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Comparing Screening and Treatment of Bacterial Vaginosis and Pregnancy Outcomes

Stephanie Severson
University of North Dakota, stephanie.severson@und.edu

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Stephanie L. Severson, PA-S

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Contributing Authors: Jeanie McHugo, PhD, PA-C, Barbara Bowman PA-S, Kristi Bohlig PA-S, Ashleigh Milbrath PA-S, Riann Collar PA-S

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ABSTRACT

Despite evidence that bacterial vaginosis can lead to poor perinatal outcomes the consensus remains against a screening and treatment protocol for all pregnant women. Due to variability in a multitude of factors, a generalized recommendation is difficult to make. There are inconsistencies among stage of gestation that screening took place and treatment selection. The multiple variables in demographics also make providing best practice recommendations difficult.

Lack of recommendations are largely due to harm of treatment in those who were misdiagnosed. The development of polymerase chain reaction (PCR) has the capability to reduce misdiagnosis. Newer studies have shown benefit of early screening and treatment and the use of clindamycin over the traditional treatment of metronidazole.

INTRODUCTION

Bacterial vaginosis (BV) occurs when there is a disruption of the normal flora present in the vagina. This is caused by an overgrowth of anaerobic bacteria and a decrease of the normal flora; *Lactobacilli*. Pathogen bacteria can include *Gardenella Vaginalis, Mobiluncus* species, *Bacteroides, Prevotella* species, and *Mycoplasma* species (Van Schalkwyk & Yudin, 2015). Disruption of the normal flora can occur for a variety of reasons; all of which are not completely understood. Bacterial vaginosis is the most common vaginal infection in women of reproductive age (Nygren, Fu, Freeman, Bougatsos, Klebanoff, Guise, 2008). Yudin & Money (2017) address that chorioamnionitis, preterm delivery, preterm rupture of membranes, and late miscarriage have all been associated with positive bacterial vaginosis during pregnancy. Despite extensive research showing this correlation, researchers have not been able to show a promising method for screening and treatment to improve outcomes. Significant contributing factors to this problem are the multiple variables in the demographics, diagnosis method, treatment modalities, and age of gestation when screening and treatment occurs.

Another contributing factor that makes recommendations difficult is that BV is present in 20-50% of women during pregnancy and most of these cases are asymptomatic (Brocklehurst, Gordon, Heatley, Milan, 2013). It is also known that up to 50% of BV cases clear without treatment. However, there is a possibility that it may recur after treatment. Knowing which infections will clear on their own and which will cause harm is undeterminable at this time. The current research shows that BV is more prevalent among minority women; African American in particular, those of low socioeconomic status, smokers, those with increased sexual partners, and women who have had previously delivered low birth weight infants (Nygren et al, 2008). To decrease poor perinatal outcomes; should all pregnant women be screened for BV and at what

stage of pregnancy? This is a question that researchers still have been unable to find a best practice answer for.

The 2008 USPSTF guidelines recommend against routine screening of pregnant women for BV. Recommendations were based on lack of consistent benefit and possible risk of harm (Nygren et al., 2008). Current CDC (2015) guidelines state, "Therefore, evidence is insufficient to recommend routine screening for BV in asymptomatic pregnant women at high or low risk for preterm delivery for the prevention of preterm birth" (Workowski & Bolan, 2015, p.71). The American College of Obstetricians and Gynecologists (ACOG), The Society of Obstetricians and Gynaecologists of Canada (SOGC), and The American Academy of Family Physicians (AAFP) all recommend against routine screening and treatment of BV in asymptomatic pregnant patients. SOGC does support the screening and treatment of those at high-risk and to complete the screening between 12- and 16-weeks' gestation (Yudin & Money, 2017). USPSTF defines high-risk as those with previous preterm delivery due to spontaneous rupture of membranes or spontaneous preterm labor. Low-risk was defined as no previous preterm delivery and no additional risk factors for preterm delivery (Nygren et al., 2008). Traditionally, the diagnostic methods have been clinically with Amsel's criteria or microbiologically with Nugent's gram stain. Intermediate flora which is a Nugent score of 4-7, has also been associated with adverse pregnancy outcomes (McNamee, Dawood, & Farquharson, 2014). All studies referenced for this paper used one of these methods. As mentioned above, there is variability in not only screening recommendations, but also treatment recommendations. CDC's first line treatments for BV positive pregnant women are oral metronidazole 250 mg three times daily for 7 days or clindamycin 300 mg orally twice daily for 7 days (Workowski & Bolan, 2015). SOGC states treatment with either oral or vaginal antibiotics are acceptable for cure, but if prevention of

adverse pregnancy outcomes is desired, only oral preparations should be used. Their recommendation is the same for clindamycin, but their recommendation for metronidazole is 500 mg twice daily for seven days. Yudin & Money (2017) addresses that these treatment modalities have shown only moderate success and recurrence rates are high. Repeat testing is recommended following treatment.

Alteration in vaginal flora increases risk for acquiring other sexually transmitted diseases; *Trichomonas vaginalis* and *Chlamydia trachomatis.* They have both been shown to increase rates of premature rupture of membranes and preterm labor (McNamee, 2014). Higher rates of *Mobiluncus* is associated with a higher Nugent score of 9-10 and one study found it to be associated with an increased incidence among asymptomatic patients (Nelson, Bellamy, Nachamkin, Ruffin, Allen-Taylor, & Friedenberg, 2008). Clindamycin has a broader range against atypical mycoplasma and *Mobiluncus* compared to the traditional treatment of metronidazole (Ugwumadu, Manyonda, Reid, & Hay, 2003).

The purpose of this scholarly project is to answer the question of which pregnant patients should be screened for BV and does identification and treatment of BV during pregnancy improve perinatal outcomes.

Statement of the Problem

BV is the most common lower genital tract syndrome in women of reproductive age (Nygren et al., 2008). Research has shown that BV is linked to poor perinatal outcomes. There are varying opinions on which pregnant patients should be screened for BV and what treatments should be used.

Research Question

It is well known that BV can cause pregnancy complications but there remains no consensus on whether all pregnant women should be screened and treated for BV. Would screening and treatment for asymptomatic BV improve perinatal outcomes?

LITERATURE REVIEW

A review of the literature yielded several high-quality meta-analyses, systematic reviews, random control trials, and cohort studies. Studies were limited to those published in 2008 or later. Searches were completed in PubMed, CINHAL, and Cochrane Database. Additional sources were found using reference lists. Search terms utilized included; bacterial vaginosis, vaginitis, pregnancy, pregnant, miscarriage, screening, pre-term, and asymptomatic. Excluded studies included those that did not discuss effects of bacterial vaginosis on pregnancy. Studies were limited to those with high levels of evidence regarding bacterial vaginosis and that did not include conflict of interest.

Background information and current guidelines

Nygren et al. (2008) reviewed the previous USPSTF recommendations from 2001 and combined that with seven new random control trials to evaluate the benefits and harms of screening asymptomatic pregnant patients for bacterial vaginosis. A search was done using English-language studies on MEDLINE from 2000 – September 2007 and from Cochrane Library databases through September 2007. Additional searches were done using reference lists and expert suggestions. Study selection was done by two reviewers and was limited to systematic reviews and individual random control trials. No studies were found comparing a screened vs. non-screened population.

Asymptomatic was defined as women who were being seen for routine prenatal care not specifically evaluation of vaginal symptoms. Using this criterion; patients who were unaware of symptoms that met criteria for bacterial vaginosis were included. Patients were categorized in low, general, or high-risk categories. High-risk qualifications were defined as previous preterm delivery due to spontaneous rupture of membranes or spontaneous preterm labor. Low-risk was defined as no previous preterm delivery and no additional risk factors for preterm delivery. The studies that qualified their participants as average risk included both low and high-risk women and the goal was to get a better picture of the general population. Patients with additional symptomatic infections were excluded; but some participants were found to have co-infection upon screening and these women were still included. Meta-analyses were done including new trials in addition to the ones used in the 2001 review. The primary outcome was the absolute risk reduction of preterm delivery prior to 37 weeks in treatment of bacterial vaginosis between the control and treatment group. Of the new studies; three looked at low-risk women, four used average-risk; general population, and one recruited women who qualified as high-risk. Studies took place in six different countries and used a variety of treatment regimens. There was also variability in rescreening and additional rounds of treatment given. Despite the variability, the addition of new studies still showed no benefit to screening and treatment of asymptomatic pregnant patients in low or average-risk categories. As for the high-risk group, conflicting evidence was found as three out of five studies showed benefit with treatment, but one showed treatment harm and another no benefit. Of the studies currently available, there is wide variability of patients involved and their risk level, timing of screening, diagnostic criteria, and treatment modalities.

Some studies have reported adverse effects to the standard treatment regimen of using metronidazole and so it has become a question of whether further studies are able to be done (Nygren et al. 2008).

Van Schalkwyk and Yudin (2015) conducted a review of the literature from MEDLINE, EMBASE, CINAHL, and the Cochrane Library up to May 2014 was done to provide recommendations on screening and management of vaginitis; bacterial vaginosis included. This was an update of the Society of Obstetricians and Gynaecologists of Canada (SOGC) clinical practice guidelines. The search was restricted to systematic reviews, randomized control trials, controlled clinical trials, and observational studies. English and French were the only languages selected and there were no date restrictions. The guideline was prepared by an infectious disease committee and then reviewed by the Family Physician Advisory Committee.

BV is the most common lower genital tract infection of both pregnant and non-pregnant women. Its prevalence has been linked to a variety of complications; preterm labor and delivery, preterm premature rupture of membranes, spontaneous abortion. As well as, postpartum effects on both mom and baby, including endometritis, post-cesarean wound infections, and subclinical pelvic inflammatory disease. There appears to be a higher incidence among black women, those who smoke, and those who use vaginal douches or intravaginal products. BV is not a sexually transmitted disease, but its incidence increases among those with and increased number of sexual partners, as well as those who engage in sexual intercourse more frequently. *Lactobacillus* is the predominant species found in normal vaginal flora. It should account for greater than 95% of the bacteria present. BV occurs when normal flora is disrupted; allowing for pathogenic bacteria to thrive. The

diagnosis of BV is traditionally done clinically using Amsel's criteria. Criteria diagnosis can be made with three of the four following signs; adherent and homogenous vaginal discharge, vaginal pH greater than 4.5, detection of clue cells, and amine odor after addition of KOH (positive whiff test). The most common microbiologic method used is Nugent's Criteria. This method quantifies the number of *Lactobacillus* and pathogenic bacteria. Results are scored from 0-10. 0-3 being normal, 4-6 considered intermediate flora, and 7-10 meets criteria for the diagnosis of BV. It has been shown that up to one-third of women who are treated have a recurrence of BV within three months. Currently, treatment is recommended for only those with symptomatic BV. First line treatment is oral metronidazole 500 mg twice daily for seven days. Alternatives include, intravaginal metronidazole or intravaginal or oral clindamycin. These treatments have produced moderate success with cure and high rates of recurrence are still seen (Van Schalkwyk & Yudin, 2015).

Yudin and Money (2017) conducted a review of the English literature using MEDLINE, EMBASE, CINAHL, and Cochrane databases up to June 2007. The guideline was again reviewed by SOGC's Infectious Disease Committee in March of 2015 and was reaffirmed for continued use. There remains no consensus for screening or treatment for bacterial vaginosis in the general population of pregnant patients. Currently, SOGC states there is fair evidence (I-B) that asymptomatic women and women without identified risk factors for preterm birth should not undergo routine screening for or treatment of BV. They also state fair evidence (I-B) that if treatment is chosen and the goal is prevention of adverse pregnancy outcomes, it should be done with 500 mg metronidazole orally twice daily for seven days or clindamycin 300 mg orally twice daily for seven days. Vaginal

therapy is not recommended for the indication of preventing adverse pregnancy outcomes (I-B). There is currently insufficient evidence (III-L) for rescreening one month after treatment (Yudin & Money, 2017).

Incidence rate of bacterial vaginosis and poor perinatal outcomes; miscarriage and preterm birth

Koumans et al. (2011) conducted a retrospective cohort study of Syracuse Healthy Start's Program to evaluate outcomes of screening prior to 22 weeks gestation, treatment, and rescreening for BV. Charts from live births between the dates of January 2000 and March 2002 were abstracted. The data cohort consisted of women who were living in high infant mortality zip codes in the Syracuse area. A total of 838 women were screened prior to 22 weeks gestation. Outcomes were compared between screened women who had BV or abnormal flora and were treated vs when no treatment was documented vs those who had normal flora. Screening for Chlamydia, Gonorrhea, and bacteriuria was also done. All swabs were sent to the same facility and were interpreted by trained laboratory technicians. As part of the program, providers were encouraged to treat abnormal flora, rescreen in 4-6 weeks, and retreat if abnormal flora or BV remained. Data was abstracted via chart reviews and was done so by blinded reviewers. Reviewers were from the major delivery hospital's nursing or clinical staff and took a training course prior. Premature delivery was defined as birth prior to 37 weeks gestation and extremely premature was defined as birth prior to 28 weeks gestation. Statistical analysis was done using student's t-test, ANOVA for continuous variables, and chi-squared tests for discrete and dichotomous variables, as appropriate. Bivariate and multivariate logistic regression was used to examine association between numerous variables. Similarities among those who

delivered early were; 29 years of age or older, 1st prenatal visit in the 2nd trimester, previous preterm birth, and a correlation with certain prenatal care providers. Average age of gestation at initial screening was 11.8 weeks with a standard deviation (SD) of 4.8. Some women were only screened once, and others were re-screened three or more times. Initial screening found 406 (48%) had abnormal flora or BV. Those who screened positive for abnormal flora or BV were more likely to be black, younger than 30, not married, smokers, education level of high school or less, have more than two children, and enrolled in Syracuse Healthy Start (SHS) and Women Infants and Children (WIC). There were also higher incidence rates at certain prenatal care sites. There was variability among treatment options; some were given 500 mg metronidazole twice daily for 7 days (59%), 250 mg of metronidazole three times daily for 7 days (19%), 2 gm metronidazole once (12%), intravaginal metronidazole for 5 days (9%), and intravaginal clindamycin (2%). Women who were treated for abnormal flora or BV had improved outcomes vs those who were not treated and had abnormal flora or BV; OR 0.4, 95% CI 0.2-0.7. There was no statistical significance for preterm delivery between women with normal flora vs those who were treated for abnormal flora or BV. Those who were positive for abnormal flora or BV had some commonalities; race, marital status, education level, and socioeconomic status. This study did not decipher between asymptomatic and symptomatic patients as all patients were screened regardless of symptoms. Other limitations of this study included a variety of treatments used, the decision of the provider to screen and treat, treatments not being recorded in the medical record, and the potential for medications not being taken as prescribed. Only looking at live births, they did not extract data on abnormal flora or BV effecting miscarriage. This study did show that

screening prior to the fusion of the decidua, which usually takes place between 14 and16 weeks shows promise in decreasing the rates of preterm delivery (Koumans et al., 2011).

McNamee et al. (2014) conducted a retrospective study looking at causes of mid-trimester pregnancy loss. Infection appears to play a larger role in miscarriage during mid-trimester compared to first trimester. Mid-trimester is defined as loss between 12- and 24-weeks' gestation. This time period is often overlapped with first trimester loss, preterm delivery (PTD), or preterm prelabor rupture of membranes (PPROM). According to a retrospective study including 7000 spontaneous deliveries; chorioamnionitis was present in 94% prior to 24 weeks gestion, 40% between 25 and 28 weeks, and 11% after 33 weeks. BV which is an alteration in vaginal flora, increases risk for acquiring other sexually transmitted diseases; Trichomonas Vaginalis and Chlamydia Trachomatis which have both been shown to increase rates of premature rupture of membranes and preterm labor as well. The use of clindamycin for BV or intermediate vaginal flora has been shown to reduce mid-trimester loss. Both oral and vaginal cream show promise but screening and treatment needs to be done early. Without a history of mid-trimester pregnancy loss or preterm delivery there is limited data to support screening of the general obstetric community (McNamee et al., 2014).

Nelson et al. (2008) conducted a cohort study of 1916 pregnant women, over 30 months, who were 12 weeks gestation or less was done to help determine what clinical, behavioral, or demographic factors play a role in asymptomatic BV. The study also compared pregnancy outcomes of those with who were asymptomatic to those who were BV positive and symptomatic. Specifically looking at prior prelabor rupture of membranes (PPROM), spontaneous preterm delivery (SPTD), and low birth weight (LBW).

Participants were all patients of the obstetrics department at the Hospital of the University of Pennsylvania between September 2001 and June 2004. Gestation was based on report of last menstrual period and all women were required to reside in Philadelphia to be qualified for the study. Excluded were those who did not speak English, multiple gestations, those found to be farther along than 12 weeks, or who had an ectopic or molar pregnancy. A total of 1916 women were enrolled and 754 tested positive for BV. Nugent criteria was used for diagnosis. Those with values of seven to ten were included. Those with normal or intermediate flora were excluded. Of the two sites recruiting participants, one provided care to only privately insured women; 53% and other for publicly insured; 47%. All participants had a vaginal swab collected at their first prenatal visit; 53% were self-collected. A questionnaire was also required which included questions on demographics, prior and current obstetric and gynecologic history, vaginal bleeding, vaginal symptoms, current and past feminine hygiene and health behaviors as well as history regarding sexual practices, sexually transmitted diseases, past or current alcohol and drug use and perceived stress in the prior one month. Stress was measured using Cohen's perceived stress scale. The questionnaire was facilitated by a female nurse in a confidential setting. All interviewers, abstractors, and obstetricians were blinded to the Gram stain results. To categorize previous pregnancy outcomes; medical records were abstracted. Those defined as symptomatic reported either abnormal vaginal odor or abnormal vaginal discharge since last menstrual period (LMP). Risk factors for testing positive were African American, lower social economic status, earlier sexual activity, higher psychosocial stress, history of vaginal douching, and history of cigarette use. Of those who tested positive, 66.6% were asymptomatic. The results found a weak

relationship between asymptomatic BV and less stress RR 0.78; CI 0.67-0.89, history of at least one STD RR 1.03, 95% CI: 1.01-1.07, and higher quantity of the *Mobiluncus* bacteria RR 1.04, 95% CI 1.01-1.07. Symptomatic BV positive women had a slightly higher Nugent score compared to the asymptomatic group; p=0.05. This study showed a similar incidence of PPROM, SPTD, and LBW in both asymptomatic and symptomatic patients (Nelson et al., 2008).

The study did not address if treatment was done or what treatment modality was used. Screening of co-existing STDs or *Candida* was not done. The questionnaire used to evaluate stress level was validated in African American women but not in pregnant women. Higher scores on the Cohen scale were correlated with current unemployment, non-married women, and those with a lower education level. The cohort of this study is not a good representation of the general population. Despite self-collection being documented as a reliable and valid way of sample collection; all swabs were not collected in the same way.

Usher-Pines, Hanlon, and Nelson, (2009) conducted a prospective cohort study of 1,886 pregnant women. It was done to help determine predictors of BV and BV-related microorganisms by racial group. The population consisted of urban African American and non-African American women in their first trimester. Those in the non-African American group were 60% white and 20% Asian. BV was measured using Nugent Gram Stain criteria. Smoking was evaluated by urine cotinine levels and stress using Cohen's perceived stress scale. Participants were all patients of the obstetrics department at the Hospital of the University of Pennsylvania between September 2001 and June 2004. Gestation was based on report of last menstrual period and all women were required to reside in Philadelphia

to be qualified for the study. Excluded were those who did not speak English, had multiple gestations, those found to be farther along than 12 weeks, or who had an ectopic or molar pregnancy. The primary outcomes were to determine predictors of BV and to evaluate BV status and levels of the three common BV-related microorganisms; *Lactobacillus*, *Mobiluncus*, and Bacteroides/*Gardnerella*. A Nugent score of 7-10 met criteria for BV. Quantities of each bacteria were graded 0-4, 4 being the highest level; 30 or more organisms per oil immersion field. Stress was evaluated at enrollment and again at 20 weeks gestation. Smokers were identified with a urinalysis cotinine value greater than 500 ng/ml. This indicates use of cigarettes in the past 72 hours. Private vs government or uninsured was used to classify socio-economic status. Total number of sexual partners and previous STDs used to quantify higher risk sexual practices. Vaginal bleeding and African-American race were both self-reported yes or no questions. Statistical analysis was done using Chi-square and t-tests for behavior, demographic, and pregnancy outcomes. Additional models were used when comparing levels of each microorganism; maternal age, insurance, stress score, douching during pregnancy, smoking confirmed by urinalysis, history of STD, number of sexual partners, and marital status. Participants were split up between African American and non-African American. BV positive predictors were found to be African American race; OR =3.26, 95% CI: 2.29-4.63, unmarried; OR=1.42, 95% CI: 1.00-1.29, smokers; OR=1.72, 95% CI 1.19-2.50, and reporting of multiple sexual partners; OR =1.13, 95% CI: 1.00-1.29. African-American women were found to have lower levels of *Lactobacillus* compared to non-African American. Women who douched also had lower levels compared to those who did not. High *Mobiluncus* & high *Gardneralla* levels were correlated with African-

American race, single women, and smokers. Limitations include the method used to evaluate stress does not include anxiety or stressful life events. The sample population did not allow for further breakdown beyond non-African American. Only the three microorganisms used for Nugent criteria were included; others that commonly coexist were not included. The recurrence of BV was not assessed. This cohort does not represent the general population. It is unclear if those who were found to have low birth weight (LBW), spontaneous preterm birth (SPTB), spontaneous preterm labor (sPTL), or spontaneous abortion (SAB) through medical review were positive or negative for BV with previous pregnancies. Other studies have shown risk of poor perinatal outcomes with intermediate flora defined as a Nugent score of 4-6. This particular study did not abstract the data on those women (Usher-Pines et al. 2009).

Van Oostrum, De Sutter, Meys, and Verstraelen, (2013) conducted a meta-analysis and systematic review on bacterial vaginosis and infertility. Specifically, they looked at the prevalence of BV in infertility patients; twelve studies, the association between BV and the cause of infertility; three studies, effect on conception; six studies, and role in early preclinical and clinical pregnancy loss; six studies. An initial literature search was done using MEDLINE from 1966-September 2012. Further searches of EMBASE, CINAHL, the Cochrane Library, and ISI Web of Knowledge did not yield additional studies. MeSH terms included were; bacterial vaginosis, Gardnerella, vaginitis, vaginal flora, and subfertility, infertility, sub fertile, infertile, and IVF. All languages were included. Two of the authors performed the literature review and data extraction. All studies included used standardized diagnostic criteria of BV such as Nugent, Hay-lson, or Amsel criteria. MOOSE guidelines were applied, and raw data was extracted to for calculation based on

events per women vs. per cycle. Studies included analyzed at least one of the outcome measures. Outcomes were broken up into four categories; prevalence of BV in infertility, association of BV with the cause of infertility, conception rate in infertility patients with BV, and risk of early pregnancy loss in infertility patients with BV. Exclusion was based on abstract and if at least one outcome measure was not reported on. Subjects for the studies reviewed were recruited from IVF clinics in varying countries; five in the UK, two in the US, two in Egypt, one in Republic of Ireland, one in India, and one in the Netherlands.

The overall incidence of BV and abnormal microflora is higher among infertility patients compared with antenatal women in the same reference group. The prevalence of BV among infertile women was 19%; 95% CI: 14-25%. When intermediate flora was included with BV incidence was 39%; 95% CI 26-52%. Two studies included in this review found that BV is more prevalent in cases of unexplained infertility. There was a significant association between BV and preclinical pregnancy loss; 95% CI, $p < 0.01$. The authors concluded that BV does not affect the rates of conception; OR = 1.03, 0.79-1.33. However, these results are limited to those women receiving IVF. One disadvantage of this study is of all those included; none defined fertility but referred to patients that were attending infertility clinics. None of the studies included had a focus on miscarriage or preterm birth beyond the first trimester (Van Oostrum et al., 2013).

Treatment of bacterial vaginosis and effect on perinatal outcomes

Brocklehurst et al. (2013) conducted a Cochrane Review to assess antibiotic treatment of BV in pregnancy. Twenty-one trials were included involving 7847 women with either bacterial

vaginosis or intermediate flora. The primary outcome was incidence of pregnancy loss up to 24 weeks' gestation, otherwise known as a late miscarriage (LM). Additional outcomes were birth less than 37, 34, and 32 weeks gestation. Also included were perinatal deaths after 24 weeks and neonatal death up to 28 days. Birthweight was also a primary outcome. The Cochrane Pregnancy and Childbirth Group's Trial Registry (31 May 2012) was searched. Cited references from retrieved articles and abstracts, letters to the editor, and editorials were all reviewed. All languages were included. Two of the authors searched and reviewed articles for bias. Extensive work was put into the study assessing for selection, performance, detection, reporting, and attrition bias. Trials used must have included either comparison of antibiotic treatment with placebo to no treatment or comparing two different regimens for the treatment of BV. Both asymptomatic and symptomatic subjects were used. Women at any stage of pregnancy, or of any age were included. Most of the screening took place in the second trimester; some studies included results as late as 28 weeks gestation. If there was a coexisting sexually transmitted disease, this did not exclude them from the studies. Amsel or Nugent criteria was used for diagnosis. Two trials included intermediate vaginal flora in addition to BV, these studies were included in a separate comparison. Intermediate flora is defined as a Nugent score of four to six, a score of seven to ten qualifies as BV. There was a varying degree between the trials regarding how BV was diagnosed, timing of the treatment, and the choice of antibiotic for treatment. Choice of treatment varied between the 21 studies. Nine used oral metronidazole alone, one used oral metronidazole plus erythromycin, one used oral clindamycin, and one oral amoxicillin. Nine used intravaginal clindamycin and one vaginal metronidazole gel. The study also broke down the participants into sub

groups: previous preterm birth; intermediate vaginal flora (including BV), and treatment before 20 weeks' gestation. Many, but not all studies excluded women who were symptomatic. The findings of this study do not provide significant evidence that screening, and treatment of all pregnant women would yield fewer perinatal complications. However, areas of screening and treatment at earlier stages as well as looking to clindamycin compared to metronidazole did show some benefit. At this time, most studies done have largely focused on metronidazole as treatment.

Overall, antibiotic therapy was effective in eliminating BV during pregnancy; RR 0.42, 95% CI 0.31-0.56 as well as reducing the risk of late miscarriage (LM); RR 0.20, 95% CI 0.05-0.76. The studies that showed a reduction in LM were limited to two trials both using clindamycin. A total of 1270 women were studied. The results of subgroup analysis showed no difference in comparison of outcomes between women who did or did not have a previous preterm birth RR 0.39, 95% CI 0.28-0.53. Only two studies, totaling 894 women included intermediate flora, but did find a reduction in preterm birth less than 37 weeks vs those that did not have altered flora RR 0.53, 95% CI 0.34-0.84. These results may be attributed to timing of treatment being earlier in gestation (Brocklehurst et al., 2013).

Haahr et al. (2016) conducted a systematic review to provide clinical recommendations on treatment of bacterial vaginosis in pregnancy to reduce the risk of preterm delivery. There is currently no consensus as to whether or not treatment of BV in pregnancy reduces the risk of spontaneous preterm delivery (sPTD). The goal of this review was to make a clinical recommendation based on GRADE; strong or weak recommendations. GRADE quality was determined by risk of bias. Searches were done using Guidelines

international Network, MEDLINE, EMBASE, The Cochrane Database of Systematic Reviews, Web of Science from 1999 to October 3, 2014. The national societies of obstetrics and gynecology from Scandinavia, America, Britain, and Canada were all searched. At minimum, two members of the guideline group reviewed the search results. A research librarian assisted the members in their search. Clinical recommendations address all ages, low and high risk of sPTD, and both asymptomatic and symptomatic women during pregnancy. For diagnosis; a strong recommendation was made for Nugent score as the gold standard for diagnosis. Amsel criteria and properly evaluated PCR-techniques may be alternatives. Treatment with metronidazole; a strong recommendation against treatment of BV positive pregnant women to reduce the risk of sPTD. In high-risk pregnancies, very low evidence was found that metronidazole reduces risk of PPROM; RR 0.17, 95% CI 0.04-0.74. In low risk pregnancies RR was 1.11, 95% CI 0.93-1.34. Treatment with clindamycin; a weak recommendation against treatment of BV in pregnant women to reduce the risk of sPTD. Treatment at any gestational age had a RR of 0.87; 95% CI 0.73-1.05. If clindamycin was started before 20 weeks gestation; RR was 0.95; 95% CI 0.71-1.26 (Haar et al. 2016).

Lamont, Duncan, Mandal, & Bassett (2011) conducted a systematic review and metanalysis of random control trials to determine if administration of clindamycin to women with abnormal flora and asymptomatic BV at less than 22 weeks of gestation reduced the risk of preterm birth and late miscarriage. A total of five trails and 2346 patients were included. Entities searched included; PubMed, EMBASE, CINAHL, and Lilacs all up to July 21, 2011. The Cochrane Central Register of Controlled Trials, Research Registries of ongoing trials was also used. All languages were included. Searches were completed

by two authors. Study selection was based on randomized control trials comparing treatment of women at <22 weeks gestation with abnormal flora and asymptomatic BV. Diagnose of BV was based on Gram stains in the first or early second trimester. Treatment options must have compared either oral clindamycin or clindamycin vaginal cream (CVC) vs placebo or no intervention. For this review; one study used oral and four used CVC. Studies included had a primary outcome of preterm birth (delivery <37 weeks). 414 of the 428 potentially relevant citations were excluded based on title or after review of the abstract. Of those fourteen, only five met criteria and were included in the analysis. The number needed to treat (NNT) for late miscarriage (LM) is 66. The study found the administration of Clindamycin at <22 weeks of gestation was associated with a significant reduction in preterm birth <37 weeks RR 0.60, 95% CI 0.42-86, p<.001, decreased risk of late miscarriage (birth between 16 and 22 weeks) RR 0.20, 95% CI 0.05-0.76, and significant increase in gestational age at birth 95% CI 0.28-1.01. The route of clindamycin administration had varying outcomes. The only study that looked at oral administration showed a 61% reduction in preterm birth <37 weeks; RR 0.73, 95% CI 0.47-1.14. The four studies that looked at CVC showed only a 27% reduction in preterm birth <37 weeks RR0.73, 95% CI 0.47-1.14. Treatment with oral clindamycin appears to be more effective in women with a higher Nugent score (10). The comparison here showed 5.4% rate of PTB or LM, compared to 35.7% in the placebo group. Clindamycin does carry the risk of clostridium difficile. The vaginal preparation has only 4% systemic absorption but was found to be less effective than the oral preparation. The wide variability among trials looking at BV is addressed in this study. Some variations include; the definition of BV, gestational age at diagnosis and enrollment, the choice of

antimicrobial agent, dose, and route, follow up on clearance of BV, primary outcomes, and patient population. At this time, most studies have focused on metronidazole as the treatment for BV and these studies have not shown significant results. (Lamont et al., 2011).

Sangkomkamhang, Lumbiganon, Prasertcharoensuk, Laopaiboon, (2015) conducted a Cochrane review looking at screening and treatment programs for preventing preterm delivery. A search was done using the Cochrane Pregnancy and Childbirths Group's Trials Register up to November 30th, 2014, the Cochrane Central Register of Controlled Trials, and references lists of retrieved reports. Studies of all languages were included that compared screening vs no screening of antenatal lower genital tract infections. Two of the authors assessed all trails for risk of bias, inclusion, extracted data, and checked for accuracy. One study of 4155 women at less than 20 weeks' gestation met inclusion criteria. All participants were asymptomatic. Screening took place between 15- and 19-weeks' gestation. The study took place in Vienna, Austria. Assessment and risk of bias was done for each study checking for possible selection, performance, detection, attrition, and reporting bias. Subgroup analyses were done on early vs late trimester screening and low risk vs. high risk of preterm birth. All participants of the randomized control trial were screened using Gram stain. The intervention group received either 2% vaginal clindamycin for BV or 300 mg clindamycin twice daily for seven days for recurrent BV. None of the participants reported side effects during treatment. The control groups' Gram stain results were not revealed. The primary outcome measured was preterm birth at less than 37 weeks gestation. This study showed statistically significant evidence that screening and treatment for antenatal lower genital tract infections reduce preterm birth;

RR 0.55, 95% CI 0.41-0.75 and, low birth weight infants; RR 0.48, 95% CI 0.34-0.66, and very low birth weight infants; RR 0.34, 95% CI 0.15-0.75. (Sangkomkamhang et al. 2015).

Workowski & Bolan (2015) updated the sexually transmitted diseases treatment guidelines by the Center for Disease Control (CDC). This is an update from 2006 guidelines. A systematic review of the literature was done by CDC staff members looking for new information published since the 2006 Guidelines were published. Treatment for all symptomatic pregnant patients is recommended. Recommended treatment from the CDC remains metronidazole orally 250mg, 500 mg, or intravaginal gel. Clindamycin cream is also first line. Although metronidazole crosses the placenta, a link between teratogenic or mutagenic effects on newborns with metronidazole use during pregnancy has not been found and more recent studies have determined vaginal clindamycin to also be safe. Oral and vaginal therapy have shown similar cure rates and either treatment route can be used. The treatment of asymptomatic pregnant women remains unclear. Regarding high risk women, four out of seven trials showed benefit. Research remains even more unclear when it comes to asymptomatic BV and low risk pregnancies.

DISCUSSION

Despite evidence that BV can lead to poor perinatal outcomes, the consensus remains against a screening and treatment protocol for all pregnant women. Currently, there are no studies that address the harms of screening specifically. However, there is some concern regarding misdiagnosis and unnecessary treatment. The lack of recommendation for regular screening was in part due to treating women with false positive test results. The 2001 USPSTF review made the following statement regarding asymptomatic treatment.

> …2 studies identified in the previous review, bacterial vaginosis-negative women who received antibiotics had more deliveries before 34 weeks than those not given antibiotics; this was statistically significant in 1 study and borderline statistically significant in the other. In addition, 1 study reported a statistically significantly greater frequency of neonatal sepsis. (Nygren, 2008 p.230)

Of the treatment trials used for the USPSTF recommendations, one found asymptomatic women who were treated with metronidazole had increased risk of preterm delivery. All the other treatment trials used for USPSTF recommendations, found no statistically significant adverse effects to pregnancy outcomes. Many of the studies do not report side effects of the medications without regard to affecting the outcome of the pregnancy.

Due to variability in a multitude of factors, a generalized recommendation is difficult to make. There is inconsistency among techniques used for diagnosis, stage of gestation screening taking place, treatment selection, and route of administration. Ethnicity and socioeconomic differences among patients also makes providing best practice recommendations difficult. In discussion, most studies address the fact that if screening is done, it needs to be done early. Some

even suggest preconception screening and treatment. When looking closely at the studies used to make these recommendations, much of the screening for asymptomatic BV took place after the 14-16 gestational week window that appears to be pivotal to developing chorioamnionitis. Koumans et al. (2011) writes, "Vaginal contents are in communication with the uterus until the fusion of the *decidua capsularis* with the *decidua paretalis* at 14-16 weeks of gestation". (Koumans et al. 2011, p. 1021)

Should all pregnant women be screened for bacterial vaginosis vs only those who are symptomatic to improve perinatal outcomes?

There were few studies that compared asymptomatic vs symptomatic patients. Nelson et al. (2008) looked at characteristics related to asymptomatic BV. Being 72% of the sample was African American, generalizability is limited. They found, compared to the symptomatic individuals, the asymptomatic group had a higher incidence of *Mobiluncus*, lower Nugent scores, as well as a history of more STDs and lower reported stress levels. Interestingly, higher stress scores were found in both BV positive and BV negative women who reported symptoms. Uscher-pines (2009) wrote, "…adjusting for high-risk behaviors linked to stress, such as smoking, removes the independent role of stress of BV development" (Uscher-Pines 2009, p. 516). It appears stress alone cannot be used as a predictor. Nelson et al. (2008) found pregnancy outcomes appeared similar for PPROM, SPTD, birthweight, and chorioamnionitis among both asymptomatic and symptomatic participants. Unfortunately, participants were not screened for co-existing STDs or Candida at time of BV screening and treatment was not disclosed in this study.

It is well known that the African American race is a risk factor for BV. Uscher-Pines et al.(2008) discussed a higher incidence of BV and *Mobiluncus* species and absence of *Lactobacillus* among African American women when compared to whites, symptomatic and asymptomatic included. Features that may predict higher *Mobiluncus* and *Gardernella* levels were African-American race, single women, and smokers. Lower levels of *Lactobacillus* were related to douching and smoking. These two studies only addressed those with a Nugent score of 7-10 and not those who qualified as having intermediate flora. Symptomatology was not specified as Koumans et al. (2010) completed a retrospective study that found a higher incidence of abnormal flora and BV among women who were African American, less than 30 years old, not married, smokers, had more than two children, and had high school education or less. Lamont (2011) also addressed that *Mobiluncus* species was associated with a higher Nugent score and this group had a significantly lower rate of PTD compared to placebo when treated with clindamycin.

BV appears to have a higher incidence among women with infertility. Van Oostrum et al. (2013) found 19% prevalence rate of BV in women with infertility and a 39% incidence when including those with abnormal flora; Nugent score of 4-10. Unfortunately, these studies were specific to women undergoing in vitro fertilization (IVF). However, this specific cohort of women gave researchers the opportunity to take samples at implantation and the exact conception date was known. They found abnormal vaginal flora and BV is more common among infertility patients compared with antenatal patients from reference population. It also appears BV is associated with preclinical pregnancy loss; or loss prior to 6 weeks gestation (Ralph, Rutherford, Wilson 1999).

It is possible that BV is playing a large role in unexplained cases of infertility. According to McNamee et al. (2014) if a patient has a history of mid-trimester pregnancy loss (MTL) (loss between 12 and 24 weeks) a high vaginal swab (HVS) should be completed to check for BV in a subsequent pregnancy in the first trimester. McNamee et al. (2014) recommend using the Nugent criteria as this includes intermediate-flora as well. Two large studies showed chorioamnionitis in 94% of spontaneous deliveries before 24 weeks and another with a 77% incidence rate among spontaneous MTL. Treatment prior to 20 weeks gestation has been shown to have the most significant reduction in preterm delivery (PTD). In an interview with Sarah Hansen, DNP, NP-C, CNM, she agreed that knowing who and when to screen and treat is a difficult decision. As she has developed her practice, she has found the most benefit in screening those who are pregnant for the first time, those with a history of first trimester miscarriage, and those complaining of increased discharge. She also questions her patients regarding their sexual history and history of vaginitis and what, if any symptoms they had with those infections (S. Hansen, personal communication, November 13, 2018).

The Cochrane review done by Brocklehurst et al. (2013), showed no significant reduction in preterm birth. The review involving 21 trials found little evidence for screening and treatment of asymptomatic women to prevent PTB. However, only two studies included intermediate flora; totaling 894 women. This subgroup did show a 47% reduction in preterm birth less than 37 weeks vs those that did not have altered flora. A randomized control trial showed that "…treatment of asymptomatic intermediate abnormal vaginal flora and bacterial vaginosis in a general obstetric population reduces the occurrence of late miscarriage and spontaneous preterm delivery." (Ugwumadu et al., 2003, p.983) Antibiotic treatment used was oral clindamycin 300 mg twice daily for 5 days and was given by 17 weeks gestation (Ugwumada et al. 2003).

Brocklehurst et al. (2013) does address that these results may be attributed to timing of treatment being earlier in gestation. A significant portion of the Brocklehurst Cochrane review participants included screening occurring in the 2nd trimester; unknown if this was prior to 14-16 weeks or not; some as late as 28 weeks.

In asymptomatic patients does screening and treatment decrease the risk of miscarriage and preterm delivery?

Koumans et al. (2011) found that women from inner-city Syracuse that were treated for abnormal flora and BV had fewer premature deliveries. The same study also found no statistically significant difference between women with a negative gram stain and those who were positive and were treated. This showed that treated BV had the same risk as a pregnant patient without BV. It is also interesting to note that women who had normal flora prior to 22 weeks gestation and abnormal flora or BV after 22 weeks showed no change in outcomes. The fusion of the decidua capsularis with the decidua parietalis at 14-16 weeks seals the uterus from vaginal contents. This may be a reason late treatment has not shown significant outcome promise. According to this study, re screening and treatment is necessary and should be done until 16 weeks. Lamont et al. (2011) addresses the route that clindamycin is given plays a large role in cure of BV. “If microorganisms have gained access to the endometrium/decidua, clindamycin vaginal cream (CVC) may not be effective at this site and oral therapy may be beneficial.” (Lamont et al., 2011 p. 185) In comparison of clindamycin and metronidazole, Lamont et al. (2011) reported clindamycin to have up to a 70.8-90% cure rate compared to 40-77% cure rate after 2 days of metronidazole. Haahr et al. (2016), also reported low quality evidence of treatment with metronidazole for PTB before 37 weeks and made a strong recommendation against using metronidazole to prevent sPTD. Important to note however, is

that they were unable to identify any studies using metronidazole prior to 16 weeks gestation. They also gave a weak recommendation against clindamycin to prevent sPTD; age at gestation was not discussed here. Vaginal clindamycin is limited to 4% systemic absorption and does appear safer than oral clindamycin in regard to risk of *C. difficile* (Lamont et al., 2011).

Sangkomkamhang et al. (2015) conducted a Cochrane review that found antenatal lower genital tract infection screening and treatment can reduce preterm births up to 50%. The original study done in Vienna by Kiss et al. (2004) screened for asymptomatic vaginal infections; BV, candidiasis, and *Trichomonas vaginalis* on gram stain between 15- & 19-weeks' gestation. Only those with a Nugent score of 7-10 were included. BV was treated with 2 gm vaginal clindamycin and persistent or recurrent infection was treated with 300 mg orally twice daily for seven days. Some women were found to have concomitant *Candida* infection, or *Candida* infection alone and were treated accordingly. Not all studies used to make recommendations on screening and treatment recommendations for BV in pregnancy have tested for and treated additional vaginal infections.

APPLICABILITY TO PRACTICE

There is still not a clear picture if there should be routine screening and treatment for BV in all pregnancy. The lack of recommendation for screening and treatment has been due to a few studies reporting harm after misdiagnosis and treatment. Research has been able to identify risk factors of developing BV and more research needs to be done in looking at *Mobiluncus* species, treatment with clindamycin, and treatment prior to 14-16 weeks when the fusion of the decidua takes place. The USPSTF guidelines are currently under revision. Since their last publication in 2008; significant studies have been released regarding screening and treatment of asymptomatic BV; Brocklehurst et al. (2013), Lamont et al. (2011), and Sangkomkamhang et al. (2015) All three of these reviews found benefit to early screening and treatment. They also found greater benefit in use of clindamycin over metronidazole. Much of the research does not include if other infections were present at the time of diagnosis or if the patients have had history of vaginitis or STDs. It appears *Candida*, *Trichomonas*, and other STDs can play a role in miscarriage and also contribute to the patient being asymptomatic to a BV infection. An increase in sexual partners appears to have some correlation with the development of BV as well.

More recently, technologic advances have allowed BV to be diagnosed using polymerase chain reaction (PCR). This is becoming a more popular method used in clinical practice instead of Amsel's. PCR has an increased sensitivity and specificity compared to both Amsel and Nugent criteria. Regarding PCR, Menard et al. (2010) writes, "The molecular tool predicted bacterial vaginosis with a sensitivity of 100%, a specificity of 93%, a positive predictive value of 73%, and a negative predictive value of 100%". (Menard et al., 2010, p. 1547) As part of the results, PCR may be identifying or excluding those incorrectly diagnosed by the other two methods.

In my opinion, the development of PCR and its ability to reduce the rate of misdiagnosis will play a large factor in upcoming recommendations. Newer studies show significant benefit with early screening and treatment with clindamycin. Further studies are needed that focus on using PCR for diagnosis, screening early; prior to the closure of the decidua, and clindamycin for treatment. Additional studies should also be done that look at screening and treatment for *Candida* and *Trichomonas* as well as BV. There is now a better picture of increased risk factors that include; history of miscarriage, preterm delivery, infertility (unexplained in particular), African American race, recent history or current smoker, increased sexual partners, and history of STDs. Knowing this, can help practitioners identify those who would benefit most from asymptomatic screening. Screening may also be beneficial for those struggling with preclinical miscarriage. However, few studies have addressed this topic and more research needs to be done.

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