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Outcomes of Probiotic Use in the Treatment of Bacterial Vaginosis in Pregnant Women: A Meta-Analysis

Research Article

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Author Details

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Abstract

Background: Bacterial vaginosis (BV) in pregnant women potentially can increase the odds of preterm birth (PTB). Current interventions include antibiotics, such as Clindamycin or Metronidazole; however, there are increasing reports of antibiotic resistance. Prompting investigators to seek out new interventions.

Objective: To evaluate the potential effect of probiotic treatment in curing Bacterial Vaginosis in Pregnant Women.

Search Strategy: We evaluated studies that investigated the treatment of BV using oral probiotics. Literature searches of PubMed, Web of Science, and CINAHL databases were conducted by two separate readers. Search terms included "vaginosis, bacterial", "pregnancy", and "probiotic".

Selection Criteria: Randomized control or clinical trials that investigated the treatment of BV with oral probiotics in pregnant women were chosen for inclusion.

Data collection and Analysis: The number of participants who saw vaginal microbiota return to "normal" were evaluated with relative risk (RR) and a confidence interval of 95%. The heterogeneity between studies was evaluated using the Mantel-Haenszel model.

Main Results: The overall effect was measured to be 0.94 [0.67-1.31, p=0.70]. Heterogeneity was little to none [I^2=0%]. Three of the six studies had RR less than the line of null effect favoring the placebo, while the remaining three had RR greater than the line of null effect favoring the probiotic treatment.

Conclusions: The results indicate that probiotic treatment for BV in pregnant women is not currently a viable option to treat BV. These findings warrant further investigation.

PROSPERO Registration: CRD42023408714

Keywords: Bacterial Vaginosis, Pregnancy, Probiotics, Preterm Labor, Meta-Analysis, *Lactobacillus Rhamnosus GR-1, Lactobacillus Reuteri RC-14*

Abbreviations: BV: Bacterial Vaginosis; PTB: Preterm Birth; RR: Relative Risk; CT: Clinical Trial; CINAHL: Cumulated Index to Nursing and Allied Health Literature; CFU: Colony-Forming Unit; GBS: Group B Streptococcus

Synopsis

The following meta-analysis investigated the potential effects of probiotics in treatment of bacterial vaginosis in pregnant women. Probiotics are not currently a viable treatment option.

Introduction

Bacterial Vaginosis (BV) is a common vaginal infection characterized by a disruption in the normal vaginal microbiota [1]. While the precise etiology of BV has yet to be determined, it is believed to be caused by a reduction in *Lactobacillus spp*., a characteristic of healthy vaginal flora, and an increase in various facultative and anaerobic bacterial species [2]. The global prevalence rate of BV is roughly 21.2 million (29.2%) in reproductive-aged women (15-44 years) [3]. Symptoms of BV include an increase in vaginal discharge with an accompanying foul-smelling odor [4]. Confirmation of the diagnosis is determined using the microbiological- based Nugent scoring system or the clinically based Amsel criteria, which requires three of the four criteria to be met:

a. grayish-white discharge

b. vaginal pH exceeding 4.5

c. Clue cell presence

d. Fishy odor [4].

Much of the literature on the risk factors associated with BV diagnosis indicates an increased vulnerability to STIs, urogenital inflammation, and premature labor in pregnant women [1, 5, 6]. In addition to the risk of preterm birth, BV may also be associated with adverse neonatal outcomes in full-term births such as increased respiratory distress, sepsis, and NICU admission [7]. Given the well-documented associations between perinatal outcomes and BV diagnosis, the optimization and evaluation of current treatment strategies is of the utmost importance for new mothers and infants.

The standard of care for the treatment of BV in symptomatic women is currently oral or vaginal antibiotic therapy using Metronidazole and Clindamycin [8]. These therapies are highly effective, with initial cure rates of 80-90% [9]. However, recurrence rates are high, with 69% of women having a recurrence of BV within one year following effective antibiotic treatment [10]. Such high recurrence rates have been linked to various behavioural and social aspects of patients' lives in addition to the development of antibiotic resistance, which presents obvious difficulties in prevention from a clinical standpoint [8]. The use of probiotics has been evaluated as a solution to prevent the recurrence of BV by maintaining the sustained *Lactobacillus spp*. predominance in vaginal flora following antibiotic therapy [11]. Numerous studies have demonstrated comparable efficacy of probiotics to antibiotic therapy in the treatment of BV; however, these studies are often not targeted at one of the most at-risk populations, pregnant women [12-14]. In addition, consistency issues arise within study methodologies, assessment outcomes, and probiotic administration route and type, which need to be addressed to accurately assess the potential impact of probiotics in BV [15]. The objective of this meta-analysis is to investigate the potential effect of probiotic therapy as an effective mode of treatment of BV in pregnant women.

Methods

Two independent investigators (KPR and CW) conducted literature searches. Peer review journal articles were extracted from PubMed, Web of Science, and Cumulated Index to Nursing and Allied Health Literature (CINAHL). Searches utilized the following MeSH terms "vaginosis, bacterial", "pregnancy", "probiotic", and the conjunctive operator "AND". Inclusion criteria (Figure 1) consisted of randomized control trials (RCTs) and clinical trial (CT) articles published from 2012-2023, full free text or full text provided, inventions consisting of oral probiotics either alone or in concordance with traditional treatment methods (antibiotics), study participants needed to be pregnant and diagnosed based by Nugent scores or Amsel criteria. Exclusion criteria were articles not classified as RCTs or CT, published prior to 2012, sole interventions other than oral probiotics, non-pregnant participants, and studies that did not determine Nugent score values or Amsel criteria of participants.

Data extraction (Table 1) included first author, year of publication, country of origin, sample size, the average or median age of participants, study design, the diagnostic method utilized for determining BV, the gestation period of participants, duration of the intervention, the strand of probiotic administered, the dosage as well as the delivery method, the type of control group, and CT registration number. Statistical analysis was conducted using R language and environment for statistical computing (R version 4.2.2; R Foundation for Statistical Computing; www.r-project.org). The data was analyzed using the packages "metameta" and "robvis" [16,17]. The effect measure visualized (Figure 2) was relative risk with a confidence interval of 95%. Significant p-values were considered $P<0.05$. The Mantel-Haenszel (M-H) test was utilized to account for varying study designs as well as evaluate heterogeneity. Low heterogeneity between studies was considered to be $I2\leq50\%$ and P-value >0.1. Publication bias (Figure 2) was measured by determining the weight of each study in the meta-analysis. It was also visualized in a funnel plot (Figure 3).

The risk of bias for all six trials was analyzed utilizing the Cochrane risk-of-bias tool for randomized trials (RoB 2). This analysis was conducted independently by two investigators (KPR and CW). After resolving any disagreements with a third author (SP), the results were combined and are reported in (Figure 4). Our meta-analysis followed the *Cochrane Handbook for Systematic Reviews for Interventions* and was registered with PROSPERO (CRD42023408714).

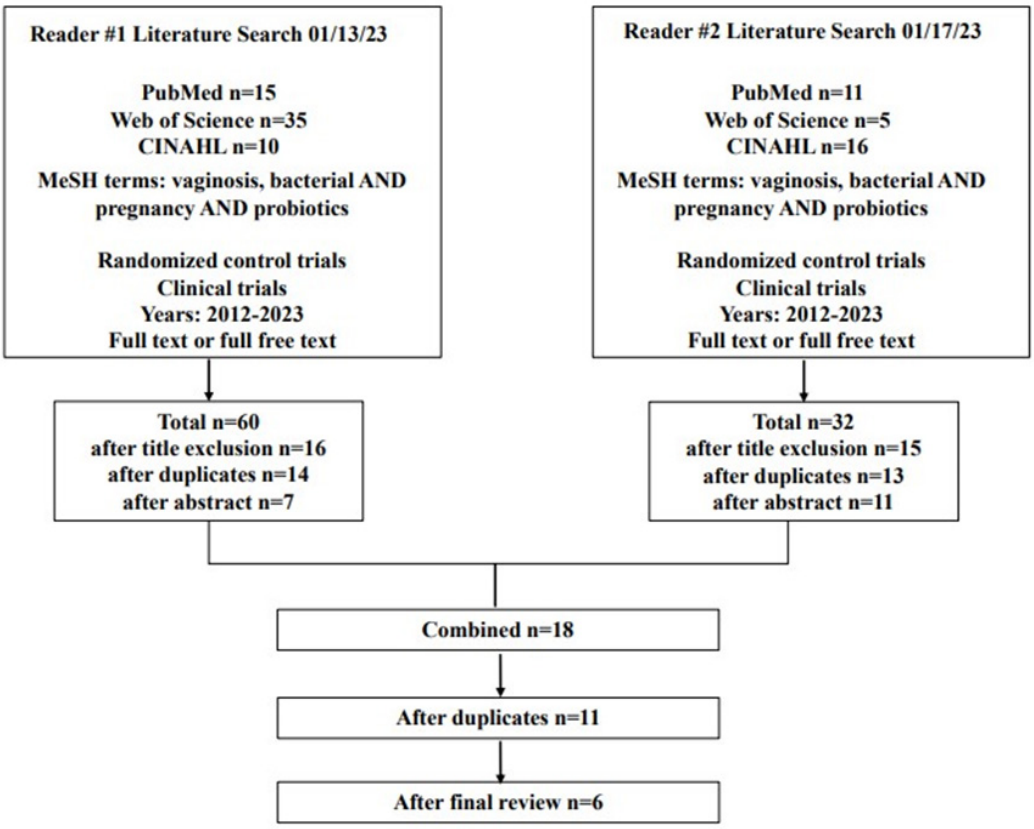

Figure 1: The following flow diagram depicts the study selection process. Two independent readers conducted separate literature searches utilizing the above-mentioned filters of MeSH terms, year of publication, and text availability. After combining all literature findings, the final number of studies to include in the meta-analysis was six.

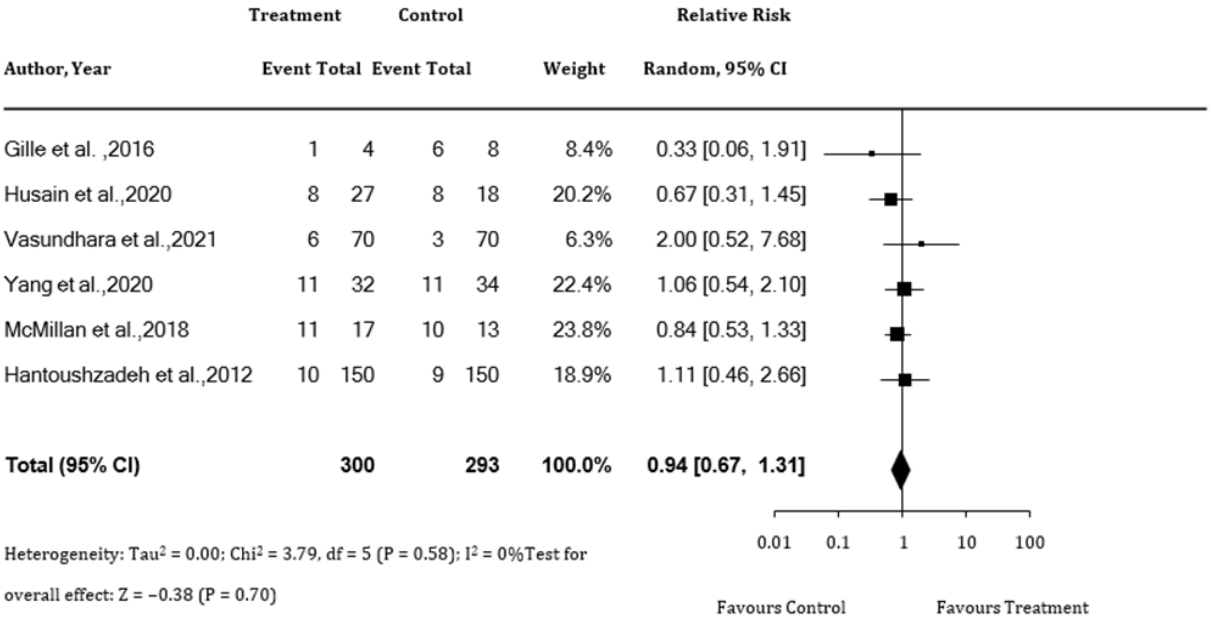

Figure 2: Forest plot of studies included the meta-analysis. The effect of measure was relative risk ratio. Mantel-Haenszel (M-H) test was utilized to account for varying study design as well as evaluate heterogeneity. In order to evaluate publication bias, the weight of each study is depicted. The studies showed low heterogeneity as the I2 valued was 0%. Confidence interval of 95% was used and a p-value of <0.05 was considered significant.

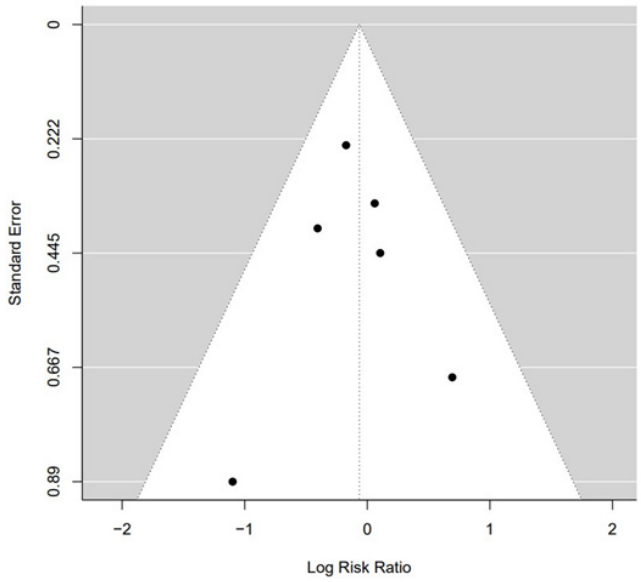

Figure 3: Funnel plot of studies included in meta-analysis with each dot representing a different study (Table 1). The studies are distributed on both sides of the effect line, with dots closer to the x-axis showing small sample size.

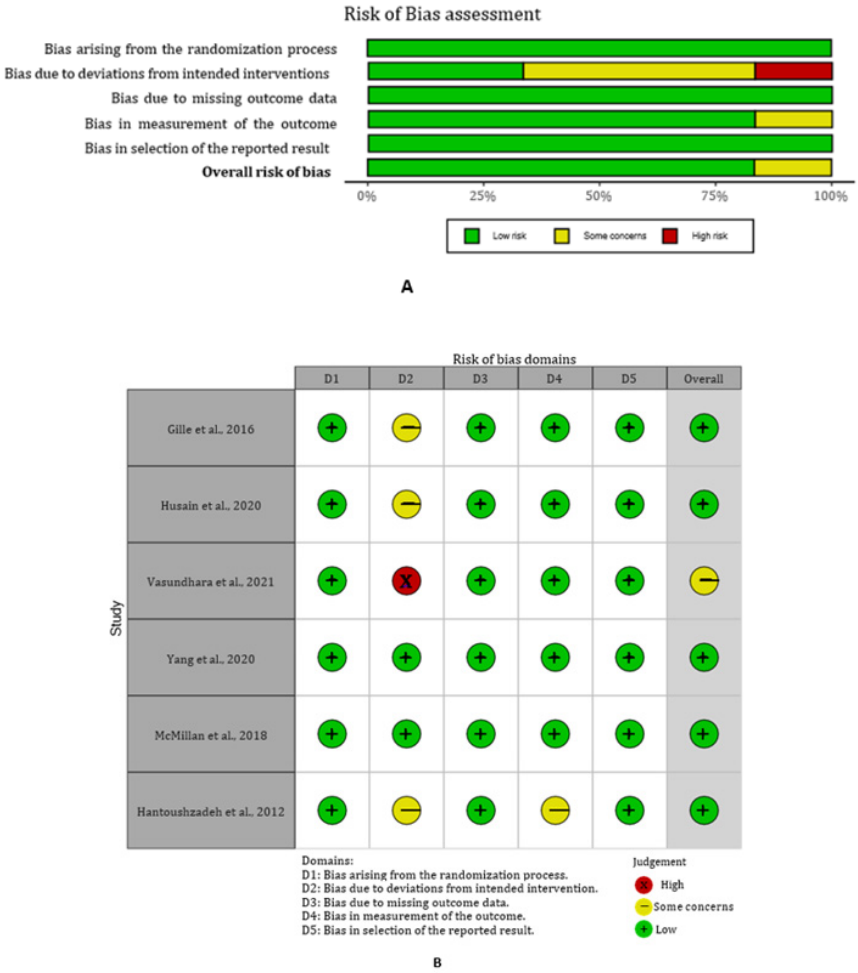

Figure 4: Risk of Bias assessment analyzed using the Cochrane risk-of-bias tool for randomized trials (RoB 2).

A. The risk of bias assessment showed that overall 75% was low risk with only 25% being of some concern with risk.

B. The traffic light figure breaks down the domains assessed for risk by each of the six included articles. Majority of the articles were determined to be low risk, except for Vasundhara, et al. 2021 that was determined to be high risk for bias due to deviations from intended intervention.

Results

Using the strategy outlined above, six studies met inclusion and were evaluated through meta-analysis. Commonalities between the studies included the design, diagnostic method, delivery of probiotics, and control type being placebo (Table 1). The design consisted of randomized, double-blind, or triple-blind, placebo-controlled trials. The diagnostic method for determining BV was either Nugent score or Amsel criteria. The route of delivery was oral probiotic. The control type for the majority of the studies was placebo, except for two studies that compared their treatment group oral clindamycin. All studies reported CT registration numbers for their country of origin.

There were several differences among the six studies including country of origin, sample size, age of participants, gestation period, duration of treatment, probiotic, and dosage (Table 1). The included studies span over four of the seven continents including Europe, North America, Africa, and Asia. The sample size consisted of three studies n>200, while the remaining three studies n<100. The age range of participants was between late-teens to mid-thirties. The gestational period and duration of treatment varied for each study with majority of studies following participants till the birth of their baby. The probiotic cocktail consisted of *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14* for four of the six studies with dosages averaging in the billions colony-forming unit (CFU).

In Figure 2, the summary of relative risk (RR) values with their 95% confidence intervals are reported. The event was determined to be the number of participants "cured" of BV by the end of the trial, with the total being the sum of participants in the group. Three of the six studies ([14], Husain et al., 2020, and McMillian et al., 2018) showed RR values less than the line of null effect at 0.94 indicating the placebo effect was favored. The remaining three studies (Vasundhara et al., 2021, Yang et al., and Hantoushzadeh et al., 2012) showed RR values greater than the line of null effect indicating the probiotic treatment was favored. The "cure" rates were quite similar for the treatment group 15.7% (47/300) and the control group 16.0% (47/293). The test for overall effect reported a Z-value of -0.38 and was not significant as the p-value was 0.70. The I^2 value (Figure 2) was estimated to be 0% indicating little to no heterogeneity. This was confirmed through a visual funnel plot (Figure 3). The solid filled dots each represent a different study evaluated. The placement of the dots suggest symmetry as the dots lay close to overall effect line. They are also equally dispersed on the left and right sides under the funnel. The two dots that fall towards the x-axis of the plot indicate small study size.

Discussion

Six studies conducted over the past ten years were evaluated through meta-analysis to determine the effect the probiotic treatment had on BV in pregnant women. Recognizing the similarities and differences of the studies can further explain the results. Overall the studies included were very similar which was reflected in their design, diagnostic method, delivery of probiotics, and control type of placebo. Additionally. Filtering for studies that were specifically RCT or CT eliminated systematic reviews and book chapters. All of the analyzed studies delivered probiotics orally and utilized probiotics which are readily available in supermarkets and local pharmacies. While the age of participants varied, the range of ages focused on active reproductive years (late teens to mid-thirties). These similarities among studies is a major strength of our meta-analysis and was reflected by the I2 value 0% indicating little or no heterogeneity.

Our findings offer a glimpse of insight into the potential of probiotic intervention in pregnant women. However, the overall effect of probiotics was found to be insignificant. This could factor from the low number of included studies or possibly the slight differences including geographical location, gestational period, duration of treatment, and/or dosage of probiotic administered. It should be noted that despite the varying sample sizes, all studies contributed around or less than 20%. Also the "cure" rates were interestingly similar 15.7% and 16.0% for treatment and control groups respectively.

The differences amongst the studies plays a major role in explaining the reported outcomes. The country of origin is the most significant difference among the listed studies. In addition to the many individual risk factors for BV occurrence and recurrence, there are geographical trends in BV prevalence which have not been extensively investigated [18]. One explanation for differences across various countries may be due, in part, to how diagnostic measures are implemented, applied, and reported [19]. Additionally, differences in cultural diet, customs, and individual social practices may influence the depletion of protective vaginal bacteria, and ultimately clinical cure rates following treatment [20]. The gestational period and duration of intervention varied dramatically across all six studies. Treatment for BV in pregnancy is typically conducted during the last few weeks before birth. Screening for BV, if completed by physicians, is completed during the time frame of the anal swab for Group B Streptococcus (GBS).

Two studies treated during the third trimester, while three treated during the second and one treated during the first trimester. The studies that chose to treat during the third trimester (Vasundhara et al., 2021, and Hantoushzadeh et al. 2012) also were the studies that favored the probiotic treatment as well as were conducted in Asia. The probiotic strand administered was almost always *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14* as these are probiotics known to survive the GI tract and are prominent in the gut. All studies administered a capsule form of probiotic except for Hantoushzadeh et al. 2012 who administered participants orally a yoghurt containing 100g of *Lactobacillus bulgaris, Streptococcus thermophilus, probiotic lactobacillus*, and *Bifidobacterium lactis*.

Despite our best efforts, our meta-analysis does have a few limitations. The major limitation is the low number of included RCTs and CTs. This stems from a combination of the year range chosen to only encompass studies published in the past ten years and the niche effect of the field. Another limitation is the availability of texts. The filter full free text or full text were selected as to show availability of texts provided by the university. This limits the possible studies published within the required criteria that were not included for review. Despite our limitations, our investigation draws attention to the need for more studies in the pregnant population for the treatment of BV with probiotics. We suggest that normalizing the study design can help to account for geographic and cultural influences for future meta-analysis comparisons.

Conclusion

In this meta-analysis, we examined RCTs and CTs that investigated the treatment of BV in pregnant women through probiotic intervention. Six studies, spanning four continents, were chosen to be included in the analysis. The overall effect measured to be 0.94 [0.67-1.31] and was not found to be significant (p-value=0.70). Heterogeneity was little to none as the I2=0%. Three of the six studies had RR less than the line of null effect favoring the placebo, while the remaining three had RR great-

er than the line of null effect favoring the probiotic treatment. The results indicate that probiotic treatment for BV in pregnant women is not currently viable option to treat BV. However, future studies are needed which could prove probiotics are a safe alternative treatment method for BV in pregnant women.

Author Contributions

KP and CW developed the protocol and performed the literature search. KP, CW, and SP finalized included studies. KP and CW extracted the data. All authors contributed to the writing and editing of the manuscript.

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None

Conflicts of Interest

The authors have no conflict of interest.

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