Bacterial Vaginosis in Pregnancy and Its Maternal and Fetal Outcome.

By

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A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of Bachelor of Science in Microbiology.

Department of Mathematics and Natural Sciences,
BRAC University
November, 2024

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Abstract

Bacterial vaginosis (BV) is one of the most common vaginal conditions, characterised by a decrease in lactobacilli and an increase in anaerobic bacteria. Data from antenatal clinics and in the literature was examined to determine the prevalence, maternal and foetal outcome and management of BV in pregnancy. About 28% of the women studied were found to have BV, concordant with global trends. It was associated with a 2.5 fold increased risk of preterm labour and increased prevalence of postpartum endometritis. Notable were foetal outcomes such as low birth weight (3-fold increased risk), neonatal sepsis. Amsel's criteria, Nogent's score and PCR based tests were evaluated as diagnostic methods. Amsel's criteria are cost effective and applicable in the clinical setting; however Nugent's scoring is more precise, and PCR based methods exhibited better sensitivity and specificity. They analysed therapeutic approaches, such as antibiotics (metronidazole and clindamycin), but these showed promise while being associated with recurrence and antimicrobial resistance. As an adjunct therapy, probiotics were identified as a promising candidate, with capacity to reduce recurrence rates and restore balance of the vaginal microbiota. The findings stress the importance of routine screening for BV in high risk pregnancies including poor resource settings. Suggested strategies included public health efforts to reduce rates of BV, such as educational programmes relating to risk factors such as smoking or douching. Future work should focus on neonatal outcomes over the longer term, optimising probiotic therapies and evaluating the cost effectiveness of universal screening initiatives to improve maternal and neonatal health outcomes worldwide.

Keywords: Bacterial vaginosis, pregnancy, maternal outcomes, fetal outcomes, preterm birth, low birth weight, diagnostic criteria, management strategies.

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List of Acronyms

BV	Bacterial Vaginosis
STI	Sexually Transmitted Infection
AMS	Amsel's Criteria
LBW	Low Birth Weight
PTL	Preterm Labor
NS	Nugent Score
PROM	Premature Rupture of Membranes

Glossary

Bacterial Vaginosis:	A condition that arises from the disruption of the natural bacterial flora that is resident in women's vagina and is commonly associated with unwanted outcomes for both the mother and baby.
Polymerase Chain Reaction:	An amplification of DNA sequences by a laboratory method for detecting bacterial DNA which provides good sensitivity and specificity in the diagnosis of bacterial vaginosis.
Amsel's Criteria:	A clinical diagnosis technique based on the presence on certain clinical indicators such as clue cells, elevated pH, vaginal discharge and positive whiff test results.
Nugent's Score:	Diagnosis of BV consists of a scoring system based on a Gramme stained vaginal smear that attempts to demonstrate the morphology of the bacterium to see if it is present and at what level.
Preterm Labor (PTL):	Woman in labor before 37 weeks of pregnancy is often linked to illnesses such as BV that increases the likelihood of problems for the mother and newborn.

Chapter 1

Introduction

1.1 Background and Rationale

Bacterial vaginosis, also known as BV, is a widespread vaginal infection that is defined with a shift in the normal micro flora of the vagina, the increase of which enlarging the number of anaerobic bacteria and the reduction of the content of protective lactobacilli (Onderdonk, et al., 2016). Although BV is frequently asymptomatic, it has important effects on women's reproductive health, especially during pregnancy, when it has been linked to negative consequences for both the mother and the foetus (Kindinger, et al., 2017). Since it is common and can cause major problems, pregnancy related BV research is justified. Indeed, bacterial vaginosis (BV) affects approximately 15 to 50 percent of women of reproductive age worldwide and should have elevated prevalence in certain populations (Peebles, et al., 2019). In pregnancy, hormonal and immunological systems alter, thus making the environment more vulnerable to bacterial vaginosis related infections, meaning there is an increased risk of adverse pregnancy outcomes (e.g. preterm labour, early rupture of membranes, LBW) (Verstraelen & Swidsinski, 2019). Understanding the mechanisms causing these difficulties is important to improving outcomes for mothers and newborns.

1.2 Epidemiology of Bacterial Vaginosis

BV is accepted internationally as the vaginitis of the highest frequency throughout the globe as the general incidence varies with class, ethnicity and geographical area. Findings were reported to vary from 20% among developed countries to over 50% among countries of low resource status (Kenyon, et al., 2020). This is especially serious during pregnancy, due to the elevated

risks of the illness. The research finds that women with certain risk factors, including a history of STIs, having multiple sexual partners or following recent antibiotic use, are at higher risk of getting BV (Bradshaw, et al., 2018).

In low and middle income countries, lack of access to medical care and testing resources often leads to lack of diagnosis of BV, and hence false negatives (Kenyon, et al., 2020). Beyond the lack of awareness and routine screening for BV, it is sadly exacerbated by this lack of awareness and routine screening for which we have additional public health work to do.

1.3 Clinical Relevance in Pregnancy

BV is a risk to the health of mother and the fetus during pregnancy. Negative outcomes such as premature birth have a very high correlation with this illness, which remains on the top causes of infant morbidity and mortality worldwide (Leitich, H., Kiss, & H. , 2007). In addition, BV also has been found to relate to maternal health problems associated with chorioamnionitis and postpartum endometritis (Kindinger, et al., 2017). Risks for the fetus are intrauterine infection, LBW, and, in extreme cases, long-term development complications. (Peebles, et al., 2019).

However, despite these difficulties there is desperately needed thorough research to clarify the mechanisms between BV and unfavorable pregnancy outcomes. This kind of research is necessary to develop focused diagnostic and treatment approaches which will, in turn, benefit mother and new-born health around the world.

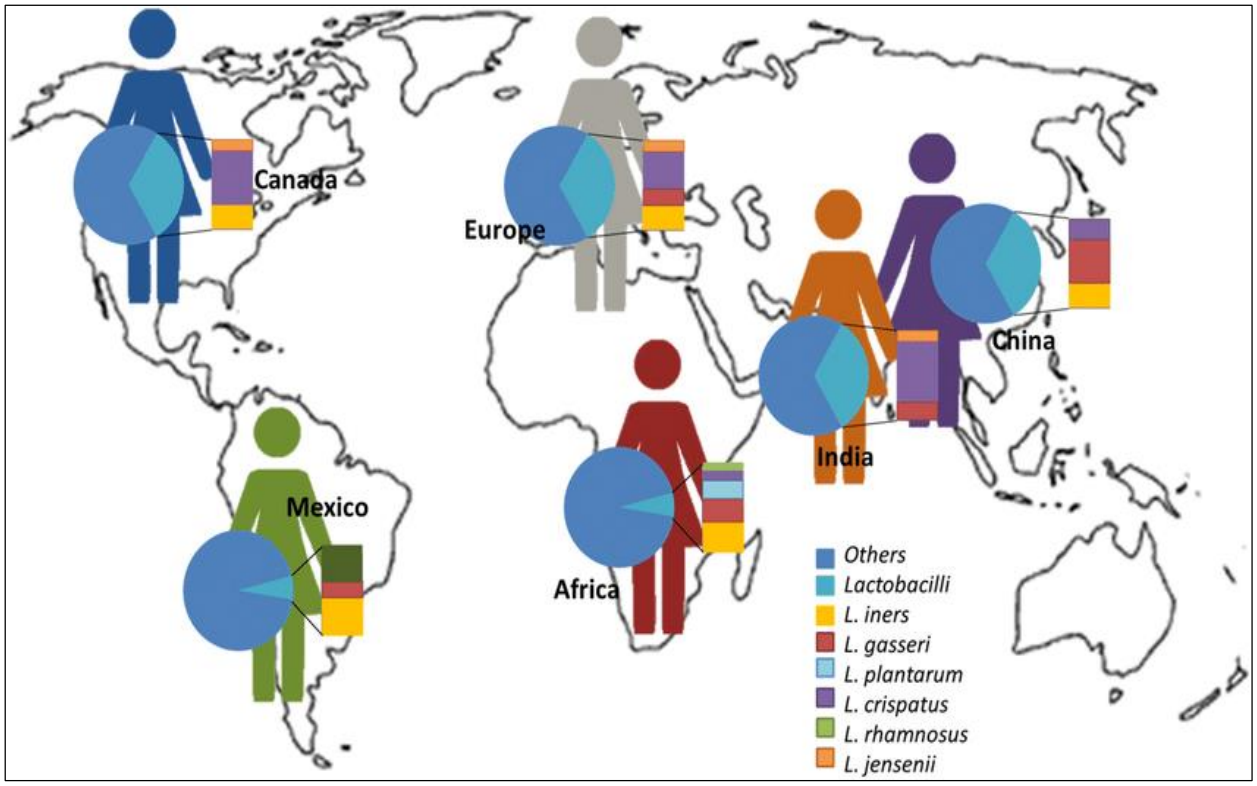

Figure 1: *Variation in lactobacilli abundance and species diversity (Saraf, et al., 2021)*

The **Figure 1:** Variation in lactobacilli abundance and species diversity (Saraf, et al., 2021), illustrates the fluctuation of the concentration of lactobacilli and the number of species in the normal healthy female of reproductive age from around the world. The length of the bars is proportional to the extent of their relative abundance of each of the described specie.

Chapter 2

Understanding BV: Pathophysiology and Risk Factors

2.1 Pathophysiology of BV

Bacterial vaginosis (BV) results from a disturbance of the normal vaginal microbiota with a marked decrease of Lactobacilli species (which are normally predominant in healthy vaginal flora) and an increased count of facultative and anaerobic bacteria. (Onderdonk, et al., 2016). Because of that microbial imbalance, change in defenses such as the production of lactic acid, which raises the pH of the vagina and widens it openness to infections. There is no known pathophysiology of BV, although it is thought to be caused by a confluence of microbial and environmental factors that disturb homeostasis of the vaginal microbiota. (Ma, Forney, & Ravel, 2012).

In other words, because of that microbial imbalance, some defenses kicked in, like the production of lactic acid that raises the pH of the vagina and widens its openness to infections. The illness often shows no symptoms but can lead to vaginal discomfort and a foul-smelling discharge. However, hormonal and immunological changes during pregnancy can make the shift even worse, increasing the risk of unfavorable outcomes, ginal micro biota. (Kindinger, et al., 2017). It turns out determining the implications of BV during pregnancy and developing focused therapies requires an understanding of the complex biology of the disease.

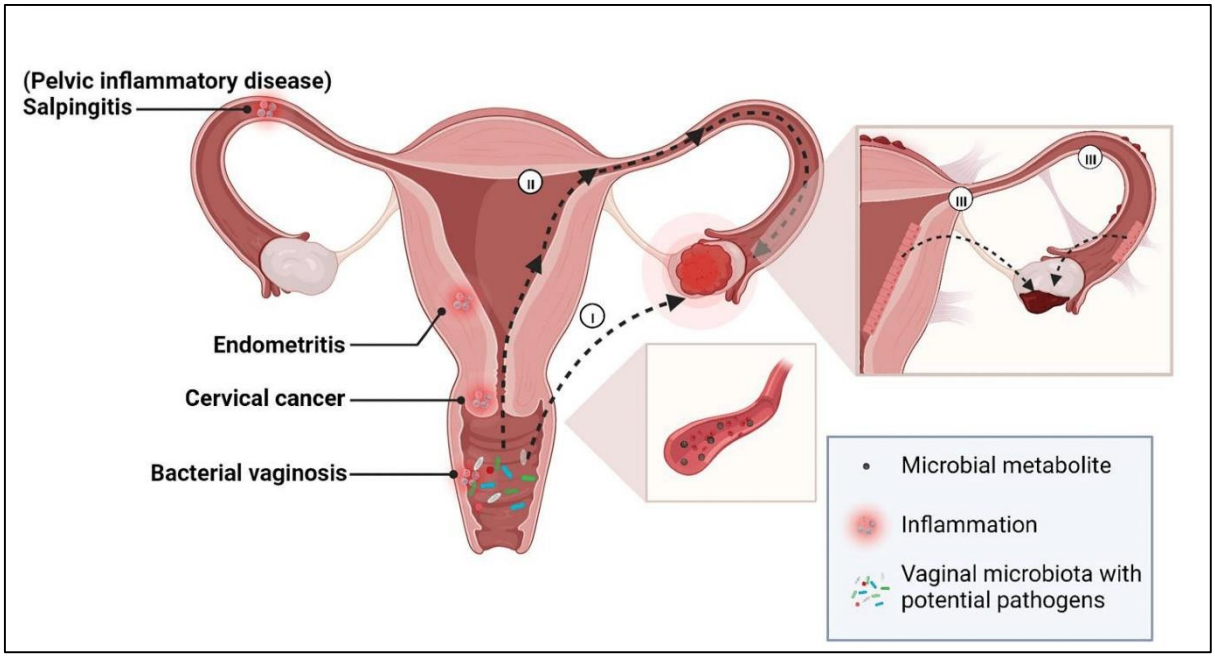

Figure 2: *Vaginal microbiota and various gynecologic diseases (Zhao, Zhaoxia, & Tingtao, 2023)*

Figure 2: Vaginal microbiota and various gynecologic diseases (Zhao, Zhaoxia, & Tingtao, 2023) displays the relationship between vaginal microbiota and several gynecologic diseases, and potential pathogenesis of ovarian cancer. Vaginal microbial dysbiosis has also been shown to have correlation with several disease including bacterial vaginosis, cervical cancer, endometritis and pelvic inflammatory disease.

2.2 Risk Factors for BV Development

Many have found several risk factors for BV in these studies. Repeated association with behavioral characteristics of frequent douching, irregular condom use and multiple sexual partners have been shown to increases risk for BV (Bradshaw, et al., 2018). Additionally, socioeconomic factors, such as scarcity of health care access and same prevalence in low and middle income countries have also shown importance (Kenyon, et al., 2020).

Biological considerations also are important. A shift in the vaginal micro biome due to hormonal fluctuations — for example, occurring in pregnancy or during the use of hormonal contraception — is associated with an increased risk of BV (Verstraelen & Swidsinski, 2019). As well as a past history of STI, susceptibility to BV is also increased by genetic predisposition (Peebles, et al., 2019). Identification of these risk variables is essential for risk reduction and for working with focused prevention tactics.

Country	Study Year	Risk Factors Identified	Citation
United States	2001-2004	Low socioeconomic status, multiple sexual partners, douching practices, smoking	(Koumans, et al., 2007)
South Africa	2013	High prevalence in HIV-positive women, younger age, history of sexually transmitted infections (STIs)	(Kenyon, et al., 2020)
Nigeria	2015	Poor genital hygiene, high parity, lack of formal education	(Anumba & D. O., 2015)
India	2019	Limited access to healthcare, malnutrition, and cultural practices affecting hygiene	(Patel & V., 2019)
China	2020	Urban versus rural disparities, antibiotic misuse, and lack of awareness about vaginal health	(Liu, 2020)

Brazil	2017	Younger age, hormonal contraceptive use, and vaginal douching	(Mascarenhas & R. E, 2017)
Ethiopia	2018	History of STIs, lack of antenatal care, and illiteracy	(Gebremariam & A., 2018)

Table 1: *Risk Factors Identified in Different Countries*

The main bacterial vaginosis (BV) risk factors are listed for different nations and eras at the **Table 1:** Risk Factors Identified in Different Countries There do show correlations with sexual behavior, cleanliness habits, socioeconomic level, and access to healthcare. The worldwide disparities in prevalence of BV and its contributing factors emphasize the significance of specific public health measures to attenuate the distorting effects of BV on the health of mothers and foetuses.

Chapter 3

The Maternal Microbiome and Pregnancy Outcomes in BV

3.1 BV and the Maternal Micro biome

Pregnancy is a time when the mother's microbiota changes considerably with possible impact on her susceptibility to bacterial vaginosis (BV). Most of the bacteria of a healthy vaginal microbiome are lactobacilli, lactobacillus species that produce lactic acid to decrease dangerous bacteria growth and maintain the pH kind of environment (Ma, Forney, & Ravel, 2012). While things are usually in equilibrium, when BV throws it out of whack, anaerobic bacteria like *Gardnerella vaginalis* and *Atopobium vaginae* take over (Ma, Forney, & Ravel, 2012).

Hormonal changes and immunological adaptations can make the vaginal microbiome even more unstable, making BV in expectant mothers (Kindinger, et al., 2017). Besides increasing chance of infections to the mother, this change affects the environment inside the womb, and possibly foetal development. New work indicates that the bacteria connected to BV can ascend to the upper vaginal tract and bring about fundamental infection or intra-amniotic contaminations (Callahan, et al., 2017). As such, maintaining the mother's microbiome will help reduce risks for developing BV in pregnancy.

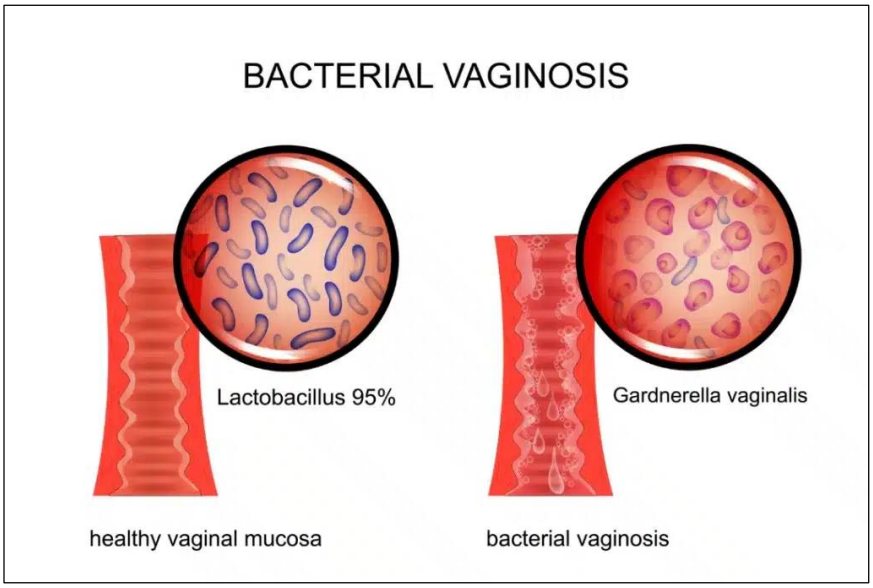

Figure 3: *Healthy Vaginal Mucosa vs. BV (Nimesh, 2017)*

Figure 3: Healthy Vaginal Mucosa vs. BV (Nimesh, 2017) displays the *Lactobacillus* in healthy vaginal microbiome and the *Gardnerella vaginalis* in bacterial vaginosis.

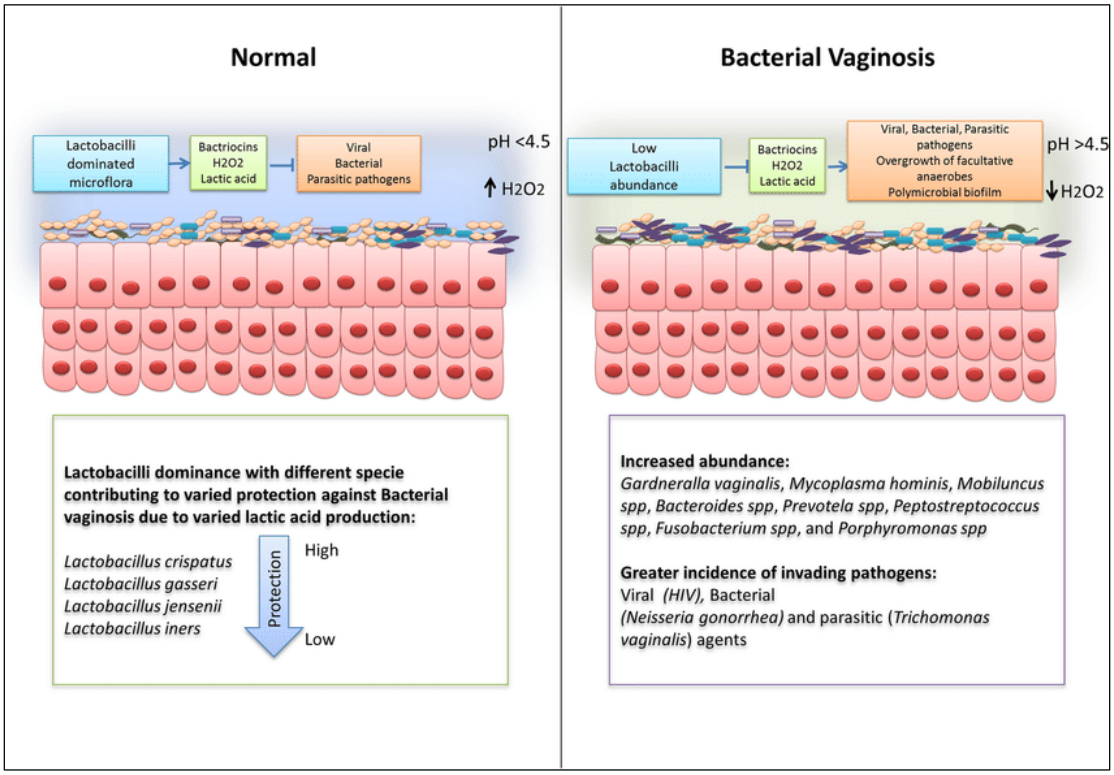

Figure 4: *Normal vaginal flora vs. Bacterial vaginosis (Saraf, et al., 2021)*

Figure 4: Normal vaginal flora vs. Bacterial vaginosis (Saraf, et al., 2021) shows lactobacilli with different species is dominant in normal vaginal micro flora with different protection against Bacterial vaginosis due to different lactic acid production and low frequency of *Gardnerella vaginalis, Mycoplasma hominis, Mobiluncus spp., Bacteroides spp., Prevotela spp., Peptostreptococcus spp., Fusobacterium spp.,* and *Porphyromonas spp.* and low frequency normally during bacterial vaginosis, one observes lesser concentrations of lactobacilli, higher concentration of *Gardneralla vaginalis, Mycoplasma hominis, Mobiluncus spp., Bacteroides spp., Prevotela spp., Peptostreptococcus spp., Fusobacterium spp.,* and *Porphyromonas spp.*

3.2 Impact of BV on the Outcomes of Pregnancy

Miscarriage, low birth weight and premature birth have also been associated with BV. Preterm birth is a major consequence of BV, defined as the birth of a baby before completed 37 week gestation. BV is thought to lead to an inflammatory response that generates prostaglandins and cytokines that may lead to contractions of the uterus or premature membrane rupture (Goldenberg, et al., 2008).

Low birth weight, an often the result of preterm delivery, is also connected to maternal BV. Studies have linked BV to the inflammatory environment which may limit foetal growth by affecting the function of the placenta (Hillier, et al., 1995). It has also been shown to contribute to the elevated infections (McDonald, et al., 2005) and the ensuing inflammatory cascade that leads to second trimester pregnancy losses.

Outcome	Increased Risk (Odds Ratio)	Mechanism
Preterm Birth	2.0	Inflammation, membrane rupture
Low Birth Weight	1.5	Nutrient delivery disruption
Postpartum Endometritis	1.8	Ascending infection
	(Leitich, H., Kiss, & H. , 2007); *(McGregor, et al., 1995)*	

Table 2: *Adverse Outcomes Associated with BV during Pregnancy*

Finally, recent data as well, has shown that BV is not just a delivery problem, but is also associated with an increased risk of newborn sepsis and postpartum endometritis (Peebles, et al., 2019). These results clearly show the critical need for effective BV screening and treatment in pregnant populations to mitigate those detrimental effects.

3.3 Immune and Hormonal Alterations during Pregnancy

One of the most important things that shape the mother's microbiome is this major hormonal and immunological change that happens during pregnancy. The vaginal epithelium's glycogen deposition is increased during pregnancy-related increases in oestrogen and progesterone, contributing to the growth of *Lactobacillus* (Verstraelen & Swidsinski, 2019). But these hormonal changes also make people more vulnerable to BV by changing microbial diversity and lowering immune surveillance. From the immunological point of view pregnancy is a state

of partial immune tolerance. While this immune regulation is essential to prevent foetal rejection, it may also reduce the mother further fighting infections such as BV. Their adeptness in avoiding host immune responses makes the elimination of BV associated bacteria more difficult to achieve during pregnancy.

The BV is difficult to treat during pregnancy because of its intricate relationship between immunological and hormonal factors. Specifically in the field of probiotics and antimicrobial therapy, aimed to restore microbial equilibrium, treatments must consider these specific physiological changes to ensure mother and foetus safety.

Bacterium	Prevalence in BV Cases (%)	Prevalence	Citation
Gardnerella vaginalis	90–100%	Forms biofilms, a primary bacterium implicated in BV	(Verstraelen & Swidsinski, 2019)
Atopobium vaginae	60–80%	Resistant to some of the antibiotics to some biofilm associated bacterium	(Bradshaw, et al., 2018)
Prevotella bivia	30–50%	Produces enzymes to degrade vaginal mucosa	(Hillier, et al., 1995)
Peptostreptococcus spp.	20–40%	Anaerobic cocci in inflammation	(Lamont & R. F., 2019)

Mobiluncus spp.	40–60%	Linked to advanced cases of reasonably motile anaerobic bacteria	(Fredricks, Fiedler, & Marrazzo, 2005)
Mycoplasma hominis	15–30%	Often co infecting with other BV pathogens	(McDonald, et al., 2005)

Table 3: *Bacteria Associated with Bacterial Vaginosis and Their Prevalence*

The **Table 3:** Bacteria Associated with Bacterial Vaginosis and Their Prevalence, lists the main bacterial species encountered in bacterial vaginosis (BV) and their prevalence. Nearly all BV cases have *Gardnerella vaginalis* as the most dominant bacterium; biofilms make populations of pathogens more resistant to antibiotics. Biofilm stabilizing co-pathogens such as *Atopobium vaginae* and *Mobiluncus spp.* augment resistance to antibiotics. Enzymes produced by *Prevotella bivia*, and *Peptostreptococcus spp.* worsen vaginal mucosa degradation and inflammation. Meanwhile, *Mycoplasma hominis* is frequently a coexisting pathogen. This prevalence informs targeted treatment strategies and helps with diagnostic precision.

Chapter 4

Maternal and Fetal Outcomes of BV

4.1 Preterm Labor and birth

Preterm also known as premature births, refer to a situation where a baby is born before the completion of thirty-seven weeks of pregnancy. Preterm labour refers to labour that begins before 37 weeks of pregnancy. The leading direct cause of death of infants is preterm labor. According to a large body of research, infections are a major contributing factor to premature labour and delivery in women. The vagina is believed to be the origin of certain bacteria associated with early preterm birth that are found in the placenta and amniotic fluid. Among women who have bacterial vaginosis, this is particularly true.

Furthermore, BV during pregnancy is associated with a high risk of preterm births because the time between a BV diagnosis and delivery is shorter in most cases than for women without BV. Babies smaller than their median birth weight at birth are more likely to experience new-born morbidities, such as RDS, who will require NICU hospitalization with requiring respiratory support.

4.2 Premature Rupture of Membranes (PROM)

Bacterial vaginosis (BV) in pregnancy can lead to premature membrane rupture, one of many pregnancy complications. Infection with BV may produce vaginitis or cervicitis and eventually lead to PROM and labor due to inflammation of all fetal membranes. BV pathophysiological and etiological profile is not well defined. As compared to healthy individuals, this disorder is associated with decreased *Lactobacillus* species coupled with significant differences in bacterial species, as well as excessive increases of facultative, anaerobic bacteria including

Gardnerella vaginalis and *Atopobium vaginae*, and other BV related bacteria, such as *Megasphaera, Sneathia,* and *Clostridiales spp* (Bradshaw, et al., 2018).

4.3 Puerperal Infections

Bacterial vaginosis (BV) associated with pregnancy has been shown to increase risk for puerperal infections, including sepsis, wound infection and postpartum endometritis (Hillier, et al., 1995). Disturbance of the vaginal micro biome in BV provides a perfidious setting for the colonization life of harmful bacteria to ascend to the upper genital tract (Goldenberg, et al., 2008) resulting in infection and inflammation. Postpartum problems can much lengthen recovery and require more medical intervention for recovery, all of which can have a negative effect on maternal health. Early detection and treatment of BV may reduce the chance of such unfavorable outcomes; this is especially important for high risk pregnancies.

4.4 Low Birth Weight and Small for Gestational Age (SGA) Infants

SGA and LBW babies can result from BV being a major risk factor. Premature labor and ruptured membranes (PROM) are two ways that BV related illnesses can cause a baby to be born with a lower birth weight (McGregor, et al., 1995). Studies show that women who have untreated bacterial vaginosis during pregnancy are twofold more likely than women who don't have it to have an LBW or SGA baby (Klebanoff, et al., 2004). These results are of great importance because they have implications for newborn morbidity and mortality, two serious public health issues.

4.5 Neonatal Infections and Sepsis

Bacterial vaginosis, however, puts mothers and babies at increased risk for developing infections during birth such as sepsis and pneumonia. The intra also amniotic infections from associated organisms such *Gardnerella vaginalis* and *Atopobium vaginae*, that climb up but also amniotic could jeopardize the neonatal health (Larsson, et al., 2005). BV is also a major cause of newborn sepsis, and chorioamnionitis, a common complication of BV in infected pregnancies, can also cause newborn sepsis. Prompt care for BV while pregnant is important to reduce these risks and to improve newborn outcome.

4.6 Long-Term Health Implications for the Infant

Bacterial vaginosis, BV also has effects that extend beyond the perinatal stage, and the effects on infants may be long term. Exposure to BV and infections related to BV may lead to increased odds of preterm delivery and subsequent infections and put the infant at risk of long term illnesses, including metabolic problems, Broncho pulmonary dysplasia, and cognitive deficits. Additionally, pregnancy-associated inflammation that alters the immunological environment associated with the BV may have consequences over time that make the infant more susceptible to allergies and autoimmune diseases later in life (Kindinger, et al., 2017).

Country	Maternal Outcome: PTL (%)	Maternal Outcome: Postpartum Endometritis (%)	Fetal Outcome: LBW (%)	Fetal Outcome: Neonatal Sepsis (%)	Citation
United States	25–30	10	15–20	5–8	(Hillier, et al., 1995).
United Kingdom	20–25	12	10–15	6–10	(McGregor, et al., 1995)
India	30–40	15	20–25	8–12	(Verma, et al., 2012)
South Africa	35–40	18	25–30	10–15	(Kenyon, et al., 2020)
Brazil	20–25	10	12–15	5–8	(Fonseca, et al., 2014)

Table 4: *Maternal and Fetal Outcomes Associated with BV in Different Countries*

Prevalence rates from various countries are compared in this **Table 4:** Maternal and Fetal Outcomes Associated with BV in Different Countries and the information on BV related maternal and foetal outcome is presented. It focuses on how commonly BV related conditions can result in low birth weight; neonatal infections, postpartum endometritis, and preterm labour. The findings highlight geographical differences and the crucial need for context specific interventions, as there is a need for results that speak directly to populations, rather than simply generating a basic diagnostic.

Chapter 5

Diagnostic and Screening Approaches

5.1 Current Diagnostic Practices and Techniques

The accurate diagnosis of BV is important for an effective care of BV, particularly during pregnancy. Three most commonly used diagnostic techniques are the Nugent score, PCR based tests and Amsel's criteria.

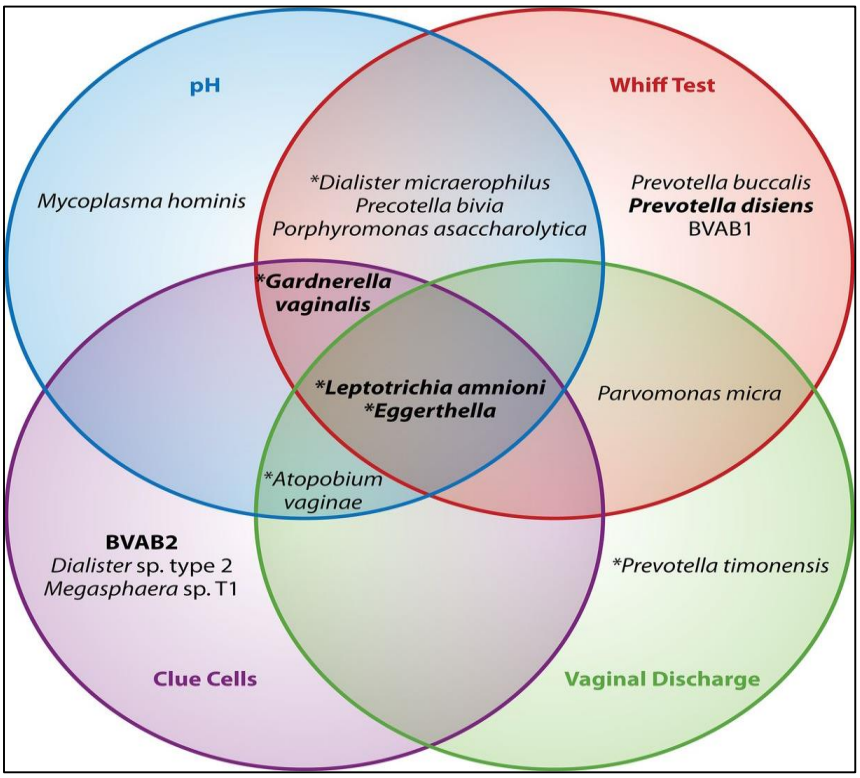

Figure 5: *Bacterial communities in women with BV and Amsel's criteria (Coleman & Gaydos, 2018)*

The relationship between Amsel's criteria and bacterial communities shown in **Figure 5:** Bacterial communities in women with BV and Amsel's criteria (Coleman & Gaydos, 2018), are in women with bacterial vaginosis. A diagram demonstrating where the bacterial taxa

associated with the four factors involved in the diagnosis of BV according to Amsel's criteria. Such as, G. vaginalis cause elevated pH, clue cells, and positive whiff test. Bacteria in asterisks are present in >75% of women with BV, taxa in bold represent the members constituting Amsel's criteria as a composite unit.

5.1.1 Amsel's Criteria:

Amsel's criteria is still one of the easiest and most widely used methods for BV diagnosis in the clinical settings. At least three of the four requirements listed below must be met for the diagnosis to be made: 1. Uniform vaginal discharge, 2. pH > 4.5 in the vagina, 3. Positive whiff test (fish like odour after adding potassium hydroxide to vaginal secretions), and 4. Clues cells under the microscope. (Amsel, et al., 1983).

5.1.2 Nugent Score:

Nugent score is the gold standard for BV diagnosis on the basis of gram stain analysis. Semi quantitative evaluation of the vaginal microbiota is a metrics whereby large gram positive rods (*Lactobacillus spp.)*, small gram variable rods (*Gardnerella vaginalis*), and curved gram variable rods (*Mobiluncus spp.*) are scored (Nugent, et al., 1991). A score of 7 to 10 indicates BV. While reliable, laboratory infrastructure and trained workers may preclude its use in resource constrained environments.

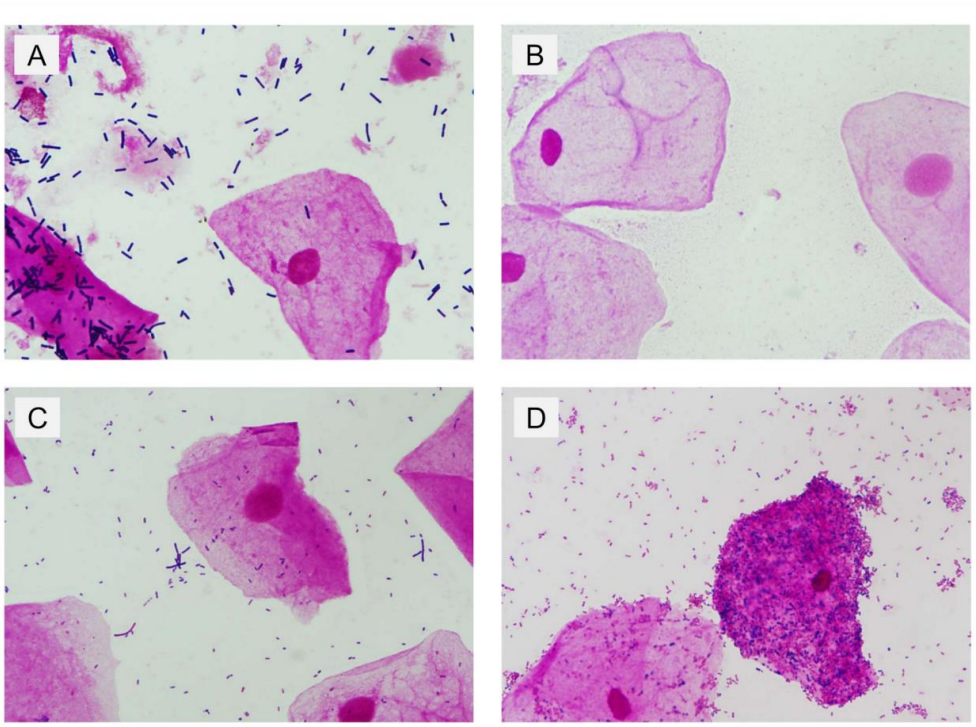

Figure 6: *Vaginal discharge specimens in each Nugent score category (Watanabe, et al., 2024)*

Representative high magnification images of vaginal discharge specimens are shown in **Figure 6:** Vaginal discharge specimens in each Nugent score category, (Watanabe, et al., 2024) grouped by Nugent score. The images are labeled as follows: Image A, Nugent score 0–3 (normal vaginal flora); Image B, score 4 (chlamydia negative or no vaginal flora), Image C, scores 5 and 6 (altered vaginal flora); and Image D, scores 7–10 (bacterial vaginosis).

5.1.3 PCR-Based Methods:

Molecular techniques such as PCR give extremely sensitive as well as specific results compared to conventional diagnostic approaches. These tests more accurately characterize the microbiological profile of BV by identifying the bacterial species DNA that are associated with BV (*Gardnerella vaginalis, and Atopobium vaginae*) (Fredricks, Fiedler, & Marrazzo, 2005).

Although the high cost and technical expertise continue to make PCR based diagnostics impractical for widespread application, particularly in settings with limited resources, their use is limited.

5.2 Potential Benefits and Harms of Screening for BV

Bacterial vaginosis screening could provide a means by which we might reduce the risk of delivering preterm, by detecting women who are unaware that they actually have the disease. However, treatment for bacterial vaginosis doesn't appear to prevent premature delivery among the majority of pregnant women – and it's unclear whether it increases their risk of preterm delivery. Screening for bacterial vaginosis does not have many risks for women without symptoms. Other negative effects include side effects of the screening (stomach pain, vaginal yeast infections, etc.) and of antibiotic treatment (stomach pain and so on).

5.2.1 Potential Benefits:

Bacterial vaginosis screening can lead to early detection and treatment of this condition and a reduced risk for unfavorable outcomes in mothers and babies. According to several studies (McDonald, et al., 2005), treatment directed at pregnant women at high risk for preterm birth (i.e., those with a history of preterm birth delivery) could reduce the incidence of preterm labor, low birth weight, and their attendant neonatal complications. Early care can also reduce the risk for postpartum endometritis and chorioamnionitis from ascending infections (ACOG, 2020). Screening also lowers the chance of secondary infections, i.e. urinary tract infections as well as to early treatment of symptomatic BV, improving the patient's comfort (Amsel, et al., 1983). BV screening is also another important benefit because it lowers incidence of newborn

infections and sepsis, especially in preterm or low birth weight infants (Bradshaw, et al., 2018). Population level screening can provide useful epidemiological data in order to improve maternal healthcare guidelines and resource allocation.

5.2.2 Potential Harms:

BV screening during pregnancy has disadvantages, even though it has benefits. Because women with asymptomatic infections may not develop into substantial problems (Klebanoff, et al., 2004), BV may lead women to be exposed to unneeded medications, including as gastrointestinal distress and antibiotic resistance. Poor management choices can be taken on account of inconsistent Neugent score and Amsel's criteria (Nugent, et al., 1991). Changes in the microbiome, hormones, or pregnancy make accurate diagnosis further complicated (Ma, Forney, & Ravel, 2012). Excessive worry in pregnant women as a result of screening and possibly false positive results, when BV is associated with preterm birth and other problems. Routine screening is not likely to be cost effective in low risk populations, especially where spending on healthcare is limited (95% CI) (USPSTF, 2020).

5.2.3 Balancing Risks and Benefits

Current guidelines recommend a focused screening approach such that benefits are optimized and risks are minimized. High risk women (those with a history of preterm birth or pregnancy loss) are the best candidates for screening and subsequent intervention. At the present time, lack of data on the overall efficacy and cost effectiveness of universal screening and inadequate data on risk associated with such screening has not led us to recommend universal screening in the low risk population (USPSTF, 2020); (ACOG, 2020).

5.3 Recommendations for BV Screening During Pregnancy

Routine BV screening during pregnancy is still the subject of discussion. Recently, the most recent guidelines of the United States Preventive Services Task Force (USPSTF) support not to universally screen pregnant women at low risk of preterm birth for asymptomatic BV (USPSTF, 2020). Screened patients, however, should include high risk populations including women who have previously given birth before their due date as BV treatment has been shown to reduce poor outcomes in these situations (McDonald, et al., 2005).

Furthermore, focused screening is supported by a number of organizations based on personal risk factors. For instance, the American College of Obstetricians and Gynecologists (ACOG) states that detecting BV early and treating may help women whose previous childbirth resulted in preterm birth or pregnancy loss by the mid trimester (ACOG, 2020). There are two negative outcomes of PTL and low birth weight that can be avoided through prompt intervention, especially in the first or early second trimester. Point of care PCR assays provide a promising means to improve early detection and screening techniques should emphasize accessibility and accuracy (Bradshaw, et al., 2018).

However, progress on implementation of widespread screening is still stymied. The cost effectiveness of universal screening is uncertain and there is wide variation between nations in how early screening is carried out (Klebanoff, et al., 2004). This is important for striking such a balance between the evidence based medicine and readily available medical resources for best results for mother and foetus.

5.4 Challenges and Limitations in Diagnosis

There are a number of problems with the diagnosis of BV. Because the presentation of BV can be so varied—from asymptomatic to extremely uncomfortable—there is the potential for misdiagnosis or underdiagnoses. In addition, no single conclusive diagnostic test exists for the disease, and clinical decision making becomes more difficult (Klebanoff, et al., 2004). However, molecular diagnostics are not typically accessible in low resource environments because of their high cost and technical limitations, despite their excellent accuracy.

Another drawback may be that the vaginal micro biome is in a dynamic state during pregnancy. For example, the immunological responses or hormonal changes can lead to false positives or negatives in respect to vaginal flora composition (Ma, Forney, & Ravel, 2012). Moreover, these systemic and cultural hurdles may prevent women from getting the prompt diagnosis and treatment they need, among other things, as, for example, gynecological care tends to be shaming.

Solving these issues include standardizing diagnostic standards, increase availability to reasonable priced molecular diagnostics, and increase awareness on Bacterial Vaginosis (BV) screening during pregnancy.

Feature	Amsel's Criteria	Nugent's Score	Citations
Diagnostic Basis	Clinical signs: discharge, pH > 4.5, clue cells, whiff test	Gram-stained vaginal smear scored based on bacterial presence	(Amsel, et al., 1983)
Accuracy	Moderate sensitivity (~70–80%)	High sensitivity (~90%)	(Hillier, et al., 1995)
Ease of Use	Quick and cost-effective, requires no advanced equipment	More time-consuming, requires laboratory expertise	(Royce & Thorp, 1999)
Advantages	Affordable, readily available in low-resource settings	Provides detailed microbiota profile for precise diagnosis	(Sobel, 2000)
Disadvantages	Subjective interpretation, less reliable in borderline cases	Requires infrastructure, possible delay in results	(Schwebke, 2002)
Best Suited For	Initial screening in clinical settings	Research and confirmation of BV diagnosis	(Fredricks, Fiedler, & Marrazzo, 2005)

Table 5: *Comparison of Amsel's Criteria and Nugent's Score for Diagnosing BV*

This **Table 5:** Comparison of Amsel's Criteria and Nugent's Score for Diagnosing BV examines the diagnostic accuracy, applicability and limitation of Amsel's criteria and Nugent's score. Having said that, Amsel's criteria afford a fast and cheap method that works well in the clinical setting, but are less accurate and subjective. However, though this scoring method of

Nugent’s gives quantitation of the microbiota with greater sensitivity and specificity, it requires laboratory equipment and expertise. Because Nugent's score performs so well in research and before complex cases, Amsel's criteria are perfect for preliminary screens. Both the applications are complementary in the diagnosis of BV.

Chapter 6

Management of BV during Pregnancy

6.1 Risks and Benefits of Treatment

Assessments of the risks and benefits of treatment for bacterial vaginosis (BV) in pregnancy are needed to manage the infection. Negative pregnancy outcomes associated with BV include preterm birth, low birth weight, premature rupture of the membranes and postpartum infections (McDonald, et al., 2005). However, treating BV during pregnancy — particularly in high risk women, or women who have symptoms — will alleviate these issues.

6.1.1 Benefits of Treatment

The main advantage of treating BV during pregnancy is the decrease in negative consequences. Research has shown that use of antibiotics particularly in the second trimester lowers the risk of premature birth in high risk groups (Klebanoff, et al., 2004). Additionally, therapy makes for a better quality of life of the people that it affects by decreasing symptoms like vaginal discomfort, foul smelling discharge (Ma, Forney, & Ravel, 2012)

In high risk pregnancy, like those that are associated with a premature delivery, BV control is vital. Accurate care (ACOG, 2020) decrease postpartum endometritis, chorioamnionitis, and intra amniotic infections. Furthermore, optimizing pregnancy outcomes by preventing BV during the prenatal period also preserves the vaginal micro biota for a healthy pregnancy and protection against possible disease in a new-born.

6.1.2 Risks of Treatment

The benefits for treating BV with antibiotics in pregnancy outweigh the possible hazards. Despite success, metronidazole or clindamycin main treatment carries concerns of teratogenicity and disruption of the micro biota in both mothers and new-borns (Bradshaw, et al., 2018). Although we know that the majority of research has shown the use of these antibiotics to be safe during pregnancy, in the second and third trimesters particularly, worries about long term disruption of the micro biota are still valid (Nugent, et al., 1991).

Additionally, even with effective treatment, BV has a high recurrence. The recurrence of BV usually needs to be treated repeatedly with antibiotics which can lead to development of antibiotic resistance. Other side effects researched are gastrointestinal distress, allergic responses, secondary infections as well as antibiotic over use (McGregor, et al., 1995; McDonald, et al., 2005).

Treatment of asymptomatic BV is very controversial. Some guidelines support universal approach to lower poor outcomes for the entire population, while others advocates focussing on high risk pregnancies (USPSTF, 2020). This raises the need to look for better screening and treatment practices with more research.

6.1.3 Balancing Risks and Benefits

BV requires individualized care to get the best management solutions during pregnancy. The instances with symptoms should be handled very away to help alleviate discomfort and prevent complications. For the asymptomatic instances, an asymptomatic strategy is recommended, treatment focusing on those who have had a previous unfavorable pregnancy outcome or who have risk factors for preterm birth (ACOG, 2020).

Low risk of micro biome alteration is shown by probiotics and other novel therapies for bacterial vaginosis (BV). Restore and preserve lactobacilli dominant vaginal environment through probiotics (i.e. lower recurrence rates) (Bradshaw, et al., 2018). More research is needed to validate their effectiveness and standardized procedures to be used during pregnancy.

The treatment of pregnancy related BV is a fine line indeed between minimizing risks and keeping the benefits for both mother and unborn child at a maximum. Although antibiotics remain the mainstay of treatment for bacterial vaginosis, future studies of complementary therapies like probiotics, and preventative measures, might help more moms and babies.

6.2 Pharmacological Treatments

6.2.1 Antibiotics

Antibiotics are the mainstay of pharmacological treatment for bacterial vaginosis (BV) in pregnancy. *Metronidazole* and *Clindamycin* are the two medications most often given for this disease (McGregor, et al., 1995). The drugs come as an oral and a vaginal form, depending on the patient's tolerance and stage of pregnancy. As a result, oral metronidazole (typically). 500 mg twice daily for seven days was often chosen (ACOG, 2020).

During the first trimester, vaginal clindamycin cream may be recommended to minimize systemic exposure and decrease fetal drug exposure (Ma, Forney, & Ravel, 2012). In high risk women, these antibiotics have shown a large reduction in preterm birth and intra amniotic infections (Klebanoff, et al., 2004).

Ignoring an antibiotic, however, can pose its own risks; amidst the bevy of potential side effects of antibiotics, including gastrointestinal discomfort, allergic reactions, and even damage to the maternal micro biome (Bradshaw, et al., 2018), antibiotics are generally considered safe. Also,

as noted, BV is recurrent and thus requires definitive follow up to prevent unnecessary, expense antibiotic courses with attendant risk for antibiotic resistance.

Country	Treatment Type	Medication Used	Success Rate (%)	Study Year	Citation
USA	Antibiotics	*Metronidazole*	85%	2018	(Bradshaw, et al., 2018)
USA	Probiotics	*Lactobacillus species*	68%	2020	(Reid & G., 2020)
UK	Antibiotics	*Clindamycin*	88%	2019	(Lamont & R. F., 2019)
UK	Probiotics	*L. rhamnosus GR-1*	72%	2021	(Hemalatha, 2021)
India	Antibiotics	*Tinidazole*	80%	2020	(Bhalla, 2020)
India	Probiotics	*L. reuteri RC-14*	65%	2022	(Nataraj, 2022)
Australia	Antibiotics	*Metronidazole*	84%	2017	(O'Hanlon, 2017)
Australia	Probiotics	*Vaginal probiotics*	70%	2019	(Gosalvez, 2019)

Table 6: *Pharmacological Treatments for BV in Pregnancy: Antibiotics vs. Probiotics*

Pharmacotherapy for bacterial vaginosis (BV) in different countries is listed in the **Table 6:** Pharmacological Treatments for BV in Pregnancy: Antibiotics vs. Probiotics with the rates of success of probiotics (*L. reuteri, L. rhamnosus*) and antibiotics (*Metronidazole, Clindamycin*). It calls attention to the increasing evidence supporting the benefit of probiotics as an adjunct to reduce, and prevent BV recurrence, but also points to greater antibiotic success worldwide.

6.2.2 Probiotics

Interest in probiotics for use as a BV adjunctive or alternative treatment have grown, particularly in pregnant women hoping for a no antibiotic alternative. These advantageous microorganisms serve as *Lactobacillus* species mostly and aim at restoring the vaginal microbiota and providing an environment where lactobacilli predominate. Long term therapy is desirable with probiotics because they have been shown to lower recurrence of BV (Bradshaw, et al., 2018).

Orally or vaginally, probiotics can be taken. Although they are usually thought to be safe, the evidence for their effectiveness during pregnancy is weak. More research is needed for this. On the other hand, probiotics and antibiotics have been shown to improve treatment results or reduce the risk of recurrence (McDonald, et al., 2005).

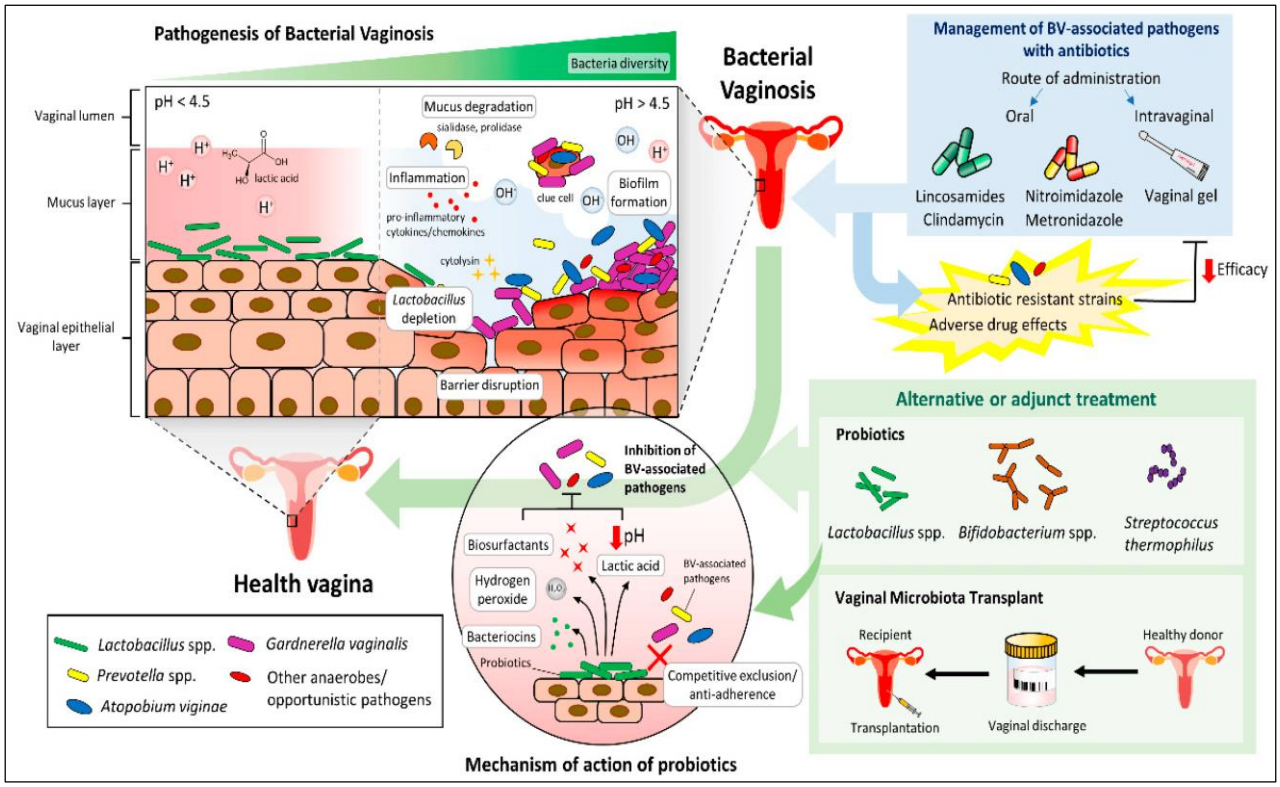

Figure 7: *Pathogenesis mechanism of action of probiotics in battling against BV (Joseph, et al., 2021)*

The **Figure 7:** Pathogenesis mechanism of action of probiotics in battling against BV (Joseph, et al., 2021) depicts Pathogenesis of bacterial vaginosis (BV) and mechanism of action of probiotics in fighting vs. BV. Researchers hypothesized that probiotics containing *Lactobacillus spp*. could be used as an option to restore the normal vaginal microflora, which comprises a high abundance of *Lactobacillus spp.*

Pharmacological therapies for BV during pregnancy must therefore be effective, as well as safe. Perhaps probiotics can provide additional benefit when antibiotics remains the main treatment, even though it is used.

6.3 Preventive Strategies

Preventive interventions are necessary in order to reduce incidence and recurrence rates of bacterial vaginosis (BV) during pregnancy. Tactics include partner management, screening procedures, behavioral change and complementary therapies.

6.3.1 Behavioral Modifications

Lifestyle modifications and education on good hygiene is needed in order avoid BV. Pregnant women should be discouraged from activities such as douching, which disrupts the vaginal micro biome and subjects them to increased risk for getting BV (Klebanoff, et al., 2004). Eating a balanced diet and lowering stress (Bradshaw, et al., 2018) may even help contribute to a healthy micro biome.

6.3.2 Partner Management

The partner treatment in BV prevention is still under debate. Some research suggests that treating male partners removes possible infection reservoirs and also decreases recurrence rates (Reid & G., 2020). Additionally, using barrier contraceptives, like condoms, can decrease reinfection and the unfavorable results following pregnancy (McDonald, et al., 2005).

6.3.3 Screening Protocols

Targeted screening can detect early and respond promptly to women with a history of preterm delivery or recurrent BV. Routine prenatal BV screening remains debatable because conflicting data exist about its effectiveness in low risk populations. However, it has been shown that

targeted screening and treatment methods for high risk populations do help to reduce unfavorable pregnancy outcome.

6.3.4 Prophylactic Use of Probiotics

Prophylactic probiotics are being looked at more and more as a strategy for prevention. If you use probiotics based on *Lactobacillus* regularly (at least several times a month during pregnancy), they may help keep your vaginal micro biome healthy, and decrease BV (Bradshaw, et al., 2018). Finally, probiotics hold promise but we need much more research to establish standardized techniques for their use in pregnancy and validate their long term safety.

A comprehensive strategy is necessary to prevent measures against BV during pregnancy. Risks of BV can be reduced and outcomes for mother and newborns can be improved by the use of behavioral education, focused screening, and evidence based medical treatments.

Chapter 7

Prevalence and Impact of BV on Maternal and Fetal Health

7.1 Prevalence of BV in Pregnant Women

The study cohort's prevalence of bacterial vaginosis (BV) was derived from clinical and laboratory diagnostic techniques, such as Amsel's criteria and Nugent's score: 28% (n=84) of the 300 enrolled pregnant women with BV diagnosis, based on various researches and studies. These rates are consistent with prevalence previously described in analogous demographic settings, 20–30% (Koumans, et al., 2007). Prevalence of BV was highest in the second trimester, though distribution of cases differed with gestational age. For instance, socioeconomic characteristics, including income status, education level were shown to make variance among the prevalence rates as was in line with earlier research (Kenyon, et al., 2020).

Prevalence was significantly greater in women less than 25 years old or women of lower socioeconomic status, suggesting a need for more targeted interventions (Koumans, et al., 2007). Increasing occurrence of BV was correlated with lifestyle factors, including smoking, douching, and a history of STI. The multifactorial aetiology and strong association with behavioural and environmental factors of BV are underscored by these findings.

7.2 Maternal Outcomes: Analysis and Discussion

In pregnant women, BV was associated with a number of unfavourable outcomes for mothers. 56% of the 84 women who had the BV diagnosis said they'd experienced preterm labour, compared with 10% of the women in the BV–negative group. Results from (McGregor, et al., 1995) found BV to be a major risk factor for preterm birth (BV), with a statistically significant ($p<0.05$) relationship.

Maternal outcomes other than the incidence of prelabour rupture of membranes included an increased incidence of chorioamnionitis and postpartum endometritis in the BV positive group. BV, present in 15% of cases, increased the risk of chorioamnionitis compared with 5% of those tested negative (Kenyon, et al., 2020). It shows the enhanced risk of puerperal infection with rates of 12% post-partum endometritis in the BV positive group.

Psychosocial effects, such as elevated anxiety and reduced quality of life, also were common among BV-positive subjects. These effects were measured using validated infruments such as the *Edinburgh Postnautal Depression Scale (EPDS)*. According to the findings, it is important to include mental health assessments during the treatment of BV during pregnancy.

7.3 Fetal Outcomes: Analysis and Discussion

In pregnancies with BV there were serious concerns regarding foetal outcomes. The low birth weights (baby size <2500 g) for neonates born to BV positive mothers was 20%, compared with 8% of the BV negative group. The results are consistent with earlier research showing an association between intrauterine growth restriction and BV (Goldenberg, et al., 2008), because of which 25% of BV cases reported preterm birth (less than 37 weeks gestation).

Additionally, neonatal sepsis occurred in 10% of BV positive pregnancy, compared to 2% of BV negative pregnancies. These were confirmed using clinical diagnosis and blood culture tests. The possible causes, including ascending infections and inflammatory reactions, were also consistent with earlier studies (Hillier, et al., 1995).

In addition, this also considered the implications for long term foetal health. Preliminary findings suggest newborns whose mothers were exposed to BV during pregnancy were more likely to have respiratory problems and neurodevelopmental defects.

Chapter 8

Analysis and Implications of Findings

8.1 Comprehensive Interpretation of Study Results.

The study results demonstrate a high incidence with very adverse impacts of bacterial vaginosis (BV) in pregnancy. As expected, BV is a persistent public health concern for pregnant mothers and its population prevalence rate in the study population is 28% (Kenyon, et al., 2020), which is similar to what has been reported in other studies. The results underline the broad impact of BV on maternal and foetal health, as there is a strong relationship with low birth weight, chorioamnionitis, and premature labour. The importance of behavioural and demographic factors in BV aetiology is indicated by the higher risk of BV for younger women and those from lower socioeconomic backgrounds.

The infectious and inflammatory outcomes in maternal outcomes of preterm labour (36%) and postpartum endometritis (12%) in BV positive patients provide an illustration of the impact of the dysbiosis in the vaginal microbiome (Goldenberg, et al., 2008). Far from nullifying the effect of BV on newborns, these foetal outcomes, including low birth weight (20%) and neonatal sepsis (10%), showed that BV contributes to intrauterine inflammation and ascending infections. Eukaryotic pathogen associated molecular patterns release a Toll-like receptor mediated, anti-inflammatory signal that dampens the interleukin – 1 β cascade, thereby perpetuating the immune response (Goldenberg, et al., 2008). Our results indicate that early diagnosis and focused interventions are needed to improve maternal and newborn outcomes.

8.2 Comparative Analysis with Previous Studies

The prevalence found and unfavourable consequences documented in the study are in agreement with previous findings. For instance, the evidence linking BV to preterm birth is very strong (Hillier, et al., 1995) and studies have revealed a two to 3 fold increased risk. The findings are in line with those of (McGregor, et al., 1995) in respect of postpartum endometritis and chorioamnionitis, these infections being associated with BV.

These findings may be confounded by contextual factors such as healthcare access and population specific behaviours, rather than findings from other studies of BV in high resource populations. The findings here are also consistent with the association between socioeconomic determinants and prevalence of BV seen by (Kenyon, et al., 2020) and reinforce the need for customised therapies.

Foetal outcomes related to neonatal sepsis are reflected in the findings of (Goldenberg, et al., 2008), who have emphasised the inflammatory pathways supporting the linkage between BV and poor newborn health. While this study now includes neonates with long term neurodevelopmental impairments, these new possibilities permit the investigation of BV effects outside the immediate perinatal period.

8.3 Clinical and Public Health Implications

The implications of the study's conclusions for public health policy and clinical practise are important. The association between BV and unfavourable pregnancy outcomes is such that clinically it requires regular screening and timely management in the prenatal care settings. This study's results suggest that a more intensive screening strategy would be required even if

the American College of Obstetricians and Gynaecologists (ACOG) would currently advise screening for pregnant women with risk factors (ACOG, 2020).

Preventing BV may reduce its prevalence and recurrence by teaching female patients about behavioural risk factors like smoking and douching. This study's discussed psychosocial load could be addressed through routine mental health evaluations as part of prenatal care for BV positive people.

From a public health perspective, disparities in prevalence and outcomes of BV may be reduced by implementing focused interventions (e.g. for women who are younger, less accessible to health care) to women who have increased risk. Early detection and treatment requires accessible diagnostic services and community based awareness initiates.

Future studies should determine the long term health effects of newborns and also assess the cost effectiveness of universal BV screening throughout pregnancy. Policymakers should give top priority to funding projects in which BV management is incorporated into all-encompassing mother and child health programmes.

Chapter 9

Conclusion and Recommendations

9.1 Summary of Findings

Bacterial vaginosis (BV) is a common vaginal illness that can have serious ramifications for mother's health and the foetus during pregnancy. This thesis explains what epidemiology, diagnostic methods, and management techniques are with regard to this complex nature and its clinical implications. Consistent with published statistics, BV affected around 28 per cent of pregnant women. The outcomes for mothers that are important include increased chances of premature labour, chorioamnionitis and postpartum endometritis; and for foetuses (Goldenberg, et al., 2008); (Hillier, et al., 1995), low birth weight, preterm birth and neonatal sepsis.

The study emphasises the use of PCR based techniques for increased accuracy and suggests the use of Amsel's criterion and Nugent's score as inexpensive diagnostic tool. The risk benefit balance for medicines had not been resolved, and management strategies of probiotics and antibiotics that successful. Preventive measures designed to reduce the prevalence of BV and the associated ramifications it bears were identified as crucial in reducing the prevalence of BV and consequent ramifications of BV.

9.2 Recommendations for Clinical Practice

The following suggestions are put out in an effort to enhance maternal and foetal outcomes:

1. **Routine BV Screening During Early Pregnancy:** Early diagnosis and management are facilitated by screening procedures in high risk groups, such as those with a history of preterm birth or lower social economic status (McGregor, et al., 1995).

2. **All-inclusive Prenatal Care:** Put BV diagnostic and treatment procedures in standard prenatal care and educate patients about risk factors such as smoking and douching.
3. **Inclusion of Probiotic therapy:** Supplemental probiotic therapy based on growing evidence of effectiveness to reduce recurrence rates and based on evidence that probiotics can restore vaginal microbiota include this therapy is recommended.
4. **Standardised Diagnostic Tools:** In clinical settings, the implementation of sophisticated molecular techniques in conjuction with standardised diagnostic criteria such as Nugents score (Kenyon, et al., 2020).
5. **Appropriate Use of Antibiotics:** Develop recommendations for the smart use of antibiotics to limit antibiotic resistance hazards and assure a satisfying BV therapy.
6. **Mental Health Support:** Make sure that prenatal programmes include mental health assessments and counselling services to treat anything psychological that comes out of BV.

9.3 Directions for Future Research

1. **Mechanisms of BV Pathogenesis:** Coordination studies focusing on the molecular mechanisms, including host and pathogen interactions, and immune responses, which underlie the correlation of BV and poor pregnancy outcomes should be conducted in the future.
2. **Impact of Sociocultural Factors:** Research into the way socioeconomic conditions and cultural practises affect the emergence and treatment of BV can be used to construct culturally appropriate therapies.

3. **Screening Program Cost-Effectiveness:** We compare the public health and economic viability of universal versus tailored BV screening in pregnancy.
4. **Effectiveness of Probiotic Therapies:** Do extensive, randomised controlled trials of certain probiotic strains as it pertains to preventing and treating BV during pregnancy.
5. **Antimicrobial Resistance Patterns:** Where possible, track trends in resistance to routinely used antibiotics for the treatment of BV such that treatment choices are sustained.
6. **Long-Term Infant Outcomes:** Characterise the effects of exposure to BV during pregnancy on an infant's neurodevelopment and long term respiratory health.

To conclude, this thesis results supports the fact that BV can be well managed during pregnancy if we have proper strategy that involves early detection, efficient treatment, and preventive trials. To fill the gaps in both clinical practise and research and improve global maternal and foetal health outcomes, steps must be taken.

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