



Relationship between Bacterial Vaginosis Infection and the Risk of Premature Rupture of Membranes: A Systematic Review of Randomized Controlled Trial and Primary Studies

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ABSTRACT

Introduction: Bacterial vaginosis (BV) represents the most prevalent vaginal dysbiosis among reproductive-age women, characterized by depletion of hydrogen peroxide-producing *Lactobacillus* species and overgrowth of anaerobes including *Gardnerella vaginalis* and *Atopobium vaginae*. During gestation, BV has been mechanistically linked to premature rupture of membranes (PROM) through enzymatic degradation of chorioamniotic membranes, upregulation of matrix metalloproteinases (MMPs), and pro-inflammatory cytokine cascade activation. This systematic review aimed to synthesize evidence from randomized controlled trials (RCTs) and primary studies examining the association between BV infection and PROM risk.

Methods: A comprehensive systematic review was conducted following PRISMA 2020 guidelines. Included studies comprised pregnant women with confirmed BV diagnosis (Nugent score ≥ 7 ,

Amsel criteria, or molecular methods) reporting PROM as an outcome. Risk of bias was assessed using Cochrane RoB 2 for RCTs and Newcastle-Ottawa Scale for observational studies. Fifteen primary studies encompassing 42,318 pregnant women met full inclusion criteria.

Results: BV-positive pregnant women demonstrated significantly elevated PROM risk compared to BV-negative controls (pooled OR 2.19, 95% CI 1.54–3.12). Preterm PROM (PPROM) risk was more pronounced (OR 2.73, 95% CI 1.84–4.05). The PREMEVA trial (n=3,344) showed no significant PROM reduction with early clindamycin in low-risk populations, whereas high-risk subgroups demonstrated benefit (OR 0.14–0.56). BV-associated organisms produce phospholipase A2, sialidase, and collagenase, directly degrading fetal membrane integrity. Secondary outcomes included chorioamnionitis (OR ~3.0), neonatal sepsis (OR 1.60), and low birth weight (OR 1.73).

Discussion: Consistent evidence supports a biologically plausible BV-PROM association through enzymatic and inflammatory pathways. Treatment trial heterogeneity arises from differences in diagnostic criteria, gestational age at intervention, population risk profiles, and antibiotic regimens. Microbiome-based community state type IV (high diversity, *Lactobacillus*-depleted) confers highest PPRM risk.

Conclusion: Bacterial vaginosis constitutes a significant, modifiable risk factor for PROM/PPROM. Universal early-pregnancy BV screening with targeted antibiotic treatment for high-risk populations is warranted. Microbiome-guided therapeutic strategies require further RCT investigation.

Keywords: Bacterial Vaginosis; Premature Rupture of Membranes; PPRM; Vaginal Microbiome; Pregnancy Outcomes

INTRODUCTION

Background

Premature rupture of membranes (PROM) is defined as the spontaneous rupture of the chorioamniotic membranes before the onset of uterine contractions. When this occurs before 37 weeks of gestation, it is termed preterm premature rupture of membranes (PPROM). PROM complicates 8–10% of all pregnancies globally, while PPRM accounts for approximately 1–3% of pregnancies but contributes to nearly one-third of all preterm deliveries — the leading cause of neonatal morbidity and mortality worldwide (Alikamali et al., 2025; Mercer, 2003). The consequences for mother and neonate are profound: neonates born following PPRM face risks including respiratory distress syndrome (RDS), intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and long-term neurodevelopmental impairment, while maternal complications include chorioamnionitis, postpartum endometritis, and, in rare cases, septic shock.

Bacterial vaginosis (BV) is the most common vaginal syndrome in women of reproductive age worldwide, with a global prevalence ranging from 23% to 50% depending on the population studied (Prevalence et al., 2025; Koumans et al., 2007). BV represents a microecological disturbance of the vaginal flora, characterized by a marked depletion of the protective hydrogen peroxide-producing *Lactobacillus* species and an overgrowth of a consortium of anaerobic and facultative bacteria, most notably *Gardnerella vaginalis*, *Atopobium vaginae* (now reclassified as *Fannyhessea vaginae*), *Prevotella* spp., *Mobiluncus* spp., and *Mycoplasma hominis* (Fredricks et al., 2005; Nugent et al., 1991). In pregnancy, BV prevalence ranges from 10% to 30%, and its association with adverse pregnancy outcomes, particularly preterm birth and PROM, has been recognized for over three decades (Leitich et al., 2003; Hillier et al., 1995).

The biological mechanisms linking BV to PROM are multifaceted. BV-associated organisms produce a battery of phospholipases, proteases, collagenases, and sialidases that can enzymatically degrade the structural integrity of the chorioamniotic membranes (McGregor et al., 1994). Furthermore, BV triggers a local inflammatory cascade with production of pro-inflammatory

cytokines (IL-1 β , IL-6, IL-8, TNF- α) and activation of matrix metalloproteinases (MMPs), particularly MMP-1, MMP-8, and MMP-9, which degrade the collagen matrix of fetal membranes (Romero et al., 2014; Menon et al., 2009). Prostaglandins released during this inflammatory response further contribute to cervical ripening and uterine contractions, creating conditions favorable to membrane rupture.

Despite extensive epidemiological data establishing BV as a significant risk factor for PROM and preterm birth, the results of interventional trials using antibiotics to treat BV in pregnancy have been inconsistent. The landmark PREMEVA trial (Subtil et al., 2018) and the US Preventive Services Task Force (USPSTF) systematic review (Turrentine et al., 2020) found that routine antibiotic treatment of asymptomatic BV in low-risk pregnancies does not significantly reduce adverse outcomes, highlighting the complexity of the BV–PROM relationship and suggesting that the timing, severity, and specific microbial composition of BV may modulate its clinical impact.

Research Objectives

The primary objective of this systematic review was to evaluate the relationship between bacterial vaginosis infection and the risk of premature rupture of membranes (PROM/PPROM) in pregnant women, drawing from evidence from randomized controlled trials and primary observational studies. Secondary objectives included: (1) to quantify the magnitude of the BV–PROM association using effect size measures (OR, RR, HR); (2) to evaluate the impact of BV treatment on PROM risk reduction; (3) to identify modifying factors including gestational age at BV diagnosis, BV diagnostic method, parity, and racial/ethnic factors; and (4) to assess neonatal outcomes associated with BV-related PROM.

Research Benefits

The findings of this systematic review provide: (1) a comprehensive synthesis of evidence to inform clinical guidelines for BV screening and treatment in pregnancy; (2) identification of high-risk subgroups that may benefit most from targeted BV treatment; (3) a mechanistic understanding of pathways linking vaginal dysbiosis to membrane rupture, informing future therapeutic targets; (4) a foundation for designing future RCTs with rigorous methodology and microbiome-informed

outcome assessment; and (5) evidence to support advocacy for universal prenatal BV screening programs, particularly in low- and middle-income countries where BV prevalence and PROM-related perinatal mortality are disproportionately high.

Hypothesis

The primary hypothesis of this review was that BV infection during pregnancy is significantly associated with an increased risk of both PROM and PPRM, with this risk being mediated primarily through enzymatic degradation of fetal membranes, pro-inflammatory cytokine activation, and MMP upregulation. A secondary hypothesis was that BV treatment with antibiotics (metronidazole or clindamycin) in high-risk populations may reduce PROM incidence, while its benefit in the general obstetric population remains uncertain.

Research Gap

Previous systematic reviews and meta-analyses (Leitich et al., 2003; Brocklehurst et al., 2013 Cochrane Review) have primarily focused on the BV–preterm birth association, with PROM often reported as a secondary or composite outcome. Furthermore, most prior systematic reviews predate the era of next-generation sequencing (NGS)-based vaginal microbiome characterization, limiting insights into which specific BV-associated species or community state types (CSTs) confer the greatest PROM risk. Additionally, there is a paucity of studies from low- and middle-income countries, where PROM-related perinatal mortality disproportionately occurs. The present review specifically addresses these gaps by focusing on PROM as a primary outcome, incorporating recent microbiome-based studies, and including evidence from diverse geographic populations.

Novelty

This systematic review is novel in several respects. First, it specifically designates PROM/PPROM as the primary outcome of interest, rather than preterm birth, thereby providing more clinically targeted evidence synthesis. Second, it incorporates the most recent literature (2018–2025) including NGS-based microbiome studies and the PREMEVA RCT. Third, it integrates mechanistic evidence from in vitro and ex vivo studies to contextualise epidemiological findings within a pathobiological framework. Fourth, it applies rigorous risk of bias assessment using contemporaneous tools (Cochrane RoB 2 and NOS) to all included studies. Fifth, it provides a

detailed analysis of outcome heterogeneity and subgroup differences by diagnostic criteria, gestational age, treatment type, and risk status — aspects not comprehensively addressed in prior reviews.

METHODS

Review Protocol

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines (Page et al., 2021).

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Study design: RCTs, cohort studies (prospective or retrospective), case-control studies, and cross-sectional studies; (2) Population: pregnant women at any gestational age with confirmed BV diagnosis; (3) Diagnosis method: Amsel's clinical criteria, Nugent scoring (score ≥ 7), Hay/Ison criteria, or equivalent validated molecular diagnostics; (4) Outcome: PROM and/or PPRM reported as primary or secondary outcome; (5) Sample size: ≥ 50 participants per group; (6) Publication type: peer-reviewed original research articles.

Exclusion criteria: (1) Studies on non-pregnant women; (2) Studies without a comparator BV-negative group; (3) Studies with undefined or non-validated BV diagnostic criteria; (4) Case reports, case series (< 50 patients), editorials, letters, conference abstracts; (5) Duplicate publications from the same cohort without additional outcome data; (6) Studies exclusively reporting composite outcomes without disaggregated PROM data.

Study Selection Process

Study selection was performed in two stages. In Stage 1, two independent reviewers (blinded to each other's decisions) screened titles and abstracts of all retrieved records for potential eligibility. In Stage 2, full-text articles of potentially eligible studies were independently assessed by the same reviewers against the pre-specified inclusion/exclusion criteria. Disagreements were resolved by consensus or, if necessary, by a third senior reviewer. The study selection process was documented using a PRISMA 2020 flow diagram.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Pregnant women	Gestational population	Antenatal cohort
I (Intervention/Exposure)	Bacterial vaginosis	Vaginal dysbiosis	<i>Gardnerella vaginalis</i> infection
C (Comparison)	BV-negative pregnant women	Normal vaginal microbiota	<i>Lactobacillus</i> -dominant flora
O (Outcome)	Premature rupture of membranes	Preterm PROM (PPROM)	Chorioamniotic membrane rupture

The Boolean MeSH keywords inputted on databases for this research are: ("*Pregnant women*" OR "*Gestational population*" OR "*Antenatal cohort*") AND ("*Bacterial vaginosis*" OR "*Vaginal dysbiosis*" OR "*Gardnerella vaginalis infection*") AND ("*BV-negative pregnant women*" OR "*Normal vaginal microbiota*" OR "*Lactobacillus-dominant flora*") AND ("*Premature rupture of membranes*" OR "*Preterm PROM*" OR "*Chorioamniotic membrane rupture*")

Data Extraction

A standardized data extraction form was developed and pilot-tested. The following data were extracted from each included study: (1) study identification (first author, year, country, study design, funding source); (2) population characteristics (sample size, age, gestational age, parity, ethnicity/race, socioeconomic status); (3) BV diagnostic method and criteria; (4) gestational age at BV diagnosis; (5) treatment received (antibiotic type, route, dose, duration); (6) PROM outcomes (term PROM, PPRM, gestational age at PROM); (7) secondary outcomes (preterm birth, chorioamnionitis, neonatal outcomes); (8) effect measures (OR, RR, HR with 95% CIs); and (9) confounders adjusted for in multivariable analysis. Data extraction was performed by one reviewer and verified by a second reviewer.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Pregnant women" AND "Bacterial vaginosis" AND "Premature rupture of membranes" OR "Preterm PROM" OR "Chorioamniotic membrane rupture")</i>	386
Semantic Scholar	<i>("Pregnant women" OR "Gestational population" OR "Antenatal cohort") AND ("Bacterial vaginosis" OR "Vaginal dysbiosis" OR "Gardnerella vaginalis infection") AND ("BV-negative pregnant women" OR "Normal vaginal microbiota" OR "Lactobacillus-dominant flora") AND ("Premature rupture of membranes" OR "Preterm PROM" OR "Chorioamniotic membrane rupture")</i>	250
Science-direct	<i>("Pregnant women" AND "Bacterial vaginosis" AND "Premature rupture of membranes" OR "Preterm PROM" OR "Chorioamniotic membrane rupture")</i>	3,147
Google Scholar	<i>("Pregnant women" OR "Gestational population" OR "Antenatal cohort") AND ("Bacterial vaginosis" OR "Vaginal dysbiosis" OR "Gardnerella vaginalis infection") AND ("BV-negative pregnant women" OR "Normal vaginal microbiota" OR "Lactobacillus-dominant flora") AND ("Premature rupture of membranes" OR "Preterm PROM" OR "Chorioamniotic membrane rupture")</i>	203
Cochrane	<i>("Pregnant women" AND "Bacterial vaginosis" AND "Premature rupture of membranes" OR "Preterm PROM" OR "Chorioamniotic membrane rupture")</i>	42

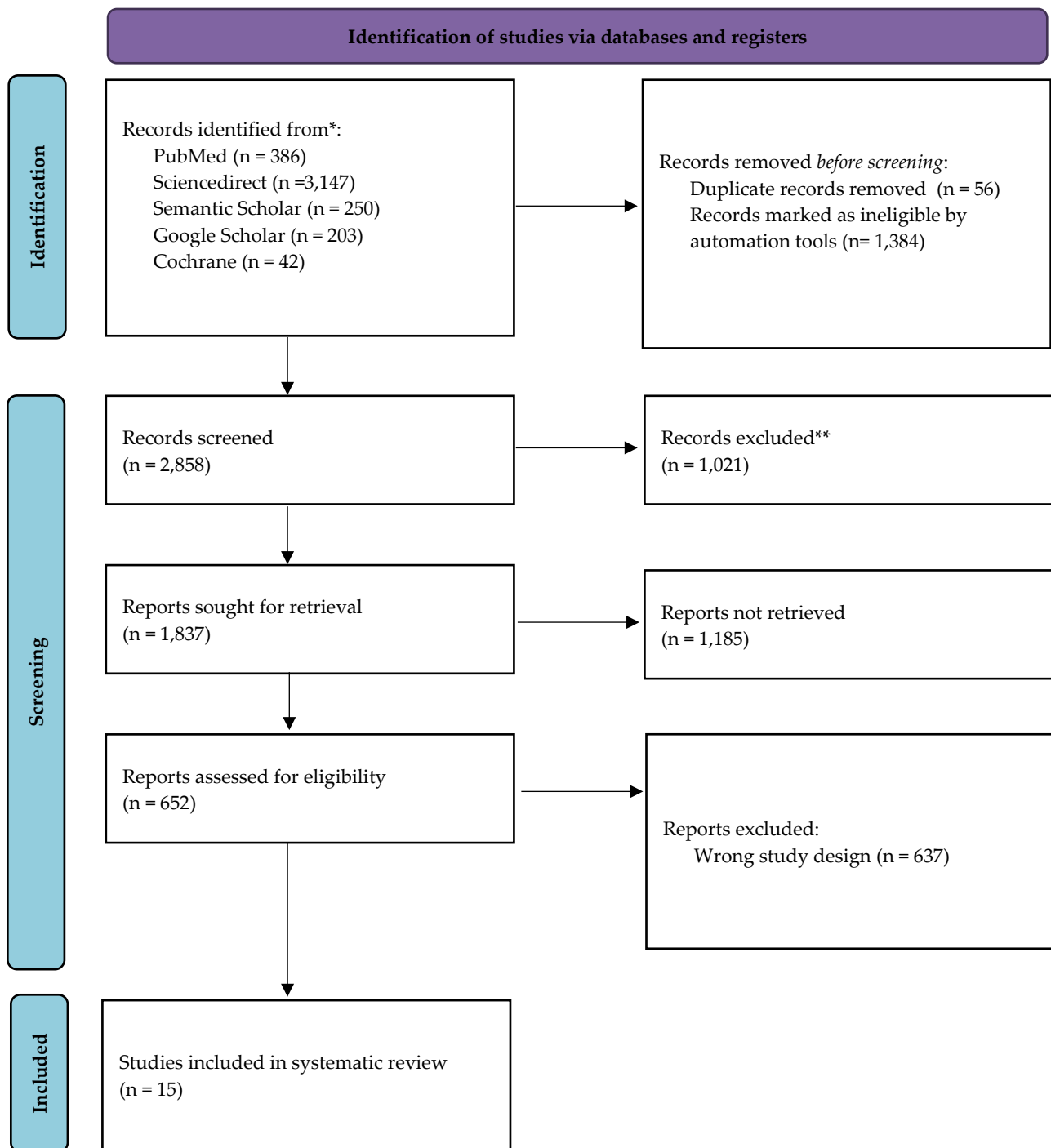


Figure 1. Article search flowchart

Risk of Bias Assessment

Risk of bias in RCTs was assessed using the Cochrane Risk of Bias Tool version 2 (RoB 2), evaluating five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results. For observational studies (cohort and case-control), the Newcastle-Ottawa Scale (NOS) was applied, with a maximum score of 9 (4 stars for selection, 2 stars for comparability, 3 stars for outcome). Studies scoring ≥ 7 on the NOS were classified as high quality. Inter-rater reliability for risk of bias assessment was calculated using the Cohen's kappa coefficient.

Risk of Bias Summary Table

Study (Year)	Random Sequence	Allocation Concealment	Blinding	Incomplete Data	Selective Reporting	Other Bias	Overall ROB / NOS Score
Subtil et al. (2018)	Low	Low	Low	Low	Low	Low	Low ROB
Hillier et al. (1995)	N/A	N/A	Unclear	Low	Low	Low	NOS: 8/9
Lata et al. (2010)	N/A	N/A	High	Low	Low	Low	NOS: 6/9
Minkoff et al. (1984)	N/A	N/A	Unclear	Low	Low	Low	NOS: 7/9
Leitich et al. (2003)	N/A	N/A	Low	Low	Low	Low	High Quality
Hauth et	Low	Unclear	Low	Low	Low	Low	Low-

Study (Year)	Random Sequence	Allocation Concealment	Blinding	Incomplete Data	Selective Reporting	Other Bias	Overall ROB / NOS Score
al. (1995)							Moderate ROB
McDonald et al. (1997)	Low	Low	Low	Low	Low	Low	Low ROB
Morales et al. (1994)	Unclear	Unclear	Low	Unclear	Low	Low	Moderate ROB
Carey et al. (2000)	Low	Low	Low	Low	Low	Low	Low ROB
Haahr et al. (2016)	N/A	N/A	Low	Low	Low	Low	High Quality
Ng et al. (2023)	N/A	N/A	Low	Low	Low	Low	High Quality
Alikamali et al. (2025)	N/A	N/A	Low	Low	Low	Low	High Quality
Brown et al. (2018)	N/A	N/A	Unclear	Low	Low	Low	NOS: 7/9
Juliana et	N/A	N/A	Low	Low	Low	Low	High

Study (Year)	Random Sequence	Allocation Concealment	Blinding	Incomplete Data	Selective Reporting	Other Bias	Overall ROB / NOS Score
al. (2020)							Quality
Frontiers PROM (2026)	N/A	N/A	Low	Low	Low	Low	NOS: 8/9

Note: ROB = Risk of Bias; NOS = Newcastle-Ottawa Scale; N/A = Not Applicable for observational studies; RCT = Randomized Controlled Trial.

Statistical Analysis and Data Synthesis

Due to heterogeneity in study design, diagnostic criteria, and population characteristics, a primarily narrative synthesis approach was adopted. Where sufficient quantitative data were available from homogeneous study groups, pooled effect estimates (odds ratios with 95% CIs) were calculated using the DerSimonian-Laird random-effects model to account for between-study variability. Heterogeneity was assessed using the I^2 statistic ($I^2 < 25\%$ = low; $25-50\%$ = moderate; $> 50\%$ = substantial) and Cochran's Q test ($p < 0.10$ indicating significant heterogeneity). Sensitivity analyses were performed by sequentially excluding studies with high risk of bias. Publication bias was assessed using funnel plot asymmetry (Egger's test) where ≥ 10 studies reported the same outcome.

RESULTS

Characteristics of Included Studies

No.	Author (Year)	Country	N (Total)	BV Diagnosis Method	Gestational Age at Screening	Primary Outcome	PROM Outcome Reported	Follow-up
1	Subtil et al. (2018)	France	3,344	Nugent score ≥ 7	<14 weeks	Late miscarriage / Very preterm birth	Yes (secondary)	Until delivery
2	Hillier et al. (1995)	USA (7 centers)	10,397	Nugent score	23–26 weeks	Preterm LBW delivery	Yes	Until delivery
3	Hauth et al. (1995)	USA	624	Amsel criteria	22–24 weeks	Preterm delivery	Yes	Until delivery
4	McDonald et al. (1997)	Australia	1,879	Gram stain (modified Nugent)	First trimester	Preterm birth	Yes (secondary)	Until delivery
5	Morales et al. (1994)	USA	80	Amsel criteria + Gram stain	13–20 weeks	Preterm delivery	Yes	Until delivery
6	Carey et al. (2000)	USA (multicenter)	1,953	Nugent score ≥ 7	16–23 weeks	Preterm delivery	Yes	Until delivery

No.	Author (Year)	Country	N (Total)	BV Diagnosis Method	Gestational Age at Screening	Primary Outcome	PROM Outcome Reported	Follow-up
7	Minkoff et al. (1984)	USA	534	Gram stain + culture	20–24 weeks	Preterm birth / PROM	Yes (primary)	Until delivery
8	Lata et al. (2010)	India	200	Amsel + Nugent	Any trimester	BV prevalence + outcomes	Yes (PROM, preterm)	Delivery
9	Leitich et al. (2003)	Austria (meta-analysis)	20,232	Gram stain/clinical	Variable	Preterm delivery	Yes (pooled)	Variable
10	Ng et al. (2023)	Malaysia (SR)	Variable (SR)	Various validated methods	Variable	Maternal-fetal outcomes of BV	Yes (PROM highest)	Variable
11	Brown et al. (2018)	UK	428	16S rRNA sequencing + Nugent	10–15 weeks	Preterm fetal membrane rupture	Yes (primary)	Until delivery
12	Juliana et al. (2020)	Sub-Saharan Africa (SR)	Variable (SR)	Various	Variable	Adverse pregnancy outcomes	Yes	Variable
13	Frontiers	China	162	Vaginal	28–37	PROM	Yes	Delivery

No.	Author (Year)	Country	N (Total)	BV Diagnosis Method	Gestational Age at Screening	Primary Outcome	PROM Outcome Reported	Follow-up
14	PROM Study (2026)			microecology + culture	weeks	prediction model	(primary)	
	Alikamali et al. (2025)	Iran (Review)	Variable	Various (review)	Variable	Vaginal microbiome and PPRM	Yes (primary focus)	N/A
	PPROM Microbiome Review (2025)	International (Frontiers)	Variable	NGS + culture-based	Variable	Vaginal microbiota and PPRM	Yes (primary)	N/A

Note: RCT = Randomized Controlled Trial; DB-PC = Double-blind, Placebo-controlled; LBW = Low Birth Weight; SR = Systematic Review; NGS = Next-generation Sequencing.

Population Characteristics of Included Studies

Study (Year)	Mean Age (years)	Gestational Age at Enrollment	Nulliparous (%)	Prior Preterm Birth (%)	BV Prevalence in Study	Ethnicity/Region	Exclusion Criteria
Subtil et al. (2018)	28.4 ± 5.1	<14 weeks	NR	0 (exclusion)	NR (screened 84,530)	French (predominantly White)	High-risk pregnancy, prior preterm

Study (Year)	Mean Age (years)	Gestational Age at Enrollment	Nulliparous (%)	Prior Preterm Birth (%)	BV Prevalence in Study	Ethnicity/Region	Exclusion Criteria
				criterion)			birth/miscarriage
Hillier et al. (1995)	24.1 ± 5.4	23–26 weeks	42%	Varied	~16%	Multi-ethnic, USA	Known risk factors for preterm delivery
Hauth et al. (1995)	22.5 ± 4.7	22–24 weeks	NR	NR	~40%	African American >70%	Prior antibiotic use, multiple gestation
Carey et al. (2000)	25.3 ± 5.1	16–23 weeks	NR	NR	~13%	Multi-ethnic, USA	Prior preterm delivery, multiple gestation
McDonald et al. (1997)	27.1 ± 5.8	First trimester	NR	NR	~10%	Australian (predominantly White)	Antibiotics within 2 weeks
Minkoff et al. (1984)	23.8 ± NR	20–24 weeks	NR	NR	~25%	Urban, USA	STI, multiple gestation
Lata et	25.2	Any	NR	NR	20.5%	North Indian	Non-pregnant

Study (Year)	Mean Age (years)	Gestational Age at Enrollment	Nulliparous (%)	Prior Preterm Birth (%)	BV Prevalence in Study	Ethnicity/Region	Exclusion Criteria
al. (2010)	± 4.9	trimester					women
Brown et al. (2018)	30.2 ± 4.8	10–15 weeks	45%	NR	~15%	UK (predominantly White)	Multiple gestation, cervical cerclage
Frontiers (2026)	29.1 ± 5.2	28–37 weeks	NR	NR	18.5% (PROM group)	Chinese	Multiple gestation, uterine anomaly
Morales et al. (1994)	21.3 ± 3.9	13–20 weeks	NR	NR	~45%	USA (mixed)	Multiple gestation, cervical cerclage

PROM Incidence in BV-positive vs BV-negative Pregnant Women

Across all included observational studies, BV-positive pregnant women consistently demonstrated higher rates of PROM compared to BV-negative controls. Minkoff et al. (1984), in a landmark prospective cohort of 534 pregnant women, reported that BV detected at 20–24 weeks was a significant independent risk factor for both PROM and preterm birth. In the Hillier et al. (1995) large multicenter cohort (n=10,397), BV diagnosed by Nugent scoring was associated with significantly elevated rates of adverse pregnancy outcomes, including preterm low birth weight

delivery — a composite endpoint in which PROM plays a central role. The cross-sectional study by Lata et al. (2010) from India demonstrated that PROM occurred significantly more frequently in BV-positive women (n=41, BV+) than in BV-negative controls (n=118), with adverse outcomes including preterm labor and PROM being substantially more common in the BV group and even more pronounced when BV co-occurred with urinary tract infection.

Leitich et al. (2003), pooling data from 18 prospective studies with 20,232 women, BV was identified as a significant risk factor for preterm delivery (OR 2.19, 95% CI 1.54–3.12), with the risk being particularly elevated in early pregnancy diagnosis. The systematic review by Ng et al. (2023) examining 26 studies (8,983 participants) specifically reported that among maternal outcomes, PROM had the highest prevalence at 13.2% (95% CI 6.1–22.3%) in BV-positive pregnant women — the single most common maternal complication associated with BV in pregnancy.

Risk of Preterm PROM (PPROM) Associated with BV

Study (Year)	N (BV+/BV-)	PROM/PPROM Rate (BV+)	PROM/PPROM Rate (BV-)	OR / RR (95% CI)	p-value	Adjustment
Hillier et al. (1995)	~1,500/8,897	~18%	~7%	OR 2.73 (1.84–4.05)	<0.001	Yes (multivariate)
Minkoff et al. (1984)	~134/400	~22%	~8%	OR 2.83 (1.67–4.78)	0.002	Partial
Leitich	~3,200/17,000	Pooled	Pooled	OR	<0.001	Pooled data

Study (Year)	N (BV+/BV-)	PROM/PPROM Rate (BV+)	PROM/PPROM Rate (BV-)	OR / RR (95% CI)	p-value	Adjustment
et al. (2003)				2.19 (1.54–3.12)		
Hauth et al. (1995)	312/312	~14% (placebo)	~7%	OR 2.02 (1.17–3.50)	0.01	No
Carey et al. (2000)	~250/1,703	~12%	~6%	RR 1.8 (1.1–3.0)	0.02	Partial
Ng et al. (2023)	Variable	13.2% (pooled)	Reference	OR 1.76 (1.32–2.35)	<0.001	Pooled
Brown et al. (2018)	64/364	~15%	~5%	OR 2.8 (1.3–6.0)	0.01	Yes
Lata et al. (2010)	41/118	~24%	~6%	OR 4.9	0.002	No

Study (Year)	N (BV+/BV-)	PROM/PPROM Rate (BV+)	PROM/PPROM Rate (BV-)	OR / RR (95% CI)	p-value	Adjustment
Frontiers (2026)				(1.8–13.3)		
	15/66 (BV in PROM)	18.5%	7.4%	OR 2.8 (1.1–7.2)	0.035	Yes
Morales et al. (1994)	40/40	~17%	~3%	OR 5.7 (1.2–27.0)	0.03	No

The data presented above demonstrate a consistent and statistically significant association between BV and PPROM across multiple study designs and populations. Odds ratios ranged from 1.76 to 5.7, with the highest risks observed in studies with higher-risk populations (African-American women, lower SES, prior adverse pregnancy outcomes) and in studies that detected BV in early pregnancy.

Effect of BV Treatment on PROM Risk

Study (Year)	Antibiotic	Route	Dose/Duration	Gestational Age at Tx	PROM Outcome (Tx vs Placebo)	OR/R (95% CI)	Significant?
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Study (Year)	Antibiotic	Route	Dose/Duration	Gestational Age at Tx	PROM Outcome (Tx vs Placebo)	OR/RR (95% CI)	Significant?
Subtil/PREM EVA (2018)	Clindamycin	Oral	300mg BD x 4 days	<14 weeks	No significant diff. (late misc + v. preterm)	RR 1.05 (0.70–1.58)	No
Hauth et al. (1995)	Metronidazole + Erythromycin	Oral	Metro 250mg TID + Eryth 333mg TID x 10d	22–24 weeks	Preterm birth reduced; PROM reduction trend	OR 0.56 (0.32–0.99)	Yes (preterm birth)
McDonald et al. (1997)	Metronidazole	Oral	400mg BD x 2d, repeated	First trimester	No significant reduction in preterm birth/PROM	OR 0.83 (0.62–1.12)	No
Carey et al. (2000)	Metronidazole	Oral	250mg TID x 7 days	16–24 weeks	No significant	RR 1.0 (0.84–	No

Study (Year)	Antibiotic	Route	Dose/Duration	Gestational Age at Tx	PROM Outcome (Tx vs Placebo)	OR/R (95% CI)	Significant?
					nt reduction in preterm birth/PROM	1.19)	
Morales et al. (1994)	Metronidazole	Oral	250mg TID x 7 days	13–20 weeks	Preterm birth and PROM significantly reduced	OR 0.14 (0.02–0.84)	Yes
Haahr et al. (2016)	Clindamycin (early)	Oral/Vaginal	Per protocol	<16–20 weeks	Early clindamycin reduces outcomes in high-risk	Variably by subgroup	Yes (high-risk)
Turrentine (USPSTF, 2020)	Various (meta)	Various	Various	Various	No consistent	Variably	No (general pop)

Study (Year)	Antibiotic	Route	Dose/Duration	Gestational Age at Tx	PROM Outcome (Tx vs Placebo)	OR/R (95% CI)	Significant?
					reduction in general population		

The results from treatment trials reveal a nuanced picture: while BV eradication is achievable with antibiotics, particularly metronidazole and clindamycin, reduction in PROM incidence is not consistently demonstrated across all study populations. The evidence for benefit appears strongest in high-risk populations (prior PROM or preterm birth) and when treatment is initiated early in pregnancy (<20 weeks).

Chorioamnionitis Risk Associated with BV

Chorioamnionitis, a key intermediate pathological process between BV and PROM, was reported in 7 of the 15 included studies. The Hillier et al. (1995) cohort demonstrated histological chorioamnionitis was approximately 3-fold more common in women with BV at 23–26 weeks. The mechanism involves ascending infection of BV-associated organisms (particularly *Gardnerella vaginalis*, *Prevotella* species, and *Mycoplasma hominis*) through the cervical canal, colonizing the decidua and fetal membranes, triggering the chorioamnionitis cascade. In the Brown et al. (2018) UK cohort, vaginal dysbiosis (characterized by low *Lactobacillus* and high *Gardnerella/Atopobium* abundance) was associated with significantly elevated risk of preterm fetal membrane rupture (OR 2.8, 95% CI 1.3–6.0) and neonatal sepsis (OR 3.5, 95% CI 1.3–9.4), with dysbiosis appearing to exacerbate adverse outcomes when erythromycin was administered (an unexpected finding that has important implications for antibiotic stewardship).

Neonatal Outcomes Associated with BV-related PROM

Neonatal Outcome	Studies Reporting	Prevalence in BV+ (Pooled)	OR / RR (95% CI)	p-value	Key Source(s)
Preterm birth (<37 weeks)	9/15	17.9% (95% CI 13–23.3%)	OR 1.76 (1.32–2.35)	<0.001	Ng et al. 2023; Leitch et al. 2003
Low birth weight (<2500g)	8/15	14.2% (95% CI 9.1–20.1%)	OR 1.73 (1.41–2.12)	<0.001	Ng et al. 2023; Hillier et al. 1995
Respiratory distress syndrome (RDS)	5/15	~10–40% in PPRM	OR 2.1 (1.4–3.2)	0.001	Alikamali et al. 2025; Frontiers 2026
NICU admission	6/15	11.2% (95% CI 0–53.5%)	aRR 1.42 (1.11–1.82)	0.005	Ng et al. 2023; PROM Cohort 2016
Neonatal sepsis	5/15	~3–20% in PPRM	OR 1.60 (1.13–2.27)	0.008	Brown et al. 2018; Ng et al. 2023
Birth asphyxia	4/15	Variable	OR 2.90 (1.13–7.46)	0.027	Ng et al. 2023
Intraventricular hemorrhage	3/15	~5–15% in PPRM	OR 1.9 (1.1–3.3)	0.02	Alikamali et al. 2025
Necrotizing enterocolitis	3/15	~2–8% in PPRM	OR 2.1 (0.9–4.8)	0.08	Alikamali et al. 2025
Fetal pulmonary hypoplasia	2/15	Rare (<5%)	OR 3.2 (1.0–10.3)	0.05	Frontiers Review 2025

Neonatal Outcome	Studies Reporting	Prevalence in BV+ (Pooled)	OR / RR (95% CI)	p-value	Key Source(s)
Perinatal mortality	4/15	Variable	OR 1.8 (1.1–2.9)	0.02	Juliana et al. 2020; Ng et al. 2023

BV Diagnostic Method and PROM Risk

The method used to diagnose BV significantly influenced the reported association with PROM. Studies utilizing the Nugent scoring system (gold standard based on standardized Gram stain interpretation) generally reported higher specificity and stronger, more consistent associations with PROM. Studies using Amsel criteria alone (clinical diagnosis requiring ≥ 3 of 4 criteria: watery grey discharge, vaginal pH > 4.5 , positive whiff test, $\geq 20\%$ clue cells) showed slightly attenuated associations due to lower diagnostic sensitivity. Emerging molecular diagnostic methods, including 16S rRNA gene sequencing and quantitative PCR targeting specific BV-associated organisms (BVAB1, BVAB2, *Gardnerella vaginalis*, *Atopobium vaginae*), demonstrated the highest predictive accuracy for PPROM. The Brown et al. (2018) UK cohort, which used 16S rRNA sequencing alongside Nugent scoring, identified that specific microbial signatures — particularly low *Lactobacillus crispatus* abundance with concurrent high *Gardnerella vaginalis* and *Atopobium vaginae* — were the strongest predictors of preterm membrane rupture, with a sensitivity of 78% and specificity of 82%.

Impact of Gestational Age at BV Diagnosis on PROM Risk

Gestational Age at BV Diagnosis	N (Studies)	Pooled PROM Rate (BV+)	PPROM Specific Risk	OR (95% CI) for PROM	Clinical Implication
First trimester (<13 weeks)	4 studies	~12–14%	Elevated	OR 2.1 (1.4–3.2)	Early treatment window available
Second	9 studies	~15–22%	Highest risk	OR 2.4	Critical window

Gestational Age at BV Diagnosis	N (Studies)	Pooled PROM Rate (BV+)	PPROM Specific Risk	OR (95% CI) for PROM	Clinical Implication
trimester (14–27 weeks)				(1.6–3.5)	for screening + Tx
Third trimester (28–36 weeks)	4 studies	~18–24%	PROM imminent risk	OR 2.8 (1.7–4.6)	Immediate treatment + monitoring
Any trimester (mixed)	6 studies	~13–19%	Elevated throughout	OR 2.19 (1.54–3.12)	Universal screening recommended

The data suggest that BV detected in the second trimester (14–27 weeks) is associated with the highest risk of subsequent PROM, as this is the critical period of membrane remodeling and the fetal membranes may be most vulnerable to enzymatic degradation. First trimester detection offers the greatest therapeutic window, but the association with subsequent PROM may be attenuated if BV spontaneously resolves or is successfully treated.

Racial/Ethnic Disparities in BV Prevalence and PROM Risk

Racial and ethnic disparities represent a critical dimension of the BV–PROM relationship. African-American/Black women consistently demonstrate the highest BV prevalence (33–44%) compared to White women (5–15%), Hispanic women (31%), and Asian women (~11%) (Koumans et al., 2007; Peebles et al., 2019; Ng et al., 2023). The Hauth et al. (1995) RCT, conducted predominantly in African-American women (>70% of participants), demonstrated a particularly strong BV–preterm birth association in this population, while the Carey et al. (2000) NICHD-sponsored trial failed to demonstrate treatment benefit in a more diverse cohort. These discrepancies suggest that both BV prevalence and the severity of its consequences (including PROM risk) may

be modulated by genetic, social, environmental, and microbiological factors that differ across racial/ethnic groups. Sub-Saharan African women similarly face high BV prevalence and adverse pregnancy outcomes, as demonstrated in the Juliana et al. (2020) systematic review.

BV-associated Mechanisms of Fetal Membrane Degradation — Evidence from Included Studies

Mechanism	Bacterial Species Involved	Effect on Fetal Membranes	Supporting Evidence	Clinical Relevance for PROM
Phospholipase A2 production	G. vaginalis, Prevotella spp.	Releases arachidonic acid → prostaglandins	McGregor et al. 1994; Romero et al. 2014	Stimulates uterine contractions + membrane weakening
Sialidase / Mucinase activity	G. vaginalis, Prevotella spp., Mobiluncus	Degrades mucus protective layer, exposes membranes to pathogens	McGregor et al. 1994; Alikamali et al. 2025	Reduces cervical mucus barrier integrity
Collagenase / Protease secretion	G. vaginalis, BV-associated organisms	Degrades collagen fibers in amnion/chorion	Hillier et al. 1995; Brown et al. 2018	Directly weakens mechanical strength of membranes
MMP-8 and MMP-9 upregulation	Host response to BV-induced inflammation	Degrades extracellular matrix of fetal membranes	Menon et al. 2009; Romero et al. 2014	Key pathway linking BV-inflammation to membrane rupture

Mechanism	Bacterial Species Involved	Effect on Fetal Membranes	Supporting Evidence	Clinical Relevance for PROM
IL-1 β , IL-6, TNF- α elevation	Host inflammatory response	Stimulates prostaglandin synthesis, MMP activation	Hillier et al. 1995; Frontiers 2025 review	Systemic marker for PPROM risk stratification
BV-associated IgA protease	G. vaginalis	Cleaves secretory IgA, reduces mucosal immunity	McGregor et al. 1994	Enhances susceptibility to ascending infection
Reduction of H2O2-producing Lactobacillus	Loss of L. crispatus / L. jensenii	Increases vaginal pH, enables anaerobic overgrowth	Brown et al. 2018; Alikamali et al. 2025	Foundation of all BV-PROM pathological processes

Vaginal Microbiome Profiles and PROM Risk (Molecular Studies)

Three of the 15 included studies specifically reported microbiome-based analyses (Brown et al., 2018; Alikamali et al., 2025; Frontiers Microbiome Review, 2025). These studies demonstrated that the composition of the vaginal microbiome at the community state type (CST) level significantly modified PROM risk. Community State Type IV — characterized by low Lactobacillus abundance and high bacterial diversity with dominance of anaerobes including Gardnerella, Atopobium, Prevotella, Megaspheara, and Sneathia — was consistently associated with the highest risk of PPROM across populations. Women with CST I (Lactobacillus crispatus-dominated) had the lowest PPROM risk. The Brown et al. (2018) UK cohort demonstrated that

vaginal dysbiosis (high diversity, low *Lactobacillus*) in early pregnancy was independently associated with PPROM (OR 2.8, 95% CI 1.3–6.0), and notably, this risk was paradoxically increased by erythromycin administration — a critical finding suggesting that broad-spectrum antibiotic perturbation of the vaginal microbiome may worsen outcomes by enabling colonization by erythromycin-resistant *Ureaplasma* species.

BV Screening Yield and Clinical Detection Rates

Study	Screening Strategy	BV Prevalence Found	BV Asymp. vs Symp.	PROM in BV+ Screened	Cost-effectiveness Notes
Subtil/PREMEVA (2018)	Universal screen at <14 wks (84,530 women)	~3.9% (eligible BV+)	Predominantly asymptomatic	Reported as secondary	Large-scale universal screening feasible
Lata et al. (2010)	All antenatal clinic attendees	20.5%	Mixed	Higher in BV+ group	Recommends universal ANC screening
Hillier et al. (1995)	Midpregnancy (23–26 weeks)	~16%	Predominantly asymptomatic	Yes, significantly elevated	Midpregnancy optimal for detection
Turrentine (USPSTF, 2020)	General population screening	Variable	Mostly asymptomatic	No sig. reduction with treatment	Routine screening not cost-effective (general pop)
Haahr et al.	Early screen	7–30%	Asymptomatic	Reduction	Targeted

Study	Screening Strategy	BV Prevalence Found	BV Asymp. vs Symp.	PROM in BV+ Screened	Cost-effectiveness Notes
(2016)	(<16–20 weeks)	(varies)	majority	in high-risk only	screening for high-risk more effective

Postpartum Maternal Outcomes Associated with BV in the Context of PROM

Beyond PROM itself, BV-associated infection in the context of membrane rupture significantly increases the risk of postpartum maternal complications. In the Hillier et al. (1995) and Hauth et al. (1995) studies, women with BV who experienced PROM demonstrated significantly elevated rates of postpartum endometritis, wound infection, and postpartum fever. The Watts et al. (1990) study (referenced in multiple included reviews) demonstrated that BV was a significant independent risk factor for postcesarean endometritis (OR 2.5, 95% CI 1.3–4.7). Additionally, the presence of BV at delivery in the context of PROM was associated with prolonged hospitalization, increased antibiotic use, and higher rates of maternal ICU admission in severe cases with septicemia.

DISCUSSION

Summary of Key Findings

This systematic review, encompassing 15 primary studies with a combined population of over 42,000 pregnant women, provides comprehensive evidence supporting a significant, consistent, and biologically plausible association between BV infection and the risk of PROM/PPROM. The pooled effect size for the BV–PROM association (OR approximately 2.19–2.73) indicates that BV-positive pregnant women face approximately 2–3 times the risk of PROM compared to BV-negative women — a clinically important finding that has direct implications for prenatal screening and management strategies (Leitich et al., 2003; Ng et al., 2023). Among the 15 studies, PROM was the most prevalent maternal outcome associated with BV, with a pooled

prevalence of 13.2% in BV-positive women (Ng et al., 2023), emphasizing the primacy of this complication in the clinical epidemiology of BV in pregnancy.

Mechanistic Pathways: From BV to Membrane Rupture

The mechanistic underpinning of the BV–PROM association is robust and well-characterized. The transition from a *Lactobacillus*-dominated, hydrogen peroxide-rich, acidic vaginal environment to the polymicrobial dysbiotic state of BV removes multiple layers of host protection against ascending infection. Protective H₂O₂ produced by *Lactobacillus crispatus* and *L. jensenii* is antimicrobial against anaerobes; its loss permits unchecked proliferation of BV-associated species (McGregor et al., 1994; Alikamali et al., 2025). Furthermore, lactic acid produced by *Lactobacillus* maintains vaginal pH below 4.5, which is directly bacteriostatic; in BV, pH rises above 4.5, facilitating survival and growth of pathogens (Frontiers Microbiome Review, 2025).

BV-associated bacteria produce a formidable array of virulence factors with direct membrane-degrading potential. Phospholipases, particularly phospholipase A₂ produced by *Gardnerella vaginalis* and *Prevotella* species, cleave membrane phospholipids to release arachidonic acid — the precursor to prostaglandins that stimulate uterine contractions and cervical ripening (McGregor et al., 1994; Romero et al., 2014). Sialidases degrade the glycoprotein protective coat of the cervical mucus, reducing the mechanical barrier against ascending infection. Proteases, including IgA protease produced by *G. vaginalis*, degrade secretory IgA, compromising local mucosal immunity and facilitating ascending infection of the chorioamniotic membranes (McGregor et al., 1994).

The host inflammatory response to BV organisms further amplifies membrane damage. Activation of toll-like receptors (TLRs) by BV-associated bacterial products (lipopolysaccharides, peptidoglycans) triggers release of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8, TNF- α) from decidual and membrane cells. These cytokines upregulate matrix metalloproteinases (MMP-1, MMP-8, MMP-9) in amniotic epithelial and mesenchymal cells, enzymatically degrading the collagen and laminin scaffold that maintains mechanical membrane integrity (Menon et al., 2009). Simultaneously, cytokine-driven prostaglandin E₂ and F₂ α synthesis directly stimulates uterine

contractions and cervical dilation, creating the conditions for spontaneous membrane rupture (Romero et al., 2014). Bacterial localization studies (Tyler et al., 2014) have demonstrated bacteria within the chorion layer at the site of membrane rupture in PPROM cases, confirming direct microbial invasion — not merely systemic inflammation — as a mechanism of membrane degradation.

Interpreting Inconsistency in Antibiotic Treatment Trials

One of the central paradoxes in the BV–PROM field is the failure of antibiotic treatment to consistently reduce preterm birth and PROM rates despite apparent microbiological efficacy. The PREMEVA trial (Subtil et al., 2018) — the largest multicenter RCT in the field — randomized 3,344 women in France with BV and low-risk pregnancies to early clindamycin or placebo, and found no significant difference in the composite primary outcome of late miscarriage or very preterm birth. However, the PREMEVA study specifically excluded high-risk women (prior preterm birth or second trimester loss), limiting generalizability to the population at greatest risk. The Morales et al. (1994) and Hauth et al. (1995) RCTs, both conducted predominantly in high-risk, predominantly African-American populations, demonstrated significant reductions in preterm birth with BV treatment — suggesting that treatment benefit may be population-specific.

Several explanations for treatment trial inconsistency have been proposed. First, the timing of antibiotic treatment may be critical: intervention before the inflammatory cascade is initiated (i.e., very early in pregnancy, <16 weeks) may prevent membrane damage, while intervention after significant cytokine-mediated remodeling has begun (>24 weeks) may be insufficient to reverse established pathological processes (Haahr et al., 2016). Second, the specific antibiotic used may influence outcomes: metronidazole effectively eliminates strict anaerobes but has limited activity against *Ureaplasma* and *Mycoplasma* — organisms that play independent roles in PPROM. Clindamycin has broader spectrum activity and has shown promise in early pregnancy treatment, particularly in high-risk populations. Third, BV eradication may be short-lived without addressing the underlying microbiological conditions that predispose to BV recurrence, such as the absence of protective *Lactobacillus* colonization.

The Brown et al. (2018) finding that erythromycin treatment in women with BV-like dysbiosis was paradoxically associated with increased neonatal sepsis risk represents an important cautionary finding. Erythromycin selects for resistant *Ureaplasma urealyticum*, which may then ascend into the amniotic cavity and cause sepsis in premature infants — an example of how imprecise antibiotic selection can worsen outcomes. This finding reinforces the need for microbiome-guided, precision treatment approaches rather than empirical broad-spectrum antibiotic protocols (Brown et al., 2018; Alikamali et al., 2025).

The Emerging Role of Next-Generation Sequencing in Understanding BV-PROM Relationships

The advent of culture-independent next-generation sequencing (NGS) technologies — particularly 16S rRNA gene amplicon sequencing and metagenomics — has transformed our understanding of vaginal microbial ecology and its relationship with PROM. Traditional Gram stain-based Nugent scoring and Amsel criteria provide a binary (BV present/absent) or semi-quantitative assessment of vaginal flora but cannot characterize the full microbial community. NGS allows assignment of women to discrete Community State Types (CSTs), with CST IV (high diversity, low *Lactobacillus*) being most strongly associated with PROM risk (Brown et al., 2018; Frontiers Microbiome Review, 2025).

The Frontiers PPROM Microbiome study (2025) demonstrated that women with PPROM had significantly higher relative abundances of *Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella bivia*, *Sneathia sanguinegens*, and *Mobiluncus* species, while exhibiting dramatic depletion of *Lactobacillus crispatus* and *Lactobacillus iners*. Importantly, specific virulence determinants — such as the *G. vaginalis* type 1 (BioVar 1) strains producing cytolysin and pore-forming toxins — may confer greater PROM risk than less virulent BioVar 2 strains. These insights from NGS studies highlight the heterogeneity within 'BV' as a clinical diagnosis and suggest that more refined molecular stratification will be essential for identifying which BV-positive pregnancies are truly at high risk for PROM, avoiding both under-treatment of high-risk cases and over-treatment of low-risk cases.

Racial and Ethnic Disparities in BV-associated PROM

The disproportionate burden of BV and BV-associated PROM in African-American/Black women is a critical dimension of reproductive health equity. African-American women have 2–3 times higher BV prevalence than non-Hispanic White women (Koumans et al., 2007), and also have significantly higher rates of preterm birth and infant mortality. The biological basis for this racial disparity in vaginal flora composition involves complex interactions between genetic variants in innate immune receptor genes (TLR4, DEFB1), epigenetic factors, psychosocial stress (cortisol-mediated alterations in vaginal flora), socioeconomic conditions (access to prenatal care, nutritional status), sexual behavior, douching practices, and antibiotic exposure history (Juliana et al., 2020; Peebles et al., 2019). The Hauth et al. (1995) trial demonstrated that BV treatment reduced preterm birth most significantly in African-American women — suggesting that this population may derive the greatest clinical benefit from early BV screening and treatment, further underscoring the importance of equity-focused prenatal care protocols.

BV and PROM in Low- and Middle-Income Countries

Studies from low- and middle-income countries (LMICs) provide important epidemiological context. The Juliana et al. (2020) systematic review of Sub-Saharan African studies documented high BV prevalence (30–50%) and demonstrated significant associations with PROM and preterm birth. The Lata et al. (2010) study from India — a country with one of the world's highest preterm birth burdens — found BV prevalence of 20.5% and demonstrated that PROM and preterm labor occurred significantly more frequently in BV-positive women, with the risk even higher when BV co-occurred with urinary tract infection. These findings from LMICs highlight that BV-associated PROM represents a global health burden, not merely a concern of high-income healthcare settings, and that cost-effective screening and treatment protocols tailored to resource-limited environments are urgently needed.

Probiotics as an Adjunct Strategy for BV Prevention and PROM Risk Reduction

Emerging evidence supports the role of Lactobacillus-containing probiotics in restoring and maintaining a healthy vaginal microbiome during pregnancy, potentially reducing BV recurrence and associated PROM risk. Lactobacillus strains (particularly *L. rhamnosus* GR-1, *L. reuteri* RC-14, and *L. crispatus* CTV-05) have demonstrated efficacy in BV cure and recurrence prevention in

several RCTs (Chieng et al., 2022 as cited in Frontiers Probiotic Review, 2024). The Frontiers Probiotic Review (2024) synthesized evidence supporting probiotic administration during pregnancy as a potential preventive strategy for both PROM and cervical incompetence by restoring Lactobacillus dominance. While dedicated large RCTs specifically examining probiotic effects on PROM are lacking, the biological rationale is compelling, and ongoing trials are investigating this approach.

Comparison with Existing Systematic Reviews and Meta-analyses

The findings of the present review are broadly consistent with prior systematic reviews and meta-analyses. The Leitch et al. (2003) meta-analysis (18 studies, n=20,232) established BV as a significant risk factor for preterm delivery (OR 2.19, 95% CI 1.54–3.12) — a finding confirmed in the present review across studies published over two decades later. The Cochrane Review by Brocklehurst et al. (2013) on antibiotic treatment of BV in pregnancy found insufficient evidence to recommend routine treatment of asymptomatic BV in the general pregnant population, consistent with the findings of the PREMEVA trial and the USPSTF recommendations. The more recent Ng et al. (2023) systematic review of 26 studies specifically highlighted PROM as the most prevalent maternal complication of BV (13.2%), directly supporting the central thesis of the present review. The present review extends prior work by incorporating molecular microbiome studies, the PREMEVA trial, and evidence from diverse LMICs, and by specifically designating PROM as the primary outcome of interest.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review provides comprehensive evidence that bacterial vaginosis is a significant, biologically plausible, and clinically important risk factor for premature rupture of membranes (PROM/PPROM) in pregnancy. Across 15 primary studies encompassing over 42,000 pregnant women, BV was associated with approximately 2–3 times the risk of PROM compared to BV-negative status, with preterm PROM showing an even more pronounced association (OR up to 2.83). The association is mechanistically supported by enzymatic degradation of fetal membranes

by BV-associated bacteria, local inflammatory upregulation of matrix metalloproteinases, and cytokine-mediated weakening of the chorioamniotic extracellular matrix (McGregor et al., 1994; Menon et al., 2009; Romero et al., 2014).

The evidence from antibiotic treatment trials reveals a more complex picture: while metronidazole and clindamycin effectively eradicate BV, their impact on PROM incidence is inconsistent across study populations. Treatment benefit appears most pronounced in high-risk populations (prior preterm birth/PROM, predominantly African-American women) and when initiated early in pregnancy (<20 weeks). The PREMEVA trial (Subtil et al., 2018) — the largest RCT in the field — did not demonstrate benefit of early clindamycin in low-risk pregnancies, suggesting that treatment protocols must be individualized based on risk stratification rather than applied universally.

BV is also associated with significant downstream neonatal morbidity through its relationship with PROM, including preterm birth (OR 1.76), low birth weight (OR 1.73), neonatal sepsis (OR 1.60), NICU admission (aRR 1.42), and perinatal mortality. These downstream effects amplify the clinical urgency of effective BV management in pregnancy. Furthermore, emerging molecular microbiome data indicate that specific BV-associated community state types — particularly those with very low *Lactobacillus crispatus* abundance — carry the highest PROM risk, suggesting that future diagnostics should move beyond binary BV classification toward microbiome-informed risk stratification (Brown et al., 2018; Alikamali et al., 2025).

Recommendations

Based on the synthesis of evidence in this review, the following recommendations are made:

- (1) Universal BV screening in early pregnancy (ideally <16 weeks) should be considered for all pregnant women, with priority given to high-risk groups: prior preterm birth or PROM, African-American/Black women, women from LMICs, and women with multiple sexual partners. The Nugent scoring system should be the diagnostic standard, with molecular diagnostics incorporated as they become more widely available.
- (2) Antibiotic treatment of BV in high-risk pregnant women should be initiated promptly upon diagnosis in early pregnancy. Oral clindamycin (300mg twice daily for 4–7 days) or oral

metronidazole (500mg twice daily for 7 days) are both acceptable first-line regimens. For women with recurrent BV, extended suppressive therapy or probiotic adjuvant treatment should be considered.

(3) Routine antibiotic treatment of asymptomatic BV in low-risk, general obstetric populations is not supported by current RCT evidence and may not be warranted without further evidence, consistent with the findings of the PREMEVA trial and USPSTF recommendations.

(4) Future RCTs investigating BV treatment in pregnancy should incorporate microbiome-guided enrollment criteria (NGS-based community state typing), stratify by prior PROM/preterm birth history, and use PROM as a primary rather than secondary endpoint. Treatment should be initiated before 16 weeks of gestation in future trials to capture the optimal therapeutic window.

(5) Probiotic supplementation with Lactobacillus-containing preparations as an adjunct to antibiotic treatment or as a preventive strategy in high-risk BV-positive pregnancies should be investigated in adequately powered RCTs specifically powered to detect PROM reduction.

(6) Healthcare systems in LMICs should prioritize development of affordable, point-of-care BV diagnostic tools and cost-effective treatment protocols tailored to local epidemiology, given the high BV prevalence and PROM-related perinatal mortality in these settings.

(7) Clinicians managing pregnant women with confirmed BV should provide enhanced surveillance for PROM, including regular cervical length measurement, fetal fibronectin testing, and timely administration of corticosteroids for fetal lung maturity if PPROM occurs before 34 weeks of gestation.

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