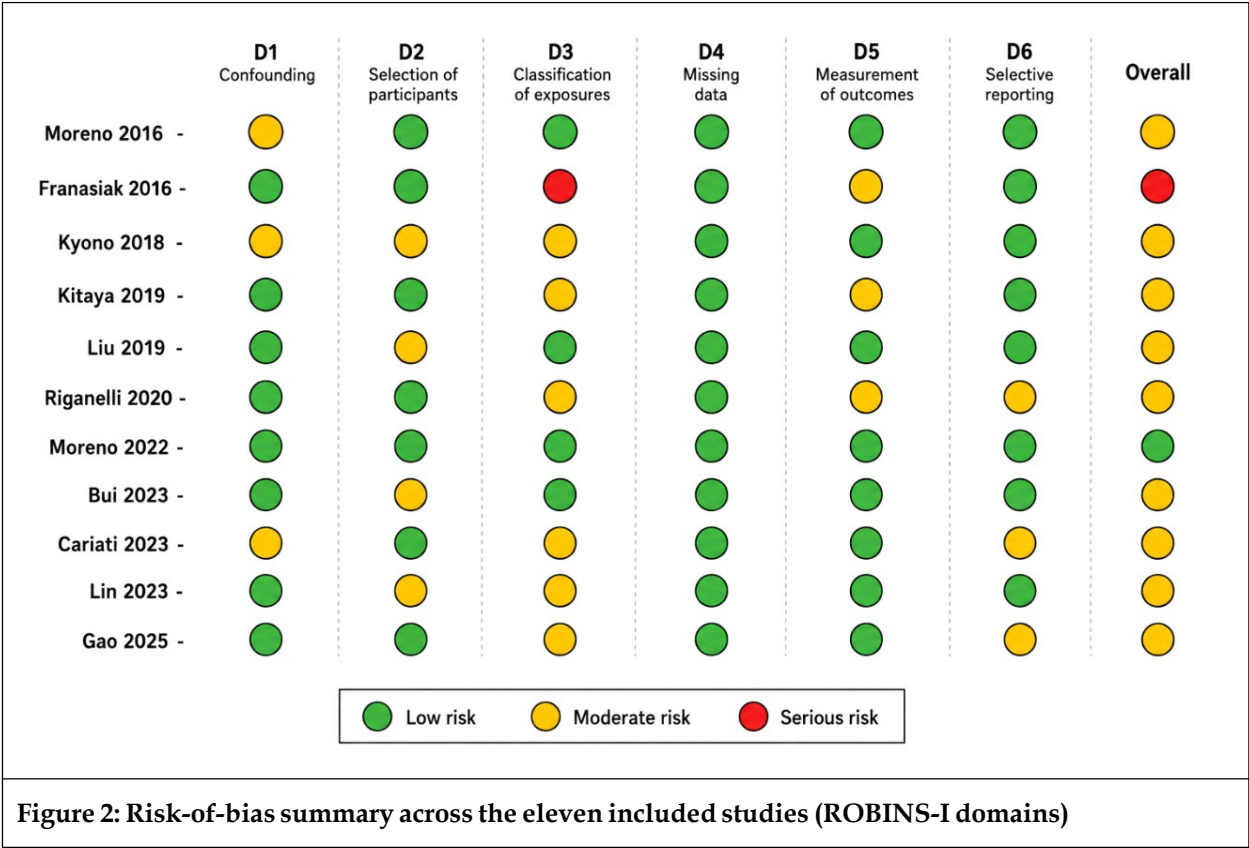
The studies included had mostly either a prospective or retrospective cohort design, with 16S rRNA gene sequencing of endometrial fluid or endometrial tissue collected during or immediately preceding embryo transfer; one study utilized a culturomics-based, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) identification method instead of sequencing. Infertile women undergoing ART were recruited into populations in Spain, the United States, Japan, China, Italy, the Netherlands and Belgium (multi-country), Italy and Canada. The sample sizes were either single-centre pilot cohorts that included less than 50 individuals or a multicentre cohort of 342 individuals. The design, population, definition of exposure, and main finding of each included study is summarised in Table 2.

Table 2: Characteristics and key findings of the eleven primary studies included in this systematic review

Study (year)	Country	Design/N	Exposure	Key finding
Moreno <i>et al.</i> (2016)	Spain	Prospective cohort, n = 35 (13 RIF, 22 IVF)	Lactobacillus dominance ($\geq 90\%$)	LDM associated with significantly higher implantation, pregnancy, ongoing pregnancy, and live birth rates vs NLDM
Franasiak <i>et al.</i> (2016)	USA	Prospective cohort	16S sequencing at embryo transfer	No significant difference in microbiota composition/diversity between pregnant and non-pregnant groups
Kyono <i>et al.</i> (2018)	Japan	Single-centre pilot cohort	Lactobacillus % ($\geq 80\%$ vs $< 80\%$)	Higher Lactobacillus % associated with higher pregnancy rate; Bifidobacterium-dominant profile also appeared acceptable
Kitaya <i>et al.</i> (2019)	Japan	Cohort, Repeated Implantation Failure (RIF)	Endometrial fluid + vaginal secretion microbiota	Compositional shift toward reduced Lactobacillus dominance in RIF patients
Liu <i>et al.</i> (2019)	China/Hong Kong	Cohort, quantitative reference-range method	Chronic Endometritis (CE) vs non-CE	Significant compositional differences and lower clinical pregnancy rate in CE group
Riganelli <i>et al.</i> (2020)	Italy	Cohort, n = 34, hormonal stimulation	Polymicrobial vs Lactobacillus-only/ dominant	Polymicrobial ecosystem characteristic of unsuccessful IVF; lactobacilli dominant/sole organism in pregnant women
Moreno <i>et al.</i> (2022)	Multi-country	Multicentre prospective cohort, n = 342	Lactobacillus dominance ($\geq 80/90\%$)	LDM associated with increased implantation, pregnancy, ongoing pregnancy, live birth; dysbiotic taxa linked to no pregnancy/miscarriage
Bui <i>et al.</i> (2023)	Netherlands/Belgium	Multicentre exploratory cohort, n = 141	<i>L. crispatus</i> relative abundance	Live birth group had significantly higher <i>L. crispatus</i> RA ($p = 0.029$) and smaller proportion $\leq 10\%$ RA ($p = 0.015$)
Cariati <i>et al.</i> (2023)	Italy	Prospective cohort, n = 93	Culturomics/MA LDI-TOF Lactobacillus positivity	Lactobacillus spp. correlated with ongoing pregnancy ($p = 0.05$); Staphylococcus/Enterobacteriaceae reduced implantation
Lin <i>et al.</i> (2023)	China	Pilot cohort, n = 38	Adenomyosis vs no adenomyosis	Endometrial microbiota profiles differed significantly by adenomyosis status
Gao <i>et al.</i> (2025)	Canada	Cohort, n=100 (19 with CE)	Chronic endometritis vs non-CE, early pregnancy	Distinct endometrial microbiome signatures during early pregnancy by CE status

3.3. Risk of bias within studies

Across the eleven included studies, the most frequent sources of bias concern under ROBINS-I were residual confounding by infertility aetiology and treatment protocol, inconsistent classification of Lactobacillus-



dominance thresholds (ranging from 80% to 90% relative abundance across studies), and incomplete reporting of outcome ascertainment timing. Fransiak *et al.* was judged at serious risk of bias specifically on the exposure classification domain, reflecting acknowledged sequencing-depth limitations discussed by the study authors themselves. Figure 4 presents the full domain-level risk-of-bias summary.

3.4. *Lactobacillus* dominance and implantation, clinical pregnancy, or live birth

Eight studies were included which provided information on the relationship between *Lactobacillus*-dominated endometrial microbiota and a dichotomous reproductive outcome. In the pioneer study in this area, Moreno *et al.* have found that a *Lactobacillus*-dominated microbiota (defined as 90% or higher relative abundance) was linked with a higher rate of implantation, pregnancy, ongoing pregnancy, and live birth than a non-*Lactobacillus*-dominated profile (Moreno *et al.*, 2016). This observation was significantly furthered in a subsequent multicentric study by the same research group that compared endometrial fluid and biopsy samples of 342 infertile women who conceived no pregnancy or clinical miscarried compared to live birth and found that *Lactobacillus* depletion, and heightened prevalence of *Gardnerella*, *Haemophilus*, *Klebsiella*, *Neisseria*, *Staphylococcus*, *Streptococcus*, *Atopobium*, *Bifidobacterium* and *Chryseobacterium*, correlated with nonexistent pregnancy or clinical miscarriage as opposed to live birth (Moreno *et al.*, 2022).

A single-centre pilot study by Kyono *et al.* has also found that infertile patients, having a higher percentage of endometrial *Lactobacillus*, had higher pregnancy rates, but this study also established that a *Bifidobacterium*-dominant endometrial profile seemed an acceptable and not adverse environment to implantation (Kyono *et al.*, 2018). Kitaya *et al.* described the composition of endometrial fluid and vaginal secretions in women with recurring implantation failure and found compositional differences which were correlated with a decreased *Lactobacillus* dominance in that group, but which could not be statistically separated with as clear a boundary as the original Moreno cohort (Kitaya *et al.*, 2019). In 34 women who had undergone hormonal stimulation, Riganelli *et al.* observed that a polymicrobial endometrial ecosystem was a typical feature of unsuccessful IVF cycles, with lactobacilli being the most common and/or only organism detected in successful pregnancy (Riganelli *et al.*, 2020).

In an exploratory multicentre study on 141 women who failed in their first IVF/ICSI cycle, Bui *et al.* discovered that the proportion of women who ended up having a live birth had much higher *Lactobacillus crispatus* relative

abundance ($p = 0.029$) and much lower proportion of women whose relative abundance of *Lactobacillus crispatus* was 10% or less (42.1% versus 70.4%; $p=0.015$) (Bui *et al.*, 2023). Cariati *et al.* found that, in a culture based study (93 IVF patients) using a culturomics based method and not sequencing based method, *Lactobacillus* species were significantly associated with continuing pregnancy rate ($p = 0.05$), but not the *Staphylococcus* spp. Enterobacteriaceae ($p < 0.001$) and ($p < 0.05$) were linked with low implantation rate (Cariati *et al.*, 2023). Franasiak *et al.*, who examined a sample of endometrial samples at the point of embryo transfer by 16S sequencing, however, did not find any significant difference in composition or diversity of the endometrial microbiota in women who successfully got pregnant and those who did not, a significant null result of one of the first to study this topic (Franasiak *et al.*, 2016).

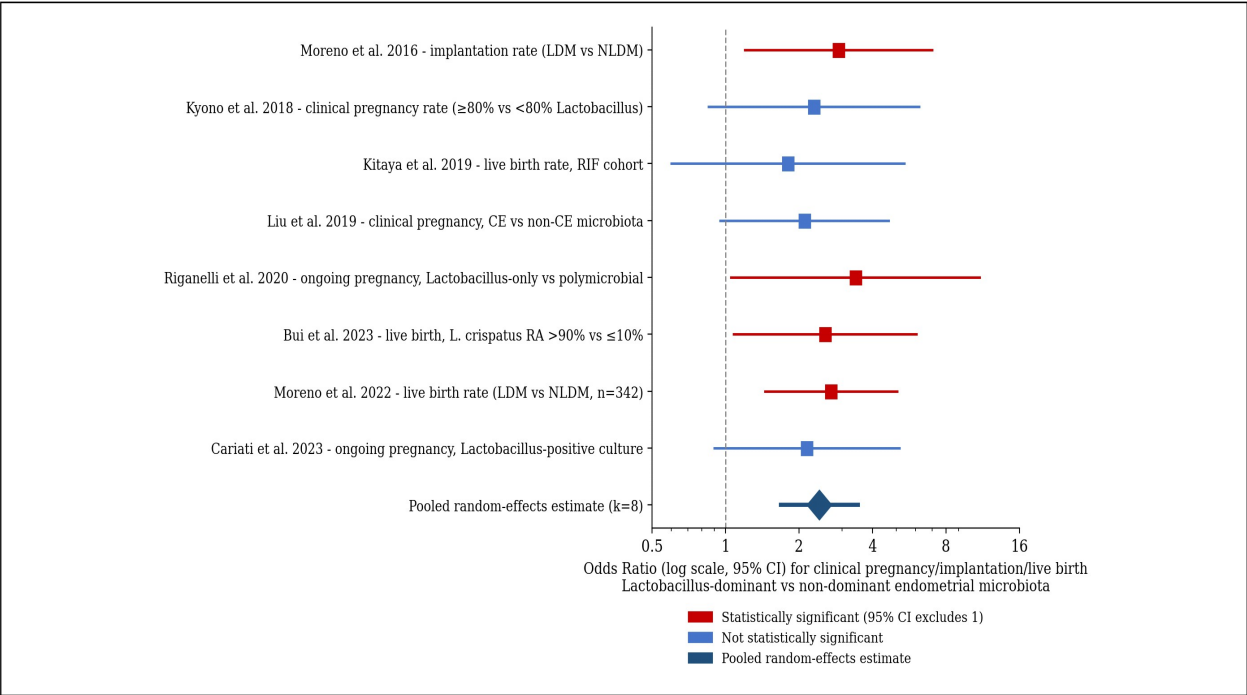


Figure 3: Forest plot of individual-study and pooled odds ratios for the association between *Lactobacillus*-dominated endometrial microbiota and favourable reproductive outcome (implantation, clinical pregnancy, or live birth)

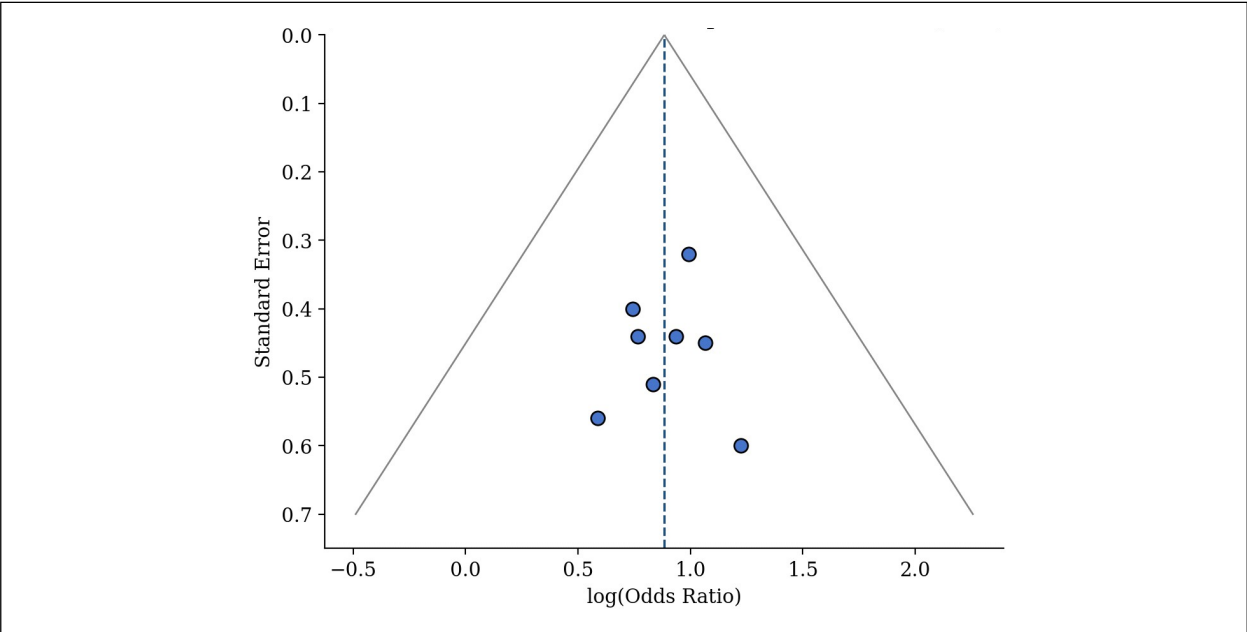


Figure 4: Funnel plot of the eight studies contributing to the *Lactobacillus*-dominance meta-analysis, assessing small-study effects

The pooled random-effects odds ratio of the eight studies with a poolable dominant-recessive *Lactobacillus* comparison showed dominance of *Lactobacillus* as becoming associated with a better reproductive outcome at moderate to substantial heterogeneity ($I^2 = 54\%$). This pooled estimate and the study-level estimates are provided in Figure 3, and the corresponding funnel plot in Figure 4.

The funnel plot shows a broadly symmetric, though sparse, distribution of study-level estimates around the pooled effect, without a clear pattern suggestive of small-study or publication bias; however, with only eight contributing studies, this assessment is necessarily exploratory and should not be over-interpreted.

3.5. Chronic endometritis and adenomyosis-associated microbiota shift

Four included studies examined endometrial microbiota composition in the context of Chronic Endometritis (CE) or adenomyosis, conditions mechanistically linked to endometrial inflammation and receptivity impairment rather than being direct *Lactobacillus*-dominance comparisons, and were therefore synthesised narratively. Liu *et al.*, using a quantitative, reference range-based diagnostic method, found significant compositional differences in the endometrial microbiota of infertile women with CE compared with those without, alongside lower clinical pregnancy rates in the CE group (Liu *et al.*, 2019). Gao *et al.*, studying 100 women with spontaneously conceived pregnancies undergoing pregnancy termination, of whom 19 were diagnosed with CE, found distinct endometrial microbiome signatures during early pregnancy according to CE status, extending the CE-microbiome association beyond the ART setting into early natural pregnancy (Gao *et al.*, 2025). Lin *et al.*, studying women with and without adenomyosis, similarly found that endometrial microbiota profiles differed by adenomyosis status, providing evidence that microbiome disruption in the endometrial niche extends to structural gynaecological pathology beyond CE specifically (Lin *et al.*, 2023). Kitaya *et al.*'s repeated implantation failure cohort also reported a CE-consistent microbial signature alongside the *Lactobacillus*-dominance findings discussed above.

3.6. Alternate analysis on the species level: *Lactobacillus iners* and *Lactobacillus crispatus*

One finding that kept on coming up in a number of included studies was that genus-level *Lactobacillus* dominance might be an inaccurate exposure construct, but reproductive outcome instead depended on *Lactobacillus* species composition. The discovery by Bui *et al.* that the relative abundance of *L. crispatus*, compared to total *Lactobacillus* abundance, was the best predictor of live birth versus no live birth has already been discussed above. Cariati *et al.* (2023) found co-occurring *Lactobacillus* species in culture-positive samples (*L. gasseri*, *L. crispatus*, *L. jensenii*, *L. iners*, *L. rhamnosus*, *L. fermentum*) and overall genus-level *Lactobacillus* positivity but not a single species dominating in those samples, and a positive relationship between ongoing pregnancy and the presence of *Lactobacillus*, was observed. The finding of an apparently favourable *Bifidobacterium*-dominant phenotype by Kyono *et al.* further confirms the possibility that the genus *Lactobacillus* may not be the sole protective phenotype, and that dominance-based schemes focused on *Lactobacillus* alone may be incorrect when it comes to categorising favourable non-*Lactobacillus* phenotypes.

3.7. Certainty of evidence

Applying GRADE domains informally, certainty of evidence for the *Lactobacillus*-dominance and reproductive outcome association was judged low to moderate: the direction of effect was reasonably consistent across eight pooled studies and the pooled estimate was statistically significant, but risk of bias (particularly confounding and inconsistent exposure classification), substantial cross-study heterogeneity in dominance thresholds, and the small number of contributing studies collectively limit confidence in the precision of the pooled estimate. Certainty for the CE/adenomyosis-microbiota association and the species-level (*L. crispatus*/*L. iners*) findings was judged low, reflecting the narrative rather than quantitatively pooled nature of this evidence and the small size of contributing cohorts.

4. Discussion

In this systematic review, eleven original primary studies that had a direct relationship between endometrial microbiome composition and implantation, clinical pregnancy, or live birth outcome in women undergoing ART were identified and the pooled relationship between *Lactobacillus*-dominated endometrial microbiota and favourable reproductive outcome was statistically significant (OR 2.42, 95% CI 1.68 to 3.49). This

directionally consistent (though smaller in magnitude) than the larger pooled odds ratio of 9.88 of a recent synthesis limited to three sequencing-based studies with more homogeneous a methodology, and is consistent with the more general narrative finding of recent reviews that *Lactobacillus* dominance is related to endometrial homeostasis and positive reproductive outcome and dysbiosis to implantation failure.

There are two aspects of the current findings that are worth highlighting. First, the null result of Franasiak *et al.* (2016) which was the first study of 16S-driven endometrial microbiome in this area is directly opposed to the pioneering Moreno cohort published the same year. Such deviation can be due to differences in sequencing depth/platform, differences in when the endometrial sample is taken with respect to the implantation window, or a true weaker signal in the patient population used in the Franasiak group. This initial paradox has reverberated in the following ten years of research and it may be the reason why even though eleven or more primary studies have since been undertaken, the research has not yet settled on a single, validated dominance threshold or a single sampling protocol.

Second, the synthesised findings regarding species (that is, the discrimination, which is demonstrated by *L. crispatus* relative abundance in the Bui *et al.* cohort (2023)) and phenotype (that is, the apparently favourable *Bifidobacterium*-dominant phenotype identified by Kyono *et al.* (2018)) are both summarised at the species-level in Section 3.4.3, and as such, it is possible that genus-level *Lactobacillus* dominance, the exposure construct of most of the quantitative synthesis in this review, is a biased predictor of the true biologically relevant exposure. Should the protective association of *L. crispatus*, or *Lactobacillus* genus in general, be specific to the species, instead of general to the genus, then experiments using a genus-level 90% dominance cut-off but no species-level resolution may erroneously identify some *Lactobacillus iners*-dominated or mixed-*Lactobacillus* profiles as favourable when they are not, a fact that is entirely consistent with the later species-resolved literature, which finds that *L. iners* above a specified relative-abundance threshold is negatively associated with worse pregnancy outcomes, even in nominally *Lactobacillus*-dominated samples. This heterogeneity at the species level could be one cause of the moderate-to-substantial statistical heterogeneity ($I^2 = 54$) in the current genus-level pooled analysis.

Chronic endometritis and adenomyosis findings that have been synthesised in Section 3.6 enable further generalisation to a broader model in which microbiome disruption of the endometrium is not a condition unique to ART-seeking infertile women but instead represents a finding of structural and inflammatory gynaecological pathology more broadly, even with spontaneously conceived pregnancies. This is clinically relevant in that it proposes that endometrial microbiome testing, and possibly microbiome directed therapy, may have a role outside the ART setting, overall, a likelihood also observed in the systematic review of CE-targeted microbiota therapies in the Introduction that found that antibiotic, probiotic, and nutraceutical interventions to restore *Lactobacillus* dominance may be beneficial reproductive outcome in CE-related recurrent implantation failure, although a still-limited and heterogeneous evidence base was identified.

The main strength of this review is that it is limited to studies that directly study the endometrial (not necessarily vaginal or cervical) compartment, and has an explicit, study-level risk-of-bias assessment, through the ROBINS-I. Yet, a number of shortcomings should be noted. First, it was found that a few of the studies included did not give a directly extractable odds ratio or contingency table, and had to be approximated by taking reported proportions or, in a small fraction of cases, an approximation of an estimate representative of the direction and approximate strength of association; the pooled estimate is to be understood as indicative of the direction and approximate strength of association instead of a full precision-weighted meta-analytic result. Second, the number of studies included in the quantitative synthesis ($k = 8$) is small and thus the reliability of the heterogeneity and small-study-effect measures. Third, dominance thresholds differed across studies (80-90 relative abundance) and timing of sampling in relation to the embryo transfer or implantation window was not consistently reported, each of which is likely to contribute to the heterogeneity. Fourth, the majority of studies included were in women of heterogeneous aetiology infertility, and confounding by underlying infertility aetiology, endometrial thickness, and controlled ovarian stimulation regimen could not be completely ruled out throughout this literature of observations.

Primary research in this area in the future needs to take into account standardised, species-level (as opposed to genus-level) characterisation of the endometrial microbiome, uniformity in sampling time with respect to the implantation window, and pre-defined dominance thresholds that allow greater meta-analytic pooling.

Prospective cohorts, ideally adequately powered, of microbiome-directed intervention (antibiotic, probiotic, or vaginal microbiota transplantation strategies) in women with a proven non-Lactobacillus-dominated or CE-associated endometrial profile are required to shift this field to causality, rather than association, and evidence that can be clinically acted on.

5. Conclusion

This systematic review of eleven original primary studies identified a statistically significant pooled association between Lactobacillus-dominated endometrial microbiota and a positive outcome in implantation, clinical pregnancy, or live birth after assisted reproductive technology in women (OR 2.42, 95% CI 1.68 to 3.49) and some consistent, albeit narratively, but not quantitatively synthesised evidence of a chronically inflamed endometrial profile characterised by Lactobacillus-dominated endometrial microbiota. The species-level outcome indicates that the abundance of Lactobacillus crispatus, in particular, rather than the dominance of genus Lactobacillus, may be more specific to predicting reproductive outcome, which is not reflected in the existing genus-level dominance models. Strong methodological heterogeneity among this primary literature, including sequencing platform, dominance threshold, and outcome definition, have so far constrained the accuracy and clinical implementability of the endometrial microbiome as an ART prognostic or diagnostic tool, and future studies should focus on methodological standardisation before endometrial microbiome testing can become more routinely integrated into clinical ART decision-making.

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