79 Bacterial vaginosis in pregnancy: Evidence-based approaches

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INTRODUCTION

Bacterial vaginosis is the most common cause of vaginal discharge and malodor among women of reproductive age (1,2). This condition has also been termed *Gardnerella* vaginitis, nonspecific vaginitis, and anaerobic colpitis. Studies have shown an association with early and late pregnancy loss, preterm birth, preterm labor, premature rupture of membranes, chorioamnionitis, amniotic fluid infection, postpartum endometritis, and cesarean section infectious morbidity (3–18). These associated complications have resulted in the recommendation for screening all pregnancies as a way to prevent adverse events. Unfortunately, studies have often been conflicting as to the exact relationship between bacterial vaginosis and poor pregnancy outcomes. Recent large-scale analysis has shown screening in the asymptomatic general population to be ineffective. Many organizations including the U.S. Preventive Services Task Force (19), American College of Obstetrics and Gynecology (19), British Association for Sexual Health and HIV/Clinical Effectiveness Group (20), and the Society of Obstetricians and Gynaecologists of Canada do not recommend screening of bacterial vaginosis in low-risk pregnant populations (21). This chapter will review bacterial vaginosis in pregnancy, the pathophysiology involved in associated adverse pregnancy outcomes, and the screening recommendations based on the current literature.

MICROBIOLOGY AND PATHOGENESIS OF BACTERIAL VAGINOSIS

Bacterial vaginosis consists of microecologic alterations in which a characteristic set of bacterial species greatly expand their populations within the vagina. This causes dramatic shifts in the biochemical make-up of vaginal fluid (Table 1) (22,23).

In the healthy vagina, between 5 and 15 microbial species are usually recoverable. High concentrations (10^5 – 10^6 /g of fluid) of lactic acid-producing acidophilic facultative lactobacilli are normally the predominant microflora found throughout the menstrual cycle (23,24). *Lactobacillus crispatus*, *Lactobacillus jensenii*, *Lactobacillus fermentum*, and *Lactobacillus gasseri* represent the predominant vaginal species (24). Many of these produce H_2O_2 along with lactic acid. Other bacteria account for the remaining 10% of bacteria recovered (23–25).

The acidic environment in the healthy vagina is maintained by microbial metabolism of glucose, produced by vaginal epithelial cells from glycogen, to lactic acid (25). In addition to maintaining an acidic vaginal environment, H_2O_2 -producing lactobacilli contribute to the maintenance of a healthy, self-sustaining vaginal ecosystem (26,27). In vitro experiments demonstrate that *Lactobacillus* species inhibit growth of bacteria by producing antimicrobial factors, including acidolin and lactacin B, in addition to H_2O_2 (26–29). The microbicidal

action of H_2O_2 is further enhanced in the presence of a halide ion, such as chloride, from cervical mucus, and peroxidase enzymes, such as myeloperoxidase, produced by neutrophils and monocytes (28).

Each of these factors is present in the vaginal fluid of healthy women in sufficient concentrations to produce in vitro bactericidal effects (28). In a longitudinal study, Hillier and colleagues (30) found that women without H_2O_2 -producing lactobacilli more often developed bacterial vaginosis and more frequently relapsed after successful treatment. These findings support the hypothesis that an absence of H_2O_2 -producing lactobacilli precedes the shift in the vaginal ecosystem toward development of bacterial vaginosis (31). This increase in pH tends to displace lactobacilli from receptor sites on vaginal epithelial cells and maximizes adherence of *Gardnerella vaginalis* and other bacterial vaginosis-associated microorganisms (31,32).

The condition of bacterial vaginosis is characterized by this dramatic decrease in normal lactobacilli and subsequent high concentrations of aerobic and anaerobic bacteria, most notably *Prevotella*, *Peptostreptococcus*, *Porphomonas*, and *Mobiluncus* species, along with *G. vaginalis*, *Mycoplasma hominis*, and *Ureaplasma urealyticum* (23,24).

Biophysical changes associated with bacterial vaginosis include elevated pH (>4.5), reduced redox potential, increased fluid concentrations of diamines, polyamines, and organic acids, as well as increased concentrations of enzymes, including mucinases, sialidases, IgA proteases, collagenases, nonspecific proteases, and phospholipases A₂ and C (24,33–39). Endotoxin (lipopolysaccharide), cytokine interleukin-1 α , and prostaglandins E₂ and F_{2 α} are also increased in the vaginal fluid of women with bacterial vaginosis (40,41). Amines, primarily trimethylamine, putrescine, and cadaverine, are produced during amino acid metabolism by bacterial vaginosis-associated anaerobic bacteria (37,42). These volatile amines are released as pH increases and are responsible for the “sharp” or “fishy” odor sometimes noticed in the presence of bacterial vaginosis (37,43). Several short-chain fatty acids, including succinate, acetate, propionate, isobutyrate, butyrate, and isovalerate, are also increased in bacterial vaginosis (24). In vitro studies demonstrate that increased succinic acid dramatically impairs neutrophil phagocytic killing, response to chemotactic stimuli, and generation of respiratory bursts required for bacterial killing (44). Butyrate inhibits lymphocyte activation by release of an endotoxin (45,46).

These virulence factors promote tissue attachment, overcome host defense mechanisms, and facilitate entrance of microorganisms and associated factors into the upper reproductive tract. Vaginal fluid protease and phospholipases probably play roles in bacterial vaginosis pathogenesis and ascent of microbes and into the uterus during pregnancy.

Mucinases and sialidases lyse protective mucin and promote bacterial attachment, allowing invasion and spread to underlying epithelial cells. These enzymes may also play a role in disruption of cervical mucus, leading to upper genital tract spread of bacterial vaginosis–associated microflora (38). During pregnancy, bacterial phospholipases A₂ and C, as well as nonspecific proteases, may act on cervical and amniochorion tissues to promote cervical ripening and amniochorion weakening (40). In addition, phospholipases A₂ and C may promote the release of arachidonic acid and prostaglandins, furthering the processes leading to preterm birth (40). Thus, these bacterial substances directly contribute to the initiation of a number of bacterial vaginosis–associated obstetric complications (38–42).

EPIDEMIOLOGY AND NATURAL HISTORY OF BACTERIAL VAGINOSIS

Numerous studies have prospectively examined bacterial vaginosis among populations of pregnant women and demonstrated prevalence ranging from 6% to 32% (Table 2) (5,7,9–13,43,46,58). Studies from Canada, Sweden, and Denmark report bacterial vaginosis among 14% of pregnant women (56,59,60), which is similar to the 16% prevalence

reported in the United States (13). Epidemiologic factors showing increased prevalence in the United States are African-American race, smoking, and multiple sexual partners and are the lowest among women with no history of heterosexual contact (5,56,57,61,62). Among nonpregnant women of reproductive age, bacterial vaginosis is detected more often among those not using any method of contraception and among women using an intrauterine contraceptive device (36,63).

Studies in pregnancy show that most women who test negative stay negative while women with bacterial vaginosis remain positive unless treated (12,61,63,64). Among pregnant women initially tested negative for bacterial vaginosis in the first trimester, 2.9% of British women and no Swedish women developed bacterial vaginosis by the follow-up examination at 28 weeks of gestation, and 47% to 55% of initially positive women continued to have findings of bacterial vaginosis at the third-trimester follow-up visit. A further 2.4% of women without bacterial vaginosis in the first trimester had developed bacterial vaginosis by term (61,65). In 31% of untreated women with bacterial vaginosis, the condition resolved by 28 weeks of gestation (63). Importantly, Joesoef and coworkers (12) determined that women with bacterial vaginosis at 16 to 20 weeks of gestation suffered

Table 1 Biochemical Factors in Bacterial Vaginosis and Their Potential Pathophysiologic Effects

Vaginal fluid constituent	Known or potential actions	Potential effects in pregnancy
pH	Attachment of anaerobic bacteria and <i>Lactobacillus</i> species attachment	Numbers of pathogenic anaerobic bacteria
Succinic acid	Impairs neutrophil phagocytic killing and response to chemotactic stimuli	Vaginal fluid host defenses
Butyrate	Toxic to fibroblasts in cell culture	effects on cervical connective tissue and amniochorion
Sialidase/Mucinase	Degrades protective surface mucin, bacterial attachment to epithelial cells	Cervical mucus barrier
IgA protease	Degrades IgA proteins	Cervical IgA
Collagenase	Degrades collagen types	Cervical ripening, amniochorion weakening
Nonspecific proteases		
Phospholipase A ₂	Induces matrix metalloproteinases, induces prostaglandins	Cervical ripening, amniochorion weakening, and uterine contractions

Table 2 Prevalence of Bacterial Vaginosis in Pregnant Women Followed Prospectively

Study population	Diagnostic method	Prevalence
USA		
Seattle, Washington (10,47–49)	Gas–liquid chromatography	14–28%
	Clinical	6–21%
	Gram stain	12–21%
Denver, Colorado (13,38)	Gram stain	18.7–23%
	Clinical	32%
Vaginal Infections and Prematurity Study (50)	Gram stain and pH > 4.5	16%
Maternal–Fetal Medicine Network Centers (51)	Gram stain and pH > 4.5	23.4%
Halifax, Nova Scotia, Canada (52)	Clinical	23%
Finland (16)	Quantitative cultures	21.4%
Göteborg, Sweden (53)	Papanicolaou's smear and pH>4.5	14.3%
Harrow, UK (54,55)	Gram stain	12–14%
Adelaide, Australia (15)	<i>Gardnerella vaginalis</i> culture (heavy growth)	28%
Jakarta, Indonesia (56)	Gram stain	17%
Canada (57)	Gram stain	14%

increased risk for preterm birth, even if they no longer had findings of bacterial vaginosis at the later follow-up visit (28–32 weeks of gestation). Prospective treatment studies show that bacterial vaginosis recurs between 20% and 80% in pregnancy, regardless of initial successful treatment (38,66). The individual factors that predispose to acquisition, persistence, resolution, and/or recurrence of bacterial vaginosis probably involve failure of H₂O₂-producing lactobacilli to recolonize and reestablish a normal, protective vaginal ecosystem following treatment (26,31,67).

DIAGNOSIS OF BACTERIAL VAGINOSIS

Clinical Diagnosis

The clinical “gold standard” established in 1983 by Amsel and colleagues (36) is based upon the presence of three of four clinical criteria:

1. homogeneous, thin vaginal fluid that adheres to the vaginal walls;
2. vaginal fluid pH > 4.5;
3. release of amine odor with alkalinization of vaginal fluid, the “whiff test”; and
4. presence of vaginal epithelial cells with borders obscured by adherent, small bacteria called “clue cells.”

Of the four Amsel’s criteria, the presence of clue cells on saline wet-mount examination is the most specific and sensitive indicator of bacterial vaginosis. Identification of clue cells accurately predicts 85% to 90% of women with clinical bacterial vaginosis (positive predictive value). Identification of clue cells may be hindered by adherence of normal bacteria, cellular debris, and availability and quality of the microscopy (65,68).

Clue cells can be microscopically distinguished from normal vaginal epithelial cells by their characteristic stippled and ragged appearance (Fig. 1). The cell borders are obscured by adherent small coccobacilli-type bacteria, in contrast to normal vaginal epithelial cells where the cell borders are distinct and clearly seen (Fig. 2). In addition to the presence of clue cells, the characteristic long rods, of *Lactobacillus* morphotypes, are absent or rare. Background bacterial flora appears greatly increased and short rods and coccobacillary forms predominate. *Mobiluncus* species may be identified by their characteristic spiral or serpent-like motility (69).

The “whiff test” is similarly sensitive for the diagnosis of bacterial vaginosis, but may also be positive in trichomoniasis. Alkalinization of vaginal fluid releases volatile amines, putrescine, cadaverine, and trimethylamine, which give off a characteristically “fishy” or sharp odor. This odor may be noticed by a woman as amines are released spontaneously during activities that raise the vaginal pH, such as sexual intercourse, douching, or menses (37,43).

Normal vaginal pH from menarche to menopause ranges between 3.8 and 4.2. Amsel and colleagues (36) determined that a vaginal fluid pH over 4.5 discriminated between bacterial vaginosis and normal vaginal fluid. Identification of pH over 4.5 is highly sensitive for the diagnosis of bacterial vaginosis, but it is not specific (2,36,70).

Other factors may raise vaginal pH, including semen, cervical mucus, menses, trichomoniasis, and possibly recent

douching. Samples for examination of vaginal fluid pH must be obtained from the lateral vaginal side wall or posterior fornices in order to reflect accurately vaginal, and not cervical, pH. Similarly, the pH indicator paper must allow distinction between the normal vaginal pH (3.8–4.2) and a pH over 4.5. The characteristic thin, homogeneous, and adherent vaginal fluid is the most subjective indicator of bacterial vaginosis.

Laboratory Diagnosis

Gram stains of vaginal fluid are used in research settings to identify the shift from predominance of *Lactobacillus* morphotypes to predominance of coccobacillary morphotypes and gram-negative rods characteristic of bacterial vaginosis. The Gram-stain diagnosis involves quantitative estimations of

Figure 1 “Clue cells” identified on microscopic examination of saline preparation.

Figure 2 Normal vaginal epithelial cells identified on microscopic examination of saline preparation.

these types of bacteria in the vaginal fluid (70–72). Normal vaginal fluid is described by a predominance of large gram-positive rods, considered *Lactobacillus* morphotypes, with or without smaller gram-variable bacilli, considered *Gardnerella* morphotypes (Fig. 2) (73). A pattern of mixed vaginal flora, which includes *Gardnerella* morphotypes, gram-negative rods, fusiforms, curved rods, gram-positive cocci, and absent or reduced numbers of *Lactobacillus* morphotypes (less than five per high-power field), is consistent with bacterial vaginosis (Fig. 3) (73). The current laboratory “gold standard” incorporates Gram stain using a scoring system, the most prevalent being the “Nugent scoring” system with a sensitivity of 89% and a specificity of 83% when compared with Amsel’s criteria (Fig. 4).

The technique of Nugent and coworkers (74) examines four bacterial morphotypes and assigns a summary score to the vaginal specimen based on the semiquantitative assessment for *Lactobacillus* morphotypes, *G. vaginalis*, *Prevotella* morphotypes, and *Mobiluncus* morphotypes. A score of 7 to 10 is considered to indicate bacterial vaginosis (74). Compared

with other diagnostic methods, this standardized scheme has superior reproducibility (73).

This reproducibility has made the “Nugent score” the standard used in the majority of recent research. The required laboratory to perform the test and time delay prevent Gram-stain scoring systems from widespread clinical settings.

Nonquantitative microbial culture for *G. vaginalis* is both an inaccurate and expensive way to diagnose bacterial vaginosis. Clinical cultures should not be used to diagnose bacterial vaginosis. Since organisms such as *G. vaginalis* can be recovered from up to 60% of women with and without bacterial vaginosis, this leads to unacceptable false-positive rates (2,59). Quantitative aerobic and anaerobic vaginal cultures have been used in clinical research studies to evaluate bacterial vaginosis, but this technique is costly and impractical for clinical use (9,10).

Newer diagnostic techniques, including nucleic acid probes to detect high concentrations of *G. vaginalis*, have become available (71,75). Such tests as the Affirm VP III Microbial Identification Test (Becton Dickinson and Company, Sparks, MD) may provide a less subjective test for bacterial vaginosis than other current methods. Briselden, Hillier, and Sheiness reported accurate detection (sensitivity) of 95% to 97% of women with clinical criteria for bacterial vaginosis using the Affirm VP III test. Specificity for this test ranged from 71% to 98% (71,75). Identification of several different vaginal fluid biochemicals associated with bacterial vaginosis such as amines (FemExam) and sialidase activity (BV Blue) have recently become available commercially. (5,6,24,37,76).

OBSTETRIC COMPLICATIONS ASSOCIATED WITH BACTERIAL VAGINOSIS

Preterm Birth

Associations between bacterial vaginosis and increased risk for adverse pregnancy outcomes have been investigated through case-control, cross-sectional, prospective cohort studies and randomized controlled treatment trials (Table 3) (4–13,38,50,54,56,60,74–76). Despite differences in study design, definitions of preterm birth, and the techniques used to identify bacterial vaginosis, research from around the world supports the association between bacterial vaginosis and increased risk of preterm labor, preterm birth, and preterm premature rupture of the membranes (Table 3) (5–13,38,56,78). Crucially, bacterial vaginosis and associated microorganisms appear to increase the risk of preterm birth at the lowest viable gestational ages (8). Two published studies report an association between previable second-trimester pregnancy loss and bacterial vaginosis, suggesting that pathophysiologic processes associated with bacterial vaginosis cause a continuum of both previable loss and birth of severely premature newborns (11,56).

Multiple prospective studies indicate that bacterial vaginosis may be detected months prior to the onset of preterm labor or preterm birth (5,7,9–13). Eschenbach and colleagues (4) and Gravett and coworkers (5,6) were the first to implicate bacterial vaginosis as a risk factor for preterm labor and low birth weight. Bacterial vaginosis was identified using gas-liquid chromatography among 19% of 534 pregnant women studied (5). The presence of bacterial vaginosis in the mid-third trimester (mean 32.6 weeks) was associated with

Figure 3 Normal vaginal fluid Gram stain.

Figure 4 Gram stain of bacterial vaginosis.

increased risk for preterm labor [odds ratio (OR) 2.0, 95% confidence interval (CI) 1.1–3.5] and preterm premature rupture of the membranes (OR 2.0, 95% CI 1.1–3.7) (5). McDonald and colleagues (9) examined bacterial vaginosis (culture for heavy colonization with *G. vaginalis*) earlier in gestation (22–28 weeks) and demonstrated similar risks for preterm birth following labor (OR 1.8) and preterm premature rupture of the membranes (OR 2.7).

Studies that examine for bacterial vaginosis at the earliest gestational ages and carefully control for intervening antimicrobial treatment demonstrate the strongest association between bacterial vaginosis and preterm birth (Table 3) (10,11). The highest relative risks (sevenfold increase) between bacterial vaginosis and preterm birth and premature rupture of the membranes were noted in a Finnish study involving women who were initially examined in the first trimester (10). In an insightful analysis, Joesoef and colleagues (12) examined the risk of preterm birth for women

found to have bacterial vaginosis between 16 and 20 weeks of gestation and/or between 28 and 32 weeks of gestation (12). Women with bacterial vaginosis in the early second trimester experienced a twofold increase in premature birth compared with women without bacterial vaginosis (12). Women with bacterial vaginosis at 28 to 32 weeks of gestation experienced somewhat less increased risk for premature birth (OR 1.5, 95% CI 0.7–3.0). Women who developed bacterial vaginosis between the screening intervals (i.e., those negative at 16–20 weeks of gestation and positive at 28–32 weeks of gestation) were not at increased risk for preterm birth (10.7% preterm birth among women developing bacterial vaginosis vs. 11.8% among women never positive for bacterial vaginosis; calculated OR 0.9) (12). As discussed, women with findings of bacterial vaginosis at 16 to 20 weeks of gestation were at increased risk for preterm birth, even if they no longer had findings of bacterial vaginosis at the later follow-up visit (20.5% preterm birth among women with bacterial

Table 3 Review of Prospective Cohort Studies Evaluating Bacterial Vaginosis and Adverse Pregnancy Outcomes

Outcome and reference	Gestational age when tested (weeks)	Number of positive outcomes	Number of negative outcomes	Relative risk (95% CI)
<u>Preterm birth (<37 weeks)</u>				
Minkoff et al. 1984 (60)	13	ND	ND	2.3 (0.96–5.5) ^a
McGregor et al. 1990 (7)	24	1/24 (4.2%)	3/110 (2.7%)	1.5 (0.2–14.2)
McDonald et al. 1992 (9)	22–28	31/135 (23%)	97/651 (14.9%)	1.8 (1.01–3.2)
Kurki et al. 1992 (10)	8–17	11/162 (6.8%)	6/571 (1.0%)	6.9 (2.5–18.8)
Joesoef et al. 1993 (12)	16–20	17/84 (20.2%)	48/406 (11.8%)	2.0 (1.0–3.9)
	28–32	11/67 (16.4%)	50/395 (12.7%)	1.5 (0.7–3.0)
McGregor et al. 1994 (38)	16–26	14/129 (10.9%)	4/122 (3.3%)	3.3 (1.2–9.1)
Hay et al. 1994 (11) 23–26	<16	7/57 (12.3%)	9/384 (2.3%)	5.2 (2.0–13.5)
	<24	8/83 (9.6%)	18/616 (2.9%)	3.3 (1.5–7.4)
McGregor et al. 1995 (56)	18	31/165 (18.8%)	37/380 (9.7%)	1.9 (1.2–3.0)
Meis, 1995	24	ND	ND	1.4 (0.9–2.0) ^b
	28	ND	ND	1.8 (1.2–3.0) ^b
Hillier et al. 1995 (13)	23–26	77/1218 (6.3%)	291/6978 (4.2%)	1.4 (1.1–1.8) ^b
<u>Preterm premature rupture of membranes</u>				
Gravett et al. 1986 (5)	32	22/102 (21.6%)	44/432 (10.2%)	2.0 (1.1–3.7)
McDonald et al. 1992 (9)	22–28	ND	ND	2.7 (1.1–6.5)
Kurki et al. 1992 (10)	8–17	6/162 (3.7%)	3/571 (0.5%)	7.3 (1.8–29.4)
McGregor et al. 1994 (38)	16–26	6/128 (4.7%)	1/121 (0.8%)	5.7 (0.9–36.1)
McGregor et al. 1995 (56)	18	10/144 (6.9%)	7/350 (2.0%)	3.5 (1.4–8.9)
Hillier et al. 1995 (13)	23–26	35/1132 (3.1%)	182/6617 (2.8%)	1.1 (0.8–1.6)
<u>Preterm labor</u>				
Minkoff et al. 1984 (60)	13	14/66 (21.2%)	21/152 (13.8%)	1.5 (0.8–2.8) ^a
Gravett et al. 1986 (5)	32	24/102 (23.5%)	53/432 (12.3%)	2.0 (1.1–3.5)
McGregor et al. 1990 (7)	24	6/23 (26.1%)	11/111 (9.9%)	2.6 (1.1–6.5)
Kurki et al. 1992 (10)	8–17	17/162 (10.5%)	25/571 (4.4%)	2.6 (1.3–4.9)
McGregor et al. 1994 (38)	16–26	23/129 (17.8%)	15/122 (12.3%)	1.5 (0.8–2.6)
<u>Low birth weight</u>				
Gravett et al. 1986 (5)	32	24/102 (23.5%)	65/432 (15.0%)	1.7 (1.0–2.9)
McGregor et al. 1994 (38)	16–26	11/128 (8.6%)	10/119 (8.4%)	1.0 (0.4–2.3)
<u>Spontaneous abortion</u>				
Hay et al. 1994 (11)	<16	4/57 (7.0%)	5/384 (1.3%)	5.4 (1.5–19.5) ^a
McGregor et al. 1995 (56)	<22	16/305 (5.2%)	11/767 (1.4%)	3.1 (1.4–6.9)
<u>Postpartum endometritis</u>				
Watts et al. 1990 (14)	ND	ND	ND	5.8 (3.0–10.9)
<u>Amniotic fluid infection</u>				
Silver et al. 1989 (15)	39	22/32 (68.8%)	43/93 (46.2%)	1.5 (1.1–2.0) ^a
Krohn et al. 1995 (77)	23–26	43/1296 (3.3%)	183/8741 (2.1%)	1.5 (1.2–2.2)

^aRisk ratio and 95% confidence intervals calculated from data provided. ^bPreterm birth defined as <35 weeks of gestation. Abbreviation: ND, not described.

vaginosis at both visits and 20.5% preterm birth among women with bacterial vaginosis only at the first visit vs. 11.8% preterm birth among women without bacterial vaginosis) (12). These findings suggest that physiologic processes present or initiated at, or prior to, 16 to 20 weeks of gestation are important for the subsequent development of preterm birth. These authors concluded that “only bacterial vaginosis in early pregnancy plays a major role as a risk factor for preterm delivery” (12). Results of a large prospective cohort study from the National Institute of Child Health and Human Development-sponsored Vaginal Infections and Prematurity Study Group demonstrated a 40% increase in risk of delivering a preterm low-birth weight infant and a 10% increase in risk of preterm premature rupture of the membranes among women with bacterial vaginosis detected between 23 and 26 weeks of gestation (13). These authors calculated a 9% attributable risk for prematurity in this study of over 10,000 subjects (13). Other populations could receive more or less benefits, depending on the prevalence of bacterial vaginosis.

Intrapartum and Postpartum Infections

Bacterial vaginosis has been linked to clinical chorioamnionitis, amniotic fluid infection, as well as postpartum endometritis and cesarean section infection. These associations were first suggested by observations that the microorganisms frequently recovered from women with these complications often include the common constituents of bacterial vaginosis, i.e., *Prevotella bivia*, *G. vaginalis*, *M. hominis*, *U. urealyticum*, and *Peptostreptococcus* species (6,14–16). Clinical studies have examined bacterial vaginosis, identified by either Gram stain or gas-liquid chromatography, and shown that women with clinical amniotic fluid infection more commonly have findings of bacterial vaginosis compared with women without clinical infection. (6,15,16) Among the 286 (2.4%) women from the Vaginal Infections and Prematurity Study who developed amniotic fluid infection, antenatal carriage (23–26 weeks of gestation) of bacterial vaginosis (relative risk 1.5, 95% CI 1.2–2.2) and bacterial vaginosis-associated microorganisms were significantly associated with amniotic fluid infection (78). This increase in risk for amniotic fluid infection associated with bacterial vaginosis was independent of duration of labor, duration of rupture of membranes, concurrent infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, group B streptococcus, and effective antimicrobial treatment (77). Postpartum endometritis occurs following 2% to 5% of vaginal births and 10% to 20% of cesarean deliveries (79). These infections are polymicrobial in nature for over 80% of affected women (80). In a series of 161 women with postpartum endometritis described by Watts and colleagues (81), the common constituents of bacterial vaginosis (i.e., *G. vaginalis*, *P. bivia*, *Peptostreptococcus* species, and *Bacteroides* species) were recovered from endometrial cultures in up to 60% of women (81). Wound infections developed among 18% (16/79) of women with endometrial bacterial vaginosis-associated flora and among 8% (4/53) of women with other bacteria recovered from the endometrium (81). Subsequent work by Watts demonstrated a 5.8-fold increased risk for post-cesarean section endometritis among women with bacterial vaginosis (14).

BACTERIAL VAGINOSIS TREATMENT IN PREGNANCY

Oral (systemic) treatment with either metronidazole or clindamycin is preferred for the treatment of bacterial vaginosis during pregnancy. Only oral treatments provide adequate antimicrobial levels in both uterine and vaginal tissues and are associated with improved pregnancy outcome in published studies. Cure rates are similar to those obtained among nonpregnant women (56,77). Initial cure rates within 1 to 2 weeks following completion of treatment are generally 25% to 35% higher than those among women examined 4 to 5 weeks posttreatment (82,83).

Oral metronidazole, 500mg two times daily for 7 days, is the standard therapy recommended by the Centers for Disease Control in the United States for treatment of bacterial vaginosis (81). Resolution of bacterial vaginosis occurs among 85% to 100% of studied women examined approximately 1 week following completion of oral metronidazole treatment (84). The percentage of women without bacterial vaginosis 4 to 5 weeks following completion of treatment ranges from 60% to 95% and averages approximately 80% (82,84). Similarly, cure rates of 70% have been seen with the use of metronidazole and erythromycin (82). Different regimens of oral metronidazole have been examined in trials and observational reports; in general, cure rates at 4 weeks post-dosing with a single 2-g dose of metronidazole range from 45% to 69% (84).

Clindamycin is also an effective treatment for bacterial vaginitis, as well as its associated microflora, including some genital mycoplasmas. Greaves and coworkers (69) examined 49 women 7 to 10 days following completion of a 7-day course of oral clindamycin, 300mg twice daily, and demonstrated a cure rate of 94% for bacterial vaginosis. McGregor and associates (56) examined 194 pregnant women and found a 92% cure rate 2 to 4 weeks post-treatment (56). Oral treatment with clindamycin may be used throughout pregnancy, including the first trimester; it provides resolution of bacterial vaginosis equivalent to that of oral metronidazole.

Intravaginal treatments for bacterial vaginosis are similarly effective at eradication of bacterial vaginosis but have not been shown to improve pregnancy outcomes (38,80,82,84). Metronidazole gel 0.75% one 5-g applicator intravaginally once a day for 5 days or clindamycin 2% one 5-g applicator for 7 days is recommended. Other treatments for bacterial vaginosis have been evaluated: ampicillin, augmentin, ofloxacin, erythromycin, triple sulfa cream, and vaginal acidification (60,84). These treatments are less effective than both oral and vaginal preparations of metronidazole or clindamycin and are not recommended. Similarly, probiotic therapy with microbial products, such as lactobacillus powders and capsules, should be avoided; many of the nondairy products are contaminated with potentially harmful bacteria such as *Clostridium sporogenes* and *Enterococcus* species (85). Therapy with yogurt or acidophilus milk is also likely to be of little benefit, since the *L. acidophilus* strains are not easily established in the vagina (86).

Treatment of sexual partners of women with bacterial vaginosis is unnecessary: randomized controlled trials that examined co-treatment of male partners failed to demonstrate reduced recurrence rates of bacterial vaginosis for women (87,88).

SCREENING IN PREGNANCY

In 2001, the U.S. Preventive Services Task Force published recommendations after review of seven randomized control trials. Screening in asymptomatic low-risk pregnancies was not recommended, and there was insufficient evidence to recommend screening for the high-risk population. In 2008, Nygren (52) and associates reviewed literature that was published following the 2001 task force findings. Seven randomized, controlled trials were included in their analysis and the results pooled with the 2001 report data. No evidence was found supporting screening in the asymptomatic low-to-moderate-risk patients. Screening in high-risk patients varied with three of five studies showing a benefit, one showing no benefit, and one showing harm with treatment (52).

Considering the current literature, there seems to be no benefit to screening the asymptomatic low-risk general population. Screening high-risk patients may provide benefit; however, there is no current consensus. The following are general guidelines that use current clinical evidence:

1. Test and treat all symptomatic patients.
2. Asymptomatic low-risk patients do not appear to benefit from universal screening.
3. Asymptomatic women at high risk for adverse pregnancy outcomes may benefit from screening and treatment. If screening is preformed, it should be done prior to 16 weeks of estimated gestational age.
4. Oral or vaginal preparations have similar organism eradication rates; however, vaginal treatments do not affect the preterm labor and delivery rates. Therefore, all patients at high risk for adverse outcomes should be treated with oral clindamycin 300mg twice a day for 7 days or metronidazole 500 mg two times a day for 7 days.
5. Test for cure should be done in 3 to 4 weeks after treatment.

CONCLUSION

Bacterial vaginosis is the most common cause of vaginal discharge in pregnant and nonpregnant women. This condition represents massive microbial and biochemical perturbations of the lower reproductive tract microecology. Diagnostic tests (Amsel's criteria) are easily performed. Treatments include oral or vaginal treatment with metronidazole or clindamycin. Descriptive and intervention studies carried out worldwide demonstrate increased risks of preterm birth and other adverse pregnancy outcomes associated with bacterial vaginosis; however, conclusive epidemiologic evidence to support screening in the general population has not been found. One explanation that has been proposed by Simhan et al. (89) involves molecular epidemiology looking at the individual patient's inflammatory response to a bacterial vaginosis infection based on genotypes. In the hypothesis by Simhan et al. (89), patients may be "hyperresponders" at risk for an overresponse of local immune factors resulting in pregnancy loss or preterm delivery, "normo-responders" with enough inflammatory mediators to promote clearing of the infection, or "hypo-responders" putting these patients at risk for ascending infection, preterm delivery, chorioamnionitis,

and postsurgical infections (89,90). These new ideas and technology may provide future researchers the tools in which to discover the contributing factors to the ongoing problem of being born "too soon."

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