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INPLASY

Vaginal Microbiota Dysbiosis and Adverse Gynaecological Outcomes: A Structured Narrative Review of Associations and Temporal Relationships

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 April 2026 and was last updated on 28 May 2026.

INTRODUCTION

Review question / Objective To synthesise the mechanistic and epidemiological evidence linking vaginal microbiota dysbiosis (CST IV / bacterial vaginosis) to seven pre-specified adverse gynaecological outcomes: BV recurrence, high-risk HPV persistence and cervical intraepithelial neoplasia (CIN), pelvic inflammatory disease (PID), endometriosis, sexually transmitted infection and HIV susceptibility, assisted reproductive technology (IVF/ART) outcomes, and spontaneous preterm birth. Using the PICOS framework — Population: reproductive-age women (18–50 years); Exposure: CST IV / Lactobacillus-depleted vaginal microbiota characterised by 16S rRNA sequencing, qPCR, or Nugent/Amsel criteria; Comparator: Lactobacillus-dominant microbiota (CST I–III, V); Outcomes: seven pre-specified gynaecological outcome domains; Study designs: prospective cohort, retrospective cohort, case-control, and randomised controlled trials.

Rationale Despite a substantial body of primary literature, no comprehensive structured narrative synthesis exists that simultaneously addresses all seven gynaecological outcome domains of vaginal dysbiosis, explicitly distinguishes mechanistic plausibility from causal evidence, incorporates GRADE certainty ratings for each outcome, and contextualises the null results of the first randomised controlled trials of dysbiosis treatment (Lactin-V RCT; Haahr 2025 IVF RCT). This review addresses three specific gaps: (1) the directionality problem — for several outcomes the association is plausible in both directions; (2) the translational paradox — strong mechanistic evidence has not consistently translated to clinical benefit; (3) ethnic and methodological heterogeneity — CST IV prevalence ranges from ~9% (European ancestry) to ~40% (sub-Saharan African).

Condition being studied Vaginal microbiota dysbiosis — community state type IV (CST IV) — in reproductive-age women. Characterised by Lactobacillus depletion and replacement by polymicrobial anaerobes (Gardnerella vaginalis,

Prevotella bivia, Fusobacterium nucleatum, Mobiluncus spp., Sneathia sanguinegens, Fannyhessea vaginae, BVAB1–3). Clinically equivalent to bacterial vaginosis (Nugent score ≥7 or Amsel criteria ≥3/4). Affects 23–50% of reproductive-age women globally.

METHODS

Search strategy PubMed/MEDLINE, EMBASE, Cochrane Library, and Web of Science searched from January 2000 to April 2026. Exposure terms: "vaginal microbiome" OR "vaginal microbiota" OR "bacterial vaginosis" OR "Lactobacillus" OR "community state type" OR "CST IV" OR "vaginal dysbiosis" OR "Gardnerella vaginalis" OR "Nugent" OR "Amsel" — combined (Boolean AND) with outcome-specific terms for each of seven domains. English language only.

Participant or population Women of reproductive age (18–50 years) with vaginal microbiota characterised by 16S rRNA gene sequencing, validated qPCR, or standard culture methods (Nugent score or Amsel criteria). Minimum 50 participants per study. No restriction on geographic location or ethnicity.

Intervention Vaginal microbiota dysbiosis (CST IV / bacterial vaginosis): Lactobacillus-depleted polymicrobial anaerobic vaginal community, defined by 16S rRNA sequencing (CST IV), Nugent score ≥7, or Amsel criteria ≥3/4.

Comparator Lactobacillus-dominant vaginal microbiota: CST I (L. crispatus), CST II (L. gasseri), CST III (L. iners), or CST V (L. jensenii); or Nugent score 0–3. In interventional studies: placebo or no treatment.

Study designs to be included Prospective cohort, retrospective cohort, case-control, and randomised controlled trials. Minimum 50 participants. Exclusions: review articles, case reports, conference abstracts without full-text, animal studies, in vitro studies.

Eligibility criteria Inclusion: Women 18–50 years; vaginal microbiota by 16S rRNA/qPCR/Nugent/Amsel; prospective/retrospective cohort, case-control, or RCT; ≥50 participants; ≥1 of 7 pre-specified outcomes with effect estimate; English language; January 2000–April 2026.
Exclusion: Review articles; case reports (<50 participants); conference abstracts without full-text; animal/in vitro studies; uterine microbiome only studies; non-English publications.

Information sources PubMed/MEDLINE, EMBASE, Cochrane Library, Web of Science Core Collection. January 2000 – April 2026. Grey literature not systematically searched.

Main outcome(s) (1) BV recurrence at 12 months post-treatment; (2) hrHPV persistence and CIN 2+ incidence; (3) incident pelvic inflammatory disease; (4) laparoscopically confirmed endometriosis; (5) incident HIV/STI acquisition; (6) IVF/ART clinical pregnancy rate and implantation rate; (7) spontaneous preterm birth (<37 weeks). Effect measures: OR, RR, aOR, or HR with 95% CI.

Additional outcome(s) GRADE evidence certainty rating for each of the seven outcome domains. Mechanistic pathway analysis (pro-inflammatory cytokine profiles, mucosal immune activation biomarkers). Post-treatment microbiota reconstitution phenotype in BV recurrence studies.

Data management Standardised extraction form: study design, country, sample size, microbiota assessment method, exposure definition, comparator, outcome measure, effect estimate with 95% CI, confounder adjustment list, NOS/AXIS quality score. Two independent reviewers (S.Ş. and F.G.Ş.); disagreements by consensus. Data managed in Microsoft Excel.

Quality assessment / Risk of bias analysis Cohort/case-control: Newcastle-Ottawa Scale (NOS; max 9 stars). Cross-sectional: AXIS tool. RCTs: Cochrane RoB 2. Evidence certainty rated using GRADE framework for each outcome domain (baseline Low for observational evidence, upgraded where applicable). Inter-rater agreement: Cohen's κ = 0.83.

Strategy of data synthesis Structured narrative synthesis following PRISMA-NR methodology. Studies grouped by outcome domain. Effect estimates in tabular form (Table 1). GRADE profiles for each outcome (Table 2). No quantitative pooling (meta-analysis) due to heterogeneity of microbiome assessment methods and outcome definitions across domains.

Subgroup analysis Within each domain: stratified by microbiome assessment method (16S rRNA vs qPCR vs culture/Nugent), study design (prospective vs retrospective vs case-control), and geographic/ethnic population where data permitted. CST I vs CST III vs CST IV subgroup comparisons reported where available.

Sensitivity analysis Not applicable (structured narrative review). Study quality assessed with

validated tools; high risk of bias studies noted explicitly and GRADE downgraded accordingly. Studies using Nugent/Amsel only (without molecular characterisation) identified separately from 16S sequencing studies.

Language restriction English only.

Country(ies) involved Turkey.

Other relevant information Review includes 5 original figures: GRADE evidence profile (Fig 1), mechanistic paradox table (Fig 2), anatomical compartment schematic (Fig 3), limitations/ research gaps panels (Fig 4), forest-plot style effect estimates (Fig 5). AI-assisted drafting employed; all content verified against primary sources by authors. Target journal: BMC Women's Health or Archives of Gynecology and Obstetrics (Springer Nature — TÜBİTAK EKUAL open access agreement).

Keywords vaginal microbiome; bacterial vaginosis; community state type; Lactobacillus crispatus; dysbiosis; cervical intraepithelial neoplasia; pelvic inflammatory disease; endometriosis; preterm birth; IVF.

Dissemination plans Submission to PubMed-indexed international journal (BMC Women's Health or Archives of Gynecology and Obstetrics). Open access publication under TÜBİTAK EKUAL institutional agreement. Findings to be presented at relevant gynaecology/reproductive medicine conferences.

Contributions of each author

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