Europasian Journal of Medical Sciences
EJMS
https://doi.org/10.46405/ejms.v5i1.475

Review Article

Bacterial Vaginosis: A Review of Pathophysiology, Epidemiology, Complications, Diagnosis, and Treatment

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ABSTRACT

Bacterial vaginosis (BV) is the most-common cause of abnormal vaginal discharge among women of reproductive age, though many are asymptomatic. It is caused by the replacement of normal vaginal Lactobacillus with Gram-negative and anaerobic organisms. BV has assumed increasing public health importance through associations with numerous adverse outcomes in both gravid and non-gravid women. Risk factors for BV include smoking, non-White race, prior BV, current other sexually transmitted diseases (STDs), inserting items in the vagina (e.g., sex, douching), and menses. Symptomatic BV has been associated with pelvic inflammatory disease (PID), miscarriage, premature rupture of membranes, chorioamnionitis, premature labor and delivery, postpartum endometritis, and post-hysterectomy vaginal cuff cellulitis. Anaerobic Gram-negative rods common to BV have also been independently associated with endometritis or PID, even in the absence of clinical BV. BV has also been independently associated with an increased risk of acquiring STDs, including acquiring and transmitting HIV. BV is not an STD, though recent sexual intercourse and multiple sex partners are risk factors. BV causes a malodorous, white or gray vaginal discharge and is diagnosed through Amsel's criteria. Treatment with metronidazole or clindamycin is important for symptom relief and to prevent adverse obstetric consequences, particularly among high-risk women who have had a previous preterm delivery or have a pre-pregnancy weight <50 kg.

Keywords bacterial vaginosis, pathophysiology, epidemiology, complications, diagnosis, treatment

INTRODUCTION

Bacterial vaginosis (BV) is the most-common cause of abnormal vaginal discharge among women of reproductive age. However, approximately half of women with BV are asymptomatic.[1] BV is associated with adverse outcomes in both gravid and non-gravid women: PID, miscarriage, premature rupture of membranes, amniotic fluid infection, premature labor and delivery, postpartum endometritis, post-hysterectomy vaginal cuff cellulitis.[2] Anaerobic Gram-negative rods common to BV have been independently associated with endometritis and PID, even in the absence of clinical BV.[3] BV has also been independently associated with an increased risk of STDs, including acquiring and transmitting HIV.[4]

This article reviews the clinical importance of BV and describes the epidemiological, microbiological, pathophysiological, and diagnostic characteristics of this reproductive tract illness, as well as treatment options.

DATA AND METHODS

We performed a systematic review via PubMed and Google Scholar database search. Keywords were "BV" and "bacterial vaginosis" and the associated terms "epidemiology," "diagnosis," "treatment," and "review." Articles published in languages other than English were excluded.

Prevalence

BV is the most-common cause of vaginal discharge, with varying prevalence between populations.[1] In the U.S., BV accounts for over 50% of cases of vaginal discharge (10-32% prevalence). Prevalence rates are very high in some places in Africa (e.g., South Africa: ~50%); however, in other African countries (e.g., Nigeria), the prevalence is much lower (~15%). BV rates are moderate in South and Southeast Asia, Latin America and the Caribbean, and lowest in Europe. Such variation is attributable to differences in race, ethnicity, geography, behavior, baseline (non-BV) microflora species, and country's level of development, as described below.[5]

Risk Factors

Numerous personal and environmental characteristics and health behaviors have been associated with BV (Table 1).[6]

Demographic Characteristics: After multivariate analysis, the Vaginal Infections and Prematurity Study (VIPS) found BV three times as common among Blacks, twice as common among Latinos and unmarried women, and 50% more common among low-income women.[7] The global prevalence of BV among reproductive-age women is significantly-higher among Blacks (33%) Hispanics (31%) compared to other racial groups (Whites: 23%, Asians: 11%). Inter-racial differences in vaginal Lactobacillus species may explain differing BV rates. Results from deep RNA sequencing of BV-associated bacteria indicate Black women's vaginal microflora is dominated by *Lactobacillus iners*, while White women's is *L. crispatus*-dominant (which is associated with healthy vaginal microenvironments).[8]

Sexual Behavior: BV is characterized by an imbalance of bacteria in the vagina, and its association with sexual partners and STDs has been a topic of significant interest and research. BV is associated with a change in partner, multiple

sexual partners, and a lack of barrier contraception; BV is more common in sexually-active women or women who receive oral sex. BV has been associated with the presence of other STDs, such as gonorrhea, chlamydia, trichomonas, and pelvic inflammatory disease (PID). A history of BV is a risk factor for re-contracting BV. There has been much debate about BV's transmissibility. Participation in sexual activities heightens the likelihood of acquiring BV. In heterosexual relationships, the presence of semen in males provide a favorable environment for BV-associated bacteria to thrive. BV is common among lesbians, with risks increasing by 60%, and is transmitted between lesbian partners through vaginal fluid, [9] though the mode of transmission remains unclear.

The risk factor profile for women with BV is similar to that for women with STDs, and history or concurrent STD (including HSV)[10] is associated with BV incidence and prevalence. Circumcised males have less BV-associated bacteria on the penis and lower rates of BV in female partners.[11] However, BV itself is not an STD and no similar infectious condition has been found among males. BV does not meet the definition of an STD, as an STD is caused by an external source, while BV results from an overgrowth of normal vaginal bacteria.

Smoking: Smoking is an independent risk factor for BV acquisition. Smoking's antiestrogenic effects leads to the accumulation of biogenic vaginal amines predisposing women to BV. Smoking contributes to a vaginal microbiota with significantly-lower levels of *Lactobacillus spp.*, which improves with smoking cessation.[12]

Douching: Vaginal douching raises intravaginal pH and is associated with acquiring BV; douching cessation lowers risk by 77%.[13]

Contraceptives: IUD use (copper more so than hormonal) has been implicated in a cross-sectional study as a risk factor for BV;[14] however, this was not supported by a prospective study of baseline BV-negative subjects initiating contraceptive use, which found IUD users no more likely to acquire BV than users of other types of contraception (pills, ring, or patch).[12] Associations between contraception and BV are likely mediated by irregular vaginal bleeding rather than the presence of a foreign body (e.g., IUD) in the uterus and vagina. Use of condoms with nonoxynol-9 does not reduce the H2O2-producing Lactobacilli, but does reduce non-H2O2 producing strains.[15]

Medication: Insertion of intravaginal medication for purposes other than BV treatment (eg, for vaginal candidiasis) is associated with 4.1 times risk of as likely to have an increase in BV-associated flora).[16] However, insertion of antibiotics against BV is curative.

Hygiene: In developing countries, where hygiene poses challenges, various risk factors contribute to BV acquisition. These include bathing in public water sources such as ponds and rivers, reusing menstrual cloths, and storing such cloths in unsanitary locations.[17] Moreover, improper anal hygiene, specifically wiping feces from the anus in a back-to-front direction, may further contribute to BV by introducing anal microbes associated with BV toward the vaginal introitus.

Nutrition: Emerging evidence suggests a link between nutritional status and BV. Diets with poor micronutrient content (e.g., vitamins A, C, E, D; beta-carotene; folate; calcium) confer risk for BV.[18] A study examining diet and the presence of BV among a predominantly-Black population revealed diets high in fat and low in folate, vitamin E and calcium were associated with an elevated likelihood of BV.[19] There is a biologically-plausible relationship between nutrition (particularly vitamin A) and the risk of developing BV. BV is characterized by increased bacterial adherence to vaginal epithelial cells. Adequate vitamin A is necessary for genital tract mucosal integrity, as it affects the differentiation of the ectocervical epithelium. Vitamin A deficiency reduces epithelial barriers and host immune mechanisms, leading to increased infections along epithelial surfaces such as the conjunctiva and respiratory, gastrointestinal, and genitourinary tracts. This relationship may explain the significant reduction in vaginal discharge among rural Nepalese pregnant women who were supplemented with vitamin A compared to their counterparts.[20] In rural Bangladeshi pregnant women, vitamin A supplementation reduced the incidence of BV during pregnancy and 3 months postpartum;[21] STD rates were also low, indicating a significant proportion of vaginal discharge may well have been due to BV.

Table 1: Risk Factors for Bacterial Vaginosis

Risk Factors	Comparison Group
Douching	Within the past 7 days vs. not
Increasing number of sex partners	
IUD	Users vs. non-users
Lack of condoms	Use of condoms
Lesbian	Non-lesbian
Malnutrition (via association with STDs)	
More than one sexual partner in the past year	
Prior BV	No prior BV
Race	Black and Latino vs. White
Recent change of sex partner	No change
Receptive oral sex	Presence vs. absence of characteristic
Smoking	Not smoking
STDs	No STDs

Microbiology/Pathophysiology

BV is marked by a disruption of the normal vaginal microflora and exists as a spectrum of illness depending on

the degree of replacement of normal flora with pathogenic flora. Normal vaginal flora consists predominantly (95%) of facultative *Lactobacillus* species (mostly hydrogen peroxide (H2O2)-producing *L. crispatus* and *L. jensenii,* along with 30-45 other bacterial species. BV was previously termed "Gardnerella vaginitis" and "non-specific vaginitis."[22] However, as it became recognized that BV is marked by proliferation of various flora (not only Gardnerella), the name was updated to "bacterial vaginosis." In BV, Lactobacilli are decreased and replaced by increasing and varying numbers of aerobic (*Gardnerella vaginalis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*) and anaerobic/facultatively-anaerobic (Bacteroides, Peptostreptococcus, viridans streptococci, Fusobacterium, Prevotella, and Mobiluncus species (especially *M. curtsii)*) organisms and their by-products.[1] *G. vaginalis* proliferates to 100-fold its non-BV concentration, and anaerobes such as Bacteroides increase from 1,000-fold to 10,000-fold.[23] Most of these species can be detected in both women with and without BV (colonization), but in vastly-different concentrations, so the mere presence of these bacteria does not mean a patient has BV. The rectum may be the reservoir for many of these species in women whose vaginas are not already colonized by them.

Normal vaginal conditions are maintained by the presence of Lactobacilli (up to 10^8/mL), which digest glycogen and convert it to lactic acid, creating an acidic environment (pH <4.5). Without high levels of circulating estrogen during the pre-pubertal years and post-menopause, the vaginal epithelium lacks glycogen and the environment is alkaline; their vaginas are colonized by skin and fecal organisms rather than *G. vaginalis*, and BV is rare.[24] An acidic environment is an important vaginal defense mechanism, preventing colonization or infection by most other bacteria, except those which cause STDs. A change from the normally-acidic vaginal environment to a more-alkaline vaginal environment favors proliferation of other bacterial species. The replacement of Lactobacilli with *G. vaginalis* and other aerobes and anaerobes results in a rising vaginal pH, occasionally greater than 7.0. Behaviors associated with loss of H2O2-producing Lactobacilli include sex more than once per week and taking antibiotics.[25] Factors other than a reduction in the number of Lactobacilli which may contribute to a more-alkaline environment include unprotected sexual intercourse (semen is alkaline), douching (also alkaline), and menstruation (possibly from the mechanical flow of blood eliminating Lactobacilli, from blood being more alkaline (pH 7.4) than normal vaginal fluid, or from hormonal influence).

Hydrogen peroxide is a second important element in the vaginal defense system. Hydrogen peroxide-producing aerobic Lactobacilli are particularly-effective in inhibiting catalase-negative organisms; the combination of vaginal H2O2, peroxidase, and chloride. H202 is particularly-toxic to *G. vaginalis* and Bacteroides species. The hazard ratio of non-H202-producing Lactobacilli compared with H202-producing Lactobacilli for BV acquisition is 4.0,[26] indicating it is the H2O2-producing quality of Lactobacilli that confers the protective advantage and that an acidic pH and the presence of H2O2 are independent protective factors against vaginal colonization or overgrowth of virulent organisms.

A vicious cycle begins when the H2O2-producing Lactobacilli begin to decline. In the high-pH, non-H2O2 environment, first *G. vaginalis* and, later, anaerobes, proliferate, as though it were an uncontained anaerobic vaginal abscess. The anaerobes use the enzyme decarboxylase to convert amino acids from *G. vaginalis* into amines. The amines produced by the anaerobes contribute to a rising pH, inhibiting Lactobacilli growth and causing the vaginal epithelium to slough, which produces an increased vaginal discharge in the absence of an inflammatory response (hence, "vaginosis" rather than "vaginitis").

Symptoms

The most-prominent symptom of BV is a malodorous, thin, white/gray, homogeneous discharge; however, some women may present instead with dysuria, dyspareunia, or vaginal itching.[27] Women may notice the odor is worse following intercourse without condoms or during menses, because of the exposure of the vaginal discharge to alkaline semen or blood. BV does not induce an inflammatory response in the host, possibly because of chemotaxis inhibition by anaerobes; it is characterized by a paucity of white blood cells in the vaginal fluid. BV symptoms may resemble those of STDs, such as trichomoniasis, gonorrhea, or chlamydia. However, BV is not associated with is fever or significant pelvic pain unless co-infected with another reproductive-tract disease. The presence of such symptoms, or a history of STDs, should prompt investigation of primary or co-infection with STD organisms. Symptoms of BV are similar-enough to those of other vaginal infections that they cannot reliably be distinguished or diagnosed either through self-diagnosis or over the phone; therefore, BV diagnosis should be made in a healthcare provider's office.[28]

Diagnosis

The conventional, widely-utilized approach for diagnosing bacterial vaginosis relies on Amsel's Criteria (~90% sensitivity and specificity): 1) a vaginal pH >4.5, 2) a white, homogeneous vaginal discharge, 3) the presence of clue cells (vaginal epithelial cells with adherent Gardnerella on high-power microscopic examination after adding a drop of normal saline to a vaginal fluid smear (wet mount)), and 4) a positive "whiff test" upon application of a few drops of 10% potassium hydroxide (alkaline solution) to a sample of vaginal fluid.[29] The odor of BV is caused by the release of the anaerobic amine gasses trimethylamine (fishy odor) and the diamines cadaverine and putrescine (amine odor) when the anaerobes are exposed to an alkaline environment. The presence of at least three out of four criteria is sufficient to make the diagnosis.[30] Use of modified Amsel Criteria (2 out of 4 criteria establish the diagnosis) is similarly-sensitive and -specific.[31] The disadvantages of these diagnostic methods are that unrelated factors such as menstruation, douching, recent intercourse (semen is alkaline and contains putrescine), and heavy cervical mucus may cause an elevated vaginal pH, and interfere with the amine odor and the quantity of vaginal discharge.

A separate technique ("Nugent score") relies on the identification of several bacterial morphologies: Lactobacillus (large Gram-positive rods), Gardnerella

and Bacteroides (both are small Gram-negative or Gram-variable rods), and Mobiluncus (curved Gram-negative or Gram-variable rods). The relative presence of these three morphotypes is used to grade the smear on the basis of a 10-point-maximum scoring system, which has excellent inter-observer reliability and correlation with clinical criteria and vaginal culture results A score of 0-3 indicates normal flora (Grade 1, Lactobacillus-predominant), 4-6 intermediate (Grade 2, mixed flora), and 7-10 indicates BV (Grade 3, Gardnerella and others predominant, few Lactobacilli). An additional advantage of the scoring system, compared Amsel Criteria, is the categorization of some smears as "intermediate," which identifies women who are more-likely to have gonorrhea, chlamydia, and trichomonas and to progress to frank BV.[32]

Amsel's Criteria and Nugent's scoring system roughly correlate as follows: the presence of zero clinical criteria corresponds to Grade 1 (normal); the presence of 1-2 clinical criteria corresponds to Grade 2 (intermediate); and the presence of 3 or 4 clinical criteria corresponds to Grade 3. There is usually agreement between the Amsel Criteria and Nugent score for diagnosing BV when applied to a case, though there are occasionally discrepancies; one study found 11% of women with BV by Amsel Criteria lacked BV by Nugent score, while 20% with BV by Nugent score lacked BV by Amsel Criteria.[33]

Accurate BV diagnosis is important to prevent future sequelae, such as PID, HIV acquisition, and obstetric complications. While both the Amsel Criteria and Nugent scoring systems have been used worldwide for many years, they have several limitations, including interobserver variability, as application of the diagnostic criteria depends on the observer's skill and experience. Diagnosis may be difficult in resource-poor locations without microscopes, potassium hydroxide, and Gram stain solutions.

Alternate Methods of Diagnosis

Clue cell detection: The presence of clue cells is the most-sensitive indicator of BV, and their absence the most-specific.[29] However, diagnosis by seeking the wet mount presence of clue cells alone leads to a significant number of false negative misdiagnoses.[34] Papanicolaou smear for clue cell detection has high sensitivity and specificity (both >90%).[35] This diagnostic method also correlates well with Gram stains for BV.[36] Because this diagnostic test is routinely performed on women, it could serve as an excellent screening exam for BV. However, unlike for Gram stains, there are no standardized scoring criteria for Papanicolaou smear diagnosis of BV, which limits its accuracy. An additional limitation is interpreter variability: one study found cytotechnologists (who commonly read Pap smears) read the Pap smears for BV inaccurately compared with a cytopathologist, suggesting the need for either special training of cytotechnologists or the use of a cytopathologist for BV analysis.[36] 36 Although the absence of clue cells is highly-specific for BV, the absence of clue cells on wet mount examination is unreliable. The Pap smear is more-reliable than the wet mount for BV diagnosis: one study showed only a 32% sensitivity of wet mount compared with Papanicolaou smear identification of clue cells.

Several laboratory diagnostic tests exist for BV. DNA oligonucleotide probes for the direct detection of *G. vaginalis* are objective and have approximately 95% sensitivity and 80% specificity.[37] However, the mere presence of *G. vaginalis* does not constitute an infection, as *G. vaginalis* is present in a significant number of asymptomatic women. Chemical assays indirectly assess the presence of BV-associated bacteria.[38] Assays for the amines responsible for the characteristic odor of BV have been developed and have a sensitivity and specificity of 61-91%. These amines are likely produced by the anaerobes that accompany *G. vaginalis* in BV, as pure G. vaginalis does not produce amines. Anaerobic bacteria produce succinic acid in high concentrations compared to lactic acid-producing Lactobacilli, and a succinate:lactate ratio of >0.4 by gas chromatography has a moderate sensitivity and high specificity.[39] Colorimetric detection of the enzyme proline aminopeptidase, which is produced by several bacteria responsible for BV, has a sensitivity and specificity greater than 90% compared with Gram stain.[40] Elevated sialidase enzyme activity, found in several Bacteroides species and 20% of *G. vaginalis* species, has high sensitivity and specificity for BV, and is eliminated in successfully-treated women, making it a potentially-useful treatment marker.[41] However, these tests are not widely-available because of the cost and special laboratory equipment necessary.

Vaginal cultures for *G. vaginalis* have sensitivities as high as 97% in women with clinical BV, but are also positive in as many as 55% women without clinical indications of BV.[42]

Clinical Significance

Symptomatic BV is present in only 20-75% of women with laboratory-detected BV.[1] Women are occasionally chronically-colonized with BV, causing prolonged symptomatology. In general, though, BV vaginal colonization is a spontaneously-waxing-and-waning condition.

Nonetheless, BV is a substantial source of morbidity among women of reproductive age, with associations with other STDs, AIDS, obstetric infections and perinatal complications (Table 2). The CDC Bacterial Vaginosis Working Group estimates that as many as 93,600 preterm deliveries, 12,225 infant morbidities and mortalities, and $1 billion could be saved each year through the appropriate treatment of BV to prevent perinatal complications, in

Table 2: Adverse Bacterial Vaginosis Consequences

Non-obstetric Infectious Consequences
HIV acquisition
Post-surgical vaginal cuff cellulitis
Subclinical PID or endometritis
Obstetric Consequences
Cerebral palsy
Chorioamnionitis
Low-birth-weight
Miscarriage
Post-abortion PID or sepsis
PPROM
Preterm delivery
Preterm labor
PROM

addition to reducing the annual total of 300,000 local or systemic postpartum infections and 1.1 million cases of PID.[10] BV is an infection of both the lower and upper genital tract. Among non-pregnant women, there is evidence bacterial organisms associated with BV ascend into the uterus and cause subclinical and histological endometritis and PID (and, consequently, tubal infertility), even in the absence of chlamydia and gonorrhea.

Association with Infections

BV has been associated with HIV acquisition. The association between BV and increased risk of acquiring HIV may be mediated by loss of hydrogen peroxide-producing, HIV-virucidal Lactobacilli, and low pH (which inhibits HIV proliferation).[43] An acidic vaginal environment provides fewer CD4 target cells for HIV infection and reduces infected-lymphocyte reproduction rate. In addition, the elevated pH that occurs with the loss of Lactobacilli favors infection with STDs known to increase HIV acquisition.[44] Furthermore, HIV is activated by *G. vaginalis*.[45] By reducing maternal BV, one might reduce HIV transmission to and from the mother, and, perhaps ultimately, perinatal transmission.

BV is linked with chorioamnionitis, which likely plays a role in instigating preterm labor, and is independently-associated with postpartum endometritis, post-abortion PID/sepsis and post-hysterectomy vaginal cuff cellulitis.[2] Treating BV with standard treatment regimens prior to these procedures reduces these complications.[46] BV is also associated with cervical intraepithelial neoplasia, perhaps acting as a co-factor to human papilloma virus.[47]

BV During Pregnancy

BV prevalence during pregnancy varies greatly between populations. BV affects approximately 800,000 pregnant women in America each year.[48] The incidence of BV is low during pregnancy: those who enter pregnancy free of BV usually remain that way throughout pregnancy (possibly because they don't have menses or due to high circulating estrogen, which increase vaginal epithelial cell glycogen levels), while those who enter with BV may or may not have spontaneous remission, reflecting the waxing and waning nature of the syndrome. Estimates of spontaneous BV resolution during pregnancy range from 12-50%.[49]

BV and Obstetric and Perinatal Outcomes

BV has been independently-associated with numerous adverse obstetric and perinatal outcomes (Table 2).

Preterm labor and delivery: Several cohort and case-control studies have linked BV or its causative organisms with preterm labor and delivery (<37 weeks), which endangers the infant because of attendant complications such as neonatal infections and neurologic under-development. Only women with BV at high-risk of preterm labor (previous preterm delivery, or pre-pregnancy weight <50 kg) are at increased risk for future BV-related preterm labor and delivery. Certain BV-associated organisms (Bacteroides, *M. hominis*, and Mobiluncus) confer particularly-high risk for preterm labor and delivery.[42] 42 One study estimated a 22% attributable risk for preterm delivery from BV.[50] BV is also associated with first trimester bleeding, and BV with first trimester bleeding is associated with preterm delivery (OR = 1.4).[51] Women with both BV and gonorrhea, chlamydia, or trichomonas also have a greater risk of preterm delivery compared to women with BV alone.[52] Several studies have observed that the earlier a woman has BV during pregnancy, the higher the likelihood of premature delivery. This may be due to greater opportunity for pathogens to proliferate in the lower genital tract, or ascend the upper genital tract, and elicit an inflammatory response of cytokines or prostaglandins which induce labor. BV (even subclinical) may trigger preterm labor and peripartum infection through bacterial virulence factors (sialidase, mucinase, and collagenase) which destroy feto-protective mucous and tissue, facilitating ascent into the feto-placental complex.[53] There has been no association found between acquiring BV beyond the second trimester of pregnancy and adverse outcomes. Therefore, if there is a role for BV screening and treatment among certain populations, it will have to be done before or early in pregnancy.[54]

Black women are more than twice as likely to suffer from preterm birth at less than 37 weeks of gestation as well as very preterm birth at less than 32 weeks compared to their White counterparts.[55] This may be because Black women are less-commonly colonized by H2O2-producing *L. crispatus* and *L. jensenii*, have higher rates of *G. vaginalis* and Mobiluncus and absence of Lactobacilli, or have a higher vaginal pH.[56] Because of this racial disparity in the prevalence of BV, the CDC Bacterial Vaginosis Working Group estimates that BV could account for up to 30% of the differences between Blacks and Whites in preterm deliveries and infant mortality.[44]

Premature Rupture of Membranes (PROM): BV has been linked with PROM and premature PROM (PPROM), with a RR as high as 7.3.[57]

Low-birthweight (<2,500 gm): BV has been associated with LBW deliveries (mean birthweight lower by 90 gm), though this appears to be mediated by BV's association with preterm birth rather than BV being an independent risk factor for low birthweight.[52]

Miscarriage: BV likely plays a role in both early (first trimester) and late (second trimester) miscarriages (OR as high as 5.4), likely related to the ascent of organisms into the feto-maternal complex.[58]

Treatment

BV should be diagnosed through analysis of vaginal fluids using Amsel's Criteria (Table 3). Indiscriminate treatment without clear diagnosis and indications is harmful; treatment of BV-negative women increases the risk of preterm delivery[59] and neonatal sepsis.[60] All symptomatic women, whether pregnant or not, should be treated for BV. Among non-pregnant women, the goal is symptom relief, although future studies may reveal a secondary benefit in treating symptomatic (and screening and treating asymptomatic women) in terms of reducing PID/endometritis. Although BV is associated with preterm birth among women with previous preterm delivery or pre-pregnancy weight <50 kg, there is no official recommendation to screen for BV in this population owing to insufficient evidence to assess the risks and benefits of such screening.[61] Pregnant women at low-risk for preterm birth should not be screened for BV, as

their treatment does not reduce preterm delivery, PPROM, or low birth weight.[57]

For non-pregnant women with BV, the CDC recommends as first-line treatment oral metronidazole 500 mg twice per day for 7 days; cure rates are 80-90%.[62] Metronidazole 5 gm intravaginal 0.75% gel may also be used once per for 5 days with equal efficacy (but fewer side-effects) compared with the oral regimen.[63] Alternatively, clindamycin 2% vaginal cream once per day for 7 days is effective.[64] Clindamycin cream and ovules are oil-based and so reduce the efficacy of latex condoms.[65] Breastfeeding can continue during clindamycin or metronidazole treatment.[48]

For pregnant women, metronidazole 250 mg three times per day for 7 days is recommended, which reduces preterm delivery between 25-75% among women with a previous preterm delivery or pre-pregnancy weight <50 kg compared to women who aren't treated.[50] Although metronidazole is not teratogenic at any time during pregnancy, including the first trimester, a slightly-lower dose than for non-pregnant women is prescribed in order to reduce unnecessary fetal exposure. The one-time metronidazole 2 gm dose does not reduce preterm delivery and is not recommended in the treatment of BV.[62] Clindamycin 300 mg twice a day for 7 days is also effective in reducing adverse pregnancy outcomes. In one study, oral clindamycin treatment reduced both preterm delivery and PPROM by 50%.[66] Intravaginal metronidazole or clindamycin therapy cures intravaginal BV effectively, but doesn't reduce preterm labor or low birth weight, because these complications are likely due to organisms in the upper genital tract, which topical therapy does not penetrate. Sexual intercourse during therapy has no adverse effects on BV treatment or preterm delivery.[57] Treatment effectiveness can be influenced by bacterial resistance to metronidazole and clindamycin, which has increased in recent decades.[62]

Spontaneous recovery from BV may occur during pregnancy. However, the risk for preterm birth is not reduced with spontaneous remission of intravaginal BV,[67] possibly because vaginal remission does not indicate remission of chorioamniotic infection, or because the chemical pathways which initiate labor have already begun. Therefore, treatment during pregnancy should be done early, since evidence is strong that earlier infections lead to poor obstetric outcomes, and that earlier treatment reduces those poor outcomes. Test of cure (eg, vaginal fluid Gram stain) should be done one month later, and re-treatment with a different regimen if BV is still present.[57]

Clinicians should consider screening for and treating BV among women with STDs/mucopurulent cervicitis. While chlamydia and gonorrhea are the leading causes of cervicitis, BV has also been associated with this clinical entity. In one study at an STD clinic, treatment with metronidazole gel in addition to doxycycline significantly increased cervicitis cure rate.[68] Thus, persistent cervicitis despite antibiotics against the more-common causes should alert the practitioner to the possible presence of BV. Additional women whom the clinician should consider screening for BV are those with Papanicolaou smears demonstrating significant inflammation, as BV is the most-common infection associated with abnormal smears.[69]

Treatment of BV with probiotic Lactobacilli does not confer long-term success.[70] Treatment with vaginal acidification using acetic acid gel (5 ml inserted twice-a-day for 7 days) is ineffective in both lowering vaginal pH and treating BV.[71]

Table 3: Bacterial Vaginosis Treatment Regimens

Pregnancy Status	Regimen	% Cure Rate (1-2 Weeks after Treatment)	% Cure Rate (≥3 Weeks after Treatment)
Non-pregnant			
	Chlorhexidene intravaginal	63	52
	Clindamycin oral	88-94	insufficient data
	Clindamycin vaginal cream	72-96	58-94
	Clindamycin vaginal ovules	66	66
	Metronidazole 2 gm X 1	73-87	47-92
	Metronidazole 400 mg or 500 mg, 2-3 per day, 7 days	76-100	61-94
	Metronidazole gel	77-90	61-73
Pregnant			
	Metronidazole 250 mg TID, 7 days	Similar to therapy for non-pregnant women	Similar to therapy for non-pregnant women

As there is no correlated infection in male partners, and no benefit has been shown from treating male partners in reducing BV recurrence, male partners should not be treated.[62] There is no uniform definition of recurrent infection of BV and how long to follow up cases.[72] However, following treatment, BV recurred in 49-66% of cases over the course of 12 months in women who received oral metronidazole for 7 days. Recurrent BV is associated with inconsistent condom use, recent vaginal Candida infection, and having regular sex or a female sex partner. Recurrent BV may occur because *G. vaginalis* might persist and not be eradicated owing to the vaginal epithelial biofilm that may limit antibiotic penetration.[73] Alternatively, there might be failure to establish a normal vaginal ecosystem replete with Lactobacilli following successful eradication of *G. vaginalis* and anaerobes. Treatment failure may also result from antibiotic resistance. Although metronidazole resistance is not common, it is not universally-effective against *G. vaginalis,* Mobiluncus, or *M. hominis*. Recurrence should be managed with a course of alternative antibiotics,

such as clindamycin or amoxicillin-clavulanate. If this fails, metronidazole 500 mg 2 times per day for 7 days followed by intravaginal boric acid 600 mg daily for 21 days and suppressive 0.75% metronidazole gel twice weekly for 4-6 months, might be effective. Among women with persistently-recurrent BV (defined as three or more episodes per year) frequent eradication of *G. vaginalis* and anaerobes with metronidazole gel 0.75% twice weekly for 4-6 months can reduce BV recurrence rates.[57]

LIMITATIONS

BV was previously referred to as Gardnerella vaginitis owing to the primary role of *Gardnerella vaginalis* as the causative agent. The new name, bacterial vaginosis, encompasses a broader understanding that various bacteria naturally inhabit the vagina and contribute to the condition. Our literature search focused on "bacterial vaginosis" and not other terminology. Earlier studies with "Gardnerella vaginitis" in the title may have been excluded. Our literature search included only articles published in English. Relevant studies published in other languages may have been overlooked, leading to potential gaps in our description of BV.

CONCLUSION

BV is the most-common reproductive tract infection in both pregnant and non-pregnant women, though its prevalence varies widely. Diagnosis is reliably made with Amsel criteria and Nugent score. The complex etiology of BV contributes to inaccurate diagnosis, especially in asymptomatic carriers, and subsequently to poor treatment and clinical outcomes. Development of accurate, easy-to-use point-of-care tests for BV is important, particularly in resource-poor locations. All symptomatic women with BV should be treated. Treatment is particularly beneficial during early pregnancy, when the benefits extend to the fetus, as well, in the form of reduced preterm labor and delivery and low-birthweight. Additional research is needed to comprehensively-unravel the underlying mechanisms of BV, which holds significant promise in positively-impacting reproductive health outcomes.

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ABBREVIATIONS

BV	Bacterial vaginosis
HIV	Human immunodeficiency virus
IUD	Intrauterine device
PID	Pelvic inflammatory disease
PPROM	Prolonged preterm rupture of membrane
PROM	Preterm rupture of membrane
STDs	Sexually transmitted diseases
TID	Three times a day

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Ethics Approval and Consent to Participate Not applicable, as this is a review of the literature.
Conflict of Interest None declared by the authors.
Funding Support No external funding was used for preparing this review paper.

Availability of Data and Materials This was a literature review. All data summarized in this study are included in this paper.

Acknowledgments The authors would like to thank the anonymous reviewers for their many helpful comments and suggestions.

Citation

Nasir R, Guilherme S, Puca D, Menoudakos D, Wang J, Hall R, Cheta M, Iyeke L, Richman M. Bacterial vaginosis: A review of pathophysiology, epidemiology, complications, diagnosis, and treatment. Europasian J Med Sci. 2023;5(1):1-10. https://doi.org/10.46405/ejms.v5i1.475