

Bacterial Vaginosis: A Systematic Analysis on Current Treatments for Pregnant Women

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ABSTRACT

Bacterial vaginosis (BV) is a vaginal infection that causes discharge, odor, and irritation, characterized by a shift in the vaginal flora from the dominant *Lactobacillus* to a polymicrobial flora. It is a commonly reported microbiological syndrome among women of childbearing age. It has been associated with a wide array of health issues, including preterm births, pelvic inflammatory disease, increased susceptibility to HIV infection, and other chronic health problems. This systematic review provides: (1) an overview of bacterial vaginosis (BV), (2) an evaluation of the effectiveness of current treatments for BV for pregnant women, and (3) summarizes the treatment recommendations for pregnant women with bacterial vaginosis (BV). This review makes use of articles and studies found in databases such as Pubmed, Web of Science, and Cochrane. Systematic review and randomized trials have shown that treating bacterial vaginosis in pregnancies with metronidazole and clindamycin do have a significant effect in reducing the risk of preterm birth (PTB). Additionally, probiotics appear to have a significant effect in reducing the risk of preterm birth (PTB), but the evidence is still inconclusive, and further research is needed.

Key words: Bacterial Vaginosis, Pregnant Women, Preterm Labor, Treatment, Sexually Transmitted Diseases

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INTRODUCTION

Bacterial vaginosis (BV) is a vaginal infection that causes discharge, odor, and irritation, characterized by a shift in the vaginal flora from the dominant *Lactobacillus* to a polymicrobial flora. It is a commonly reported microbiological syndrome among women of childbearing age.^[1] It has been associated with a wide array of health issues, including preterm births, pelvic inflammatory disease, increased susceptibility to HIV infection, and other chronic health problems.^[1] The numbers of annual pregnancies in women living in low-income and middle-income countries are estimated to be 74 million, according to the World

Health Organization.^[2] 25 million unsafe abortions, 47 000 maternal deaths, and fifteen (15) million babies born preterm every year.^[3] Preterm labor is a significant cause of mortality and morbidity among infants and physicians suggest that infections play a key role.^[4] Specific bacteria found in the placenta as well as in amniotic fluid in association with premature birth are believed to come from the vagina.^[5] This is true for pregnant women with bacterial vaginosis (BV).^[5]

BV is an infection that alters the normal flora of the female reproductive system due to the bacterial overgrowth caused by opportunistic bacteria.^[5] Although researchers have not yet identified the etiology of BV, several studies support that the infection is caused by the depletion and replacement of the *Lactobacillus* spp. by anaerobic microorganisms, such as *Gardnerella vaginalis*, *Mobiluncus curtisii*, and *M. mulieris*.^[6] According to Saifon *et al.*, the preterm labor group had a higher prevalence of bacterial vaginosis than the labor group.^[4] BV causes preterm labor and about 800,000 pregnant women in the United States every year are infected.^[7]

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Turovskiy, Sutyak, and Chikindas mentioned that the most predominant species that inhabit the healthy microbiota of the lower genital tract of women are *Lactobacillus* spp., and the most prevalent species are *L. jensenii*, *L. crispatus*, *L. iners*.^[8] The infection can manifest as symptomatic and asymptomatic to an infected patient. In the case of symptomatic patients, abnormal vaginal odor, discharge, itching, and elevated vaginal pH is caused by a shift in vaginal microflora, causing irritation to the female reproductive system.^[9] In fact, many researchers tend to think of BV as a complicated microbial imbalance in which the indigenous vaginal lactobacilli play a key role. Patients with Bacterial vaginosis are more likely to acquire sexually transmitted diseases such as HIV as well as pelvic inflammatory disease.^[10] The Centers for Disease Control and Prevention recommends treating BV with metronidazole and clindamycin, but this doesn't eliminate every bacteria related to BV. Furthermore, these therapies contribute significantly to the spread of drug insusceptibility of *G. vaginalis*, *Peptostreptococcus* spp., as well as *Bacteroides*.

METHODOLOGY

The analysis involved a thorough review of studies that were reported on the following published literature concerning pregnant women suffering from bacterial vaginosis. Systematic literature searches were conducted in the following databases: Pubmed, Web of Science, and The Cochrane Database of Systematic Reviews from January 2016-April 2020. We independently assessed the studies by evaluating all interventional and observational studies based on predefined criteria wherein it evaluates the diagnostic accuracy of commercially available tests for bacterial vaginosis. Also, we selected appropriate studies of antibiotic treatment with clindamycin and metronidazole along with other alternative treatments such as probiotics for pregnant women with bacterial vaginosis. We excluded studies with insufficient findings, poor methodological quality, and those that do not include the target population, such as asymptomatic pregnant women with BV, among others.

Literature Search

A comprehensive literature search was conducted to find related reports and studies on the following antibiotics included in this study, namely metronidazole and clindamycin, as well as the probiotics particularly Lactoferrin, *Lactobacillus rhamnosus* GR-1 and *Lactobacillus*

reuteri RC-14. The databases used were the following: PubMed, Cochrane and Web of Science.

Keyword

PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) Guidelines were followed in conducting the systematic review.^[11] Research journals and articles were retrieved from the following databases: PubMed, Cochrane and Web of Science.

The search keywords used are the following: [Bacterial Vaginosis OR BV], [Treatments or treating], [pregnant women OR pregnancy], [outcome], [impact or effect], [alternative or other], [new or novel] [clindamycin],[metronidazole], [lactoferrin] AND [symptomatic cases].

Flowchart

The image above shows the predefined criteria that were used in the review under the following databases: Pubmed, Web of science, and The Cochrane Database of Systematic Reviews.

Inclusion Criteria

The study is limited to the effectiveness and health outcomes, the relationship, and the limitations of each current therapy. Meanwhile, the population was limited to pregnant women of any age with symptomatic bacterial vaginosis and no comorbidities. The study design is

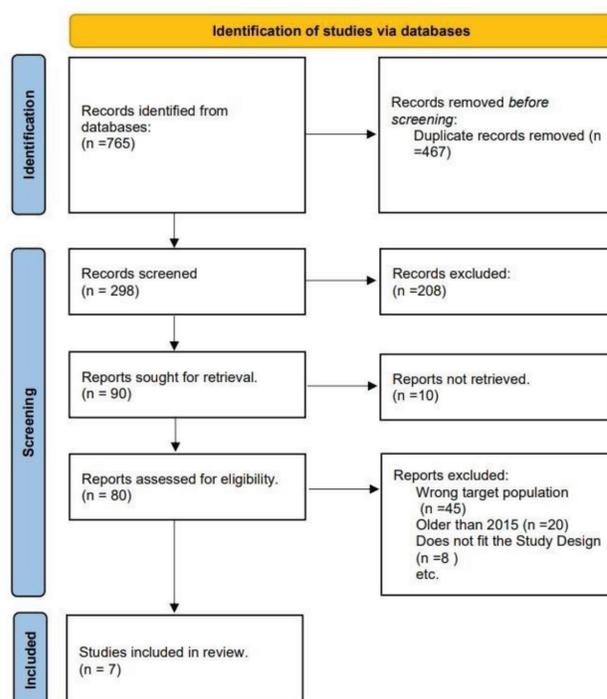


Figure 1: Flowchart.

limited to Randomized Controlled Trials (RCT), case studies, as well as retrospective cohort studies. Only those that are peer-reviewed and published in English from January 2016 to April 2020 were included. There was no restriction on the country however, studies from Asia were prioritized.

Exclusion Criteria

The study topic does not cover the factors that relate to the prevalence of Bacterial Vaginosis (BV) as well as the risk factors and screening for bacterial vaginosis among pregnant women. The population does not include asymptomatic bacterial vaginosis, pregnant women who have a history of bacterial vaginosis, non-pregnant women with bacterial vaginosis, pregnant women with comorbidities and multiple gestations. Studies that were not published, not peer-reviewed, and not written in English were also not included.

RESULTS

Globally, the suggested antibiotic therapy treatment for bacterial vaginosis (BV) is Metronidazole and Clindamycin.^[11] In the study conducted by Ijeoma *et al.* (2020), Oral metronidazole and clindamycin were used to treat pregnant patients with bacterial vaginosis. There were 136 pregnant Nigerian patients under 28 to 32 weeks of gestation period who participated in the randomized controlled trial, 69 of them were given oral metronidazole while the other 67 patients were given oral clindamycin.^[12] After a week of treatment, patients were assessed for the efficacy of the given antibiotics. The oral metronidazole acquired an 87% cumulative cure rate and the oral clindamycin acquired an 89.6% cumulative cure rate.^[12] The administration of oral antibiotic treatments has a combined failure rate of 11.8%, treatment failure was encountered by nine (13%) of the women who received oral metronidazole and seven (10.4%) of the women who received oral clindamycin. Five pregnant patients (8.3%) in the group of oral metronidazole had preterm prelabour rupture of membrane (PPROM), while four (6.7%) in the group of oral clindamycin experienced the same complication as well.^[12] The study concluded that the administration of oral metronidazole and oral clindamycin was effective in treating bacterial vaginosis with good pregnancy outcomes in most low-risk pregnant patients.^[12]

In a similar research carried out by Bellad *et al.* (2020), oral clindamycin was used for the treatment of pregnant women who had vaginal pH \geq 5.0. A total of 1,727 pregnant women between 13 to 20 weeks of gestational

period participated in the study, 866 (50.15%) of them received oral clindamycin and 861 (49.85%) received a placebo.^[13] The results show that the oral clindamycin treatment presented no decrease in preterm birth rate.

Probiotics

Different methods have been used to prevent preterm birth (PTM). Antibiotics are the most commonly recommended and claimed to be effective treatments; however, the consequences of them are poorly studied. According to some research, probiotics are a safer and more efficient alternative to antibiotics for the restoration of normal balance of the vaginal microbiota found in BV patients.^[14]

Lactoferrin

In the study conducted by Ammendola *et al.* (2019), a safer alternative approach for BV treatment using vaginal lactoferrin was offered. One hundred twenty-five (125) pregnant women with bacterial vaginosis were studied, 60 of them received vaginal lactoferrin, whereas the other 65 did not. The pregnant women who were supplemented with 300 mg vaginal lactoferrin by recommendation had displayed a significant decrease in preterm birth (PTB) rate with 25.0% of the total pregnant women participants, and a decreased rate of admission for threatened preterm labor (PTL) with 45.0%, at less than 37 weeks.^[15] In a similar study by Imai and Otsuki (2016), 6 participants: 5 pregnant women and 1 not, received lactoferrin (LF) therapy. Two out of six participants began the therapy before pregnancy while the rest started between 11 and 21 weeks of pregnancy, where they took 150 mg and 700 mg respectively, of vaginal suppositories and oral tablets every day after breakfast.^[16] This combination of oral and cervical administration increased the survival rate of fetuses with normal delivery without complications by extending the gestation period after the inoculation of bacteria.

In another study of probiotic treatment conducted by Allotey *et al.* (2019), an oral capsule containing

Lactobacillus rhamnosus (GR-1) and *Lactobacillus reuteri* (RC-14) was examined in a double-masked Randomized Controlled Trial (RCT). Three hundred four (304) pregnant women who have had PTB before were recruited and randomly tested. They were divided into probiotic and placebo groups, with 152 women each. At the 18th to 20th week of pregnancy, 123 of 152 pregnant women remain in probiotics while 115 of 152 in the placebo group. The 238 pregnant women who completed the data for primary analysis showed a BV rate of 17% in 9-14 weeks, 13% both during weeks 18 through 20 as

well as 34 through 36 of pregnancy. The test also gives a PTB rate of 8.2% (probiotics) and 6.7% (placebo); preterm birth delivered during the 36 weeks gestation. These findings have not shown any effect on the prevalence of BV or showed signs of altering the vaginal microbiota with the oral probiotics. These results have no bearing on the prevention of PTB risk, and further research is needed.^[14] In a similar study of probiotics that involved *L. rhamnosus* GR-1 and *L. reuteri* RC-14, Gille *et al.* (2016), randomly tested an oral intake of 1 capsule of probiotic to 320 pregnant women. Normal microbiota has decreased by 4.8% after probiotic treatment and placebo: from 82.6% to 77.8% in probiotic treatment and 79.1% to 74.3% in placebo, respectively. The total rate of preterm delivery (PD) was low in the treatment group with only 3.8% which prolonged the duration to 4 weeks longer compared to the placebo group with a 5.0% PD rate. These results establish an antenatal care intervention, but probiotics have no effect on the proportion of vaginal microbiota in pregnant women; however, it indicates useful prevention in preterm delivery (PD), but the exact mechanism is unclear.^[17]

Table 1 contains the tabular form of the collected studies about treatment of Bacterial vaginosis for pregnant

women to prevent preterm birth using antibiotics. Based on the collected data reviews, Clindamycin and Metronidazole significantly decreases the rate of preterm birth.

Table 2 contains the tabular form of the collected studies about treatment of Bacterial vaginosis for pregnant women to prevent preterm birth using probiotics. Based on the collected data reviews, Lactoferrin, *Lactobacillus rhamnosus* and *Lactobacillus reuteri* RC-14 showed as good alternative treatments to prevent preterm birth.

DISCUSSION

Metronidazole and Clindamycin are the standard treatment for Bacterial vaginosis, but this standard treatment applies mostly to non-pregnant women and may cause concern to pregnant women because of the possible side effects. Safer alternative treatment, such as the use of probiotics, is therefore needed to be considered.

Antibiotics

Metronidazole and Clindamycin

In the comparison study of Ijeoma *et al.*,^[12] five (5) patients who received oral metronidazole experienced

Table 1: Antibiotics.

Study	Design	Diagnostic Method	Duration of pregnancy at treatment (in weeks)	Treatment	Control	Outcome	No. of participants	Efficacy
Ijeoma <i>et al.</i> , 2020	Randomized Controlled Trial	Amsel	28 - 32	Oral Clindamycin	-	-	67	87% cumulative cure rate with good pregnancy outcome
Ijeoma <i>et al.</i> , 2020	Randomized controlled trial	Amsel	28 - 32	Oral Metronidazole	-	-	69	89.6% cumulative cure rate with good pregnancy outcome
Bellad <i>et al.</i> , 2018	Randomized placebo controlled trial	Nugent	13 - 20	Oral Clindamycin	Placebo	PTL	1,727	Oral clindamycin did not decrease the rate of PTB in women with vaginal pH of less than 5

Table 2: Probiotics.

Study	Design	Diagnostic Method	Duration of pregnancy at treatment (in weeks)	Treatment	Control	Outcome	No. of participants	Efficacy
Ammendola et al. 2019	Retrospective cohort study	-	16 - 36 (< 37)	Vaginal lactoferrin (300 mg)	-	-	125	25% significantly lower the rate of preterm birth (PTB) in less than 37 weeks.
Imai and Otsuki. 2016	Case study	-	11 - 21	Vaginal (150 mg) and oral (700 mg) lactoferrin	-	-	6	Extended the duration of Gestation; normal delivery without complications.
Allotey et al. 2019	Double-blind RCT	Nugent	9 - 14 & 18 - 20	Oral <i>Lactobacillus rhamnosus GR-1</i> and <i>Lactobacillus reuteri RC-14</i>	Placebo	PTB	304	The probiotic supplements with <i>L. rhamnosus GR-1</i> and <i>L. reuteri RC-14</i> did not affect vaginal microbiota during pregnancy, and prevention of preterm birth (PTB) risk with 8.2% rate, needs further investigation
Gille et al. 2016	Triple-blind RCT	Nugent	8 - 12	Oral <i>Lactobacillus rhamnosus GR-1</i> and <i>Lactobacillus reuteri RC-14</i>	Placebo	PTB	320	The probiotic supplements with <i>L. rhamnosus GR-1</i> and <i>L. reuteri RC-14</i> did not affect vaginal microbiota during pregnancy; however, useful for prevention in preterm delivery (PD) with 3.8% rate, but need further Investigation.

a preterm prelabour rupture of membrane (PRROM) and four patients who received oral clindamycin experienced the same complication. Despite the aforementioned obstetric complication, the study has a high confidence with the efficacy of administering oral metronidazole and oral clindamycin for treating pregnant patients infected with bacterial vaginosis because the encountered complication was not considered

statistically significant, and the study has an overall better pregnancy outcome to the majority of the participants. The study of Bellad *et al.*,^[13] however, concluded that the use of oral clindamycin did not reduce the preterm birth rate among pregnant women who have an elevated vaginal pH of >5.0. Although the study has a large sample size and high participant compliance, the lack of resources for an ultrasound

to monitor the fetus in the womb to all participants throughout the duration of the study was not able to be carried out, thus may affect the result of the study.

Probiotics

Lactoferrin

Lactoferrin is an iron-binding milk glycoprotein produced in the external fluids of most mammals.^[18] It is a critical component of the defense system that has important immunomodulatory, antioxidant, and antibacterial properties – including antibacterial, antiviral, antifungal, and antiparasitic activities.^[18] In humans, there's a good chance that lactoferrin could help prevent preterm birth and infection in the womb. In a comparison study of Ammendola *et al.*^[15] supplementation of oral vaginal lactoferrin decreases the preterm birth rate and the rate of admission for threatened preterm labor (PTL) in pregnant women diagnosed with bacterial vaginosis. Human lactoferrin has been shown to inhibit uterine cervical ripening. Patients with bacterial vaginosis have higher lactoferrin levels in their vaginal discharge which suggests that lactoferrin synthesis may have increased as a host reaction to prevent the development of iron-requiring bacteria.^[15] In the same study of Imai and Otsuki,^[16] after inoculation with bacteria, a combination of oral and cervical lactoferrin therapy lengthened gestation and increased the survival rate of fetuses with normal delivery and no health complications. This could be due to the anti-inflammatory and antibacterial effects of lactoferrin.^[16] As a result of the findings, supplementing pregnant women with bacterial vaginosis with oral or vaginal lactoferrin has been proposed as a safe alternative therapy option.

Lactobacillus reuteri RC-14

Lactobacillus reuteri RC-14 is a probiotic used in food supplements found in markets worldwide.^[19] It adheres to the epithelial surface in the uro-genital region of women.^[19] It also produces lactic acid, which promotes the inhibition of the growth of the pathogenic bacteria in the uro-genital region and intestines.^[19,20]

Like *Lactobacillus reuteri RC-14*, *Lactobacillus rhamnosus GR-1* has antagonistic properties against pathogenic bacteria in the vagina that inhibit their growth. *Lactobacillus rhamnosus GR-1* can improve the balance of vaginal microflora.^[20] This is one of the primary reasons why it is an alternative treatment to BV.

Lactobacillus reuteri RC-14 and *Lactobacillus rhamnosus GR-1* when used together are thought to produce biosurfactant that help break down the slimy barrier called biofilm

which protects the normal flora.^[19,20] This results in the inhibition of the growth of bacteria because they cannot thrive as well as when they have a barrier to protect themselves against an unfavorable environment. It may have an immune modulatory activity and it produces factors that signal the downregulation of toxin production.^[20] This suggests that the probiotic can prevent harmful toxins from being produced and may stimulate the immune system to help balance the microflora in the vagina. It is a safer alternative than synthetic drugs such as the antibiotics. To continue, these probiotics are even used as food supplements bought in the market and can be consumed by pregnant women. As such, it can be assured that they are considered safe.

CONCLUSION AND RECOMMENDATIONS

Bacterial Vaginosis (BV) is known to contribute to preterm birth (PTB). Treatments such as oral medication of Metronidazole and Clindamycin have long been established as standard medication for this disease. Aside from being an established cure for BV, evidence shows that it prevents PTB and results in a good pregnancy outcome as its cumulative cure is more than 85%. Furthermore, studies conducted that make use of Probiotics for treatment in BV have shown results in preventing PTB. Lactoferrin has been proven to be beneficial in preventing PTB in clinical studies and is regarded as a safer alternative to antibiotics in the treatment of BV in pregnant women. Though *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14* show that there is a significant effect in lowering PTB rate, it remains uncertain and further investigation must be conducted.

The researchers recommend that further studies using Probiotics, particularly *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14*, for treatment and prevention of PTB should be performed as, though it shows promising results in curing BV and lowering the PTB rate, it does not have conclusive evidence to support the implication that it lowers the PTB rate. Also, because of the scarce availability of studies that test the effectiveness of Metronidazole and Clindamycin in preventing PTB in pregnant women, the researchers recommend to give more emphasis in studying the effects of the antibiotics on preventing PTB among pregnant women with bacterial vaginosis as the preterm birth rate is high and it poses danger to both the mother and child.

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