Working Session 6C: Preterm Delivery/Low Birth Weight/Infant Mortality

Bacterial Vaginosis and Other Maternal Infections: Treatable Causes of the Black-White Gap?

Yvonne W. Fry, MD

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From the Morehouse School of Medicine.

Introduction

This article addresses the issue of bacterial vaginosis (BV) and other maternal infections as potentially treatable causes of the Black-White gap in preterm delivery (PTD) and low birth weight (LBW). Thus, we must first define LBW and PTD. A LBW delivery is one of an infant with weight ≤2,500 grams; and a PTD is one before 37 complete weeks of gestation.

Currently (2001 data), the Black LBW rate is 12.9%, while the White LBW rate is 6.7%. Overall, the LBW rate is 7.6%. The Healthy People 2010 Objective designates reduction of the LBW rate to 5% for all Americans. With respect to preterm births, the baseline data for 1998 demonstrate that the rates are as follows: African American, 17.5%; White, 10.5%; and overall, 11.6%. The Healthy People 2010 Objective is to reduce the PTD rate to 7.6% for all Americans. The Infant Mortality Rate is defined as the number of infant deaths per 1,000 live births. The corresponding Healthy People 2010 Objective is to reduce the infant mortality rate to less than or equal to 4.5 per 1,000 live births for all Americans.

In considering this maternal and child health area of disparity, PTD is the largest contributor to deaths of African-American infants. It is also the 2nd largest cause of overall infant mortality in the United States. Intrauterine infection(s) have been identified as causal agents for preterm births. Thus, these may be responsible for the Black-White disparities in LBW and PTD. These 2 issues cause the majority of neonatal (non-congenital anomaly) deaths, and contribute to greater than 50% of the costs of neonatal nursery management. The resultant morbidity includes, but is not limited to: necrotizing enterocolitis, retinopathy of prematurity, developmental delays, chronic respiratory diseases, and 50% of neurological disability.

Of note, there are several maternal infections associated with poor pregnancy outcomes. These include pyelonephritis (e. coli) and bacteriuria (group b streptococcus), neisseria gonorrhea cervicitis, chlamydia trachomatis, trichomonas vaginalis, ureaplasma urealyticum, syphilis and human immunodeficiency virus.

Briefly, I will address some aspects of the "other" maternal infections associated with poor pregnancy outcomes. This is not intended as a comprehensive review of the management of these infections in pregnancy, but rather as a reminder to consider them as possible contributors to potential poor pregnancy outcomes.

There is up to an 8% incidence of urinary tract infection (UTI) in pregnancy, with e. coli identified in 80%–90% of the infections. Other common etiologies include gram-negative rods (proteus mirabilis and klebsiella pneumonia); gram-positive organisms including Group B streptococcus and staphylococcus saprophyticus (less common); and rare causes including enterococci, gardnerella vaginalis, and ureaplasma ureolyticum. Unfortunately, it is possible to miss the diagnosis of UTI in

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a pregnant woman, as it is asymptomatic in 2%–10% of pregnant women. This can result in intrauterine growth retardation (IUGR), PTD, and LBW. Acute (symptomatic) cystitis occurs in 30% of untreated asymptomatic bacteriuria. Pyelonephritis occurs in 20%–50% of pregnant women with untreated asymptomatic bacteriuria, which can lead to PTD. Of significance to our discussion are the screening/testing guidelines of the American College of Obstetrics and Gynecology (ACOG), recommending a urine culture at the first prenatal care visit, with a repeat culture in the 3rd trimester.

Group B streptococcus bacteriuria occurs in 5% of UTIs, and 10%–30% of pregnant women are colonized. The sequelae include preterm labor or membrane rupture, UTIs, and/or chorioamnionitis. Treatment is associated with decreased PTD. For these diagnoses, the Centers for Disease Control and Prevention (CDC) recommends treatment at the time of diagnosis and during labor.

Neisseria gonorrhea cervicitis (GC) and/or chlamydia trachomatis are strongly associated with PTD. Treatment decreases PTD. Trichomonas vaginalis is associated with PTD and an increased risk of human immunodeficiency virus (HIV) infection. Of note, treatment does not appear to decrease risk. Human immunodefiency virus (HIV) is associated with higher rates of PTD only with increased use of combination antiretroviral therapy.

Clinical management of sexually transmitted diseases (STDs) in pregnancy includes use of guidelines whereby patients with high risk for contracting STDs, with a history of prior PTD ± current PROM or labor are screened for GC and chlamydia, preferably with a DNA probe. The optimal timing is unknown, but suggested to occur at the initial visit and/or in the third trimester.

Bacterial vaginosis (BV) results from replacement of vaginal lactobacilli with an overgrowth of other bacteria. Under usual conditions in the vagina, lactobacilli produce hydrogen peroxide, which is toxic to pathogens (lactobacilli are absent in BV). BV-associated bacteria have mucolytic enzymes that facilitate their progress through the cervical mucous barrier to the upper genital tract. The specific microorganisms of BV include anaerobes such as bacteroides, peptostreptococcus, and mobiluncus species, and facultative bacteria such as gardnerella vaginalis and genital mycoplasmas (hominis). The prevalence of BV ranges from 10%–30% of pregnant women to 50% in high-risk women. BV is not considered an STD, though it has been associated with sexual activity, such as oral sex, new or multiple partners, lack of condom use, douching, sex during menses, and lesbian sexual activity.

The occurrence of BV facilitates the overgrowth of potential pathogens. Specifically, lactobacilli convert glucose to lactic acid and maintain the acidic pH of 4 in the normal genital tract. One has an alkaline vaginal pH in BV. Significantly, the normal acidity was protective from HIV and other pathogens (GC, chlamydia, syphilis, and trichomonas).

The clinical diagnosis of BV can usually be optimally made using the Amsel criteria: characteristic discharge (thin, homogenous vaginal D/C); clue cells (epithelial cells with adherent organisms) on a wet mount; vaginal pH >4.5; or an amine ("whiff test") test with 10% potassium hydroxide (fishy odor).

In the research arena, one may also use the Nugent criteria for gram stain (score 7+ and pH 4.5+ diagnostic for BV). Here a score of 0–3 is normal; 4–6 is intermediate; 7+ is BV. Normal is consistent with lactobacillus (large gram + rods) predominant (hydrogen peroxide producing, with low vaginal pH); intermediate represents mixed flora; and BV is demonstrated by the presence of anaerobic bacteria and facultative aerobic bacteria with an alkaline vaginal pH.

Typically, the clinical presentation of BV involves: a fishy vaginal odor, excessive vaginal discharge, vulvar pruritus or burning. On the other hand, 50% of patients are asymptomatic. You should consider a work up to rule out BV if the patient exhibits signs or symptoms of an upper genital tract infection such as those suggestive of pelvic inflammatory disease, coital dyspareunia, dysfunctional uterine bleeding, or new onset dysmenorrhea. Morbidity from BV falls into 2 categories: non-obstetrical and obstetrical. The non-obstetrical classification includes pelvic inflammatory disease, cervicitis, abnormal pap smears, post-surgical gynecologic infections, increased risk of HIV, and recurrent cystitis. The obstetrical complications include chorioamnionitis, UTIs, premature rupture of membranes, preterm labor, PTD, postpartum endometritis, and post-abortion infections. Of note, and giving us a potential opportunity to make a difference, is the possible link between BV and other STDs. Gonorrhea, chlamydia, syphilis, and trichomoniasis all demonstrate increased prevalence due to the abnormal vaginal flora (low number of lactobacillus) resulting from BV. Bacterial vaginosis (BV) and HIV infections are possibly linked secondary to a vaginal pH shift from acidity to alkalinity. This may lead/contribute to male-to-female HIV transmission.

Recommendations for BV include the following: high risk women should be tested during the pregnancy; and management of BV should be per the CDC guidelines (initiate early in 2nd trimester), with oral regimens, specifically either Metronidazole 250 mg po

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TID for 7 days, or Clindamycin 300 mg po BID for 7 days. A test of cure should be done after one month.

There has been much controversy regarding BV and PTD/LBW. Multiple studies evaluated treatment for BV and PTD/LBW, and their results were highly inconsistent. On the one hand, pregnant women with asymptomatic BV (without a history of prior PTD) were not found to benefit from treatment. Conversely, studies did show a reduction in PTD in high-risk pregnant women diagnosed with and treated for BV in pregnancy.

Cary et al conducted a randomized clinical trial of antibiotics in 1,953 patients asymptomatic for BV, but BV+. This was done in collaboration with 13 Centers in the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (NICHD MFMU Network). The study methods used were as follows: BV was diagnosed by gram stain using Nugent's criteria. Patients were randomized between 16 and 24 weeks EGA. Treatment consisted of two 2-g doses of either flagyl or placebo, given 48 hours apart. Patients were retreated between 24 and 30 weeks EGA. The results demonstrated no benefit to high or low-risk women. One potential limitation of the study was the very brief antimicrobial therapy.

Hauth et al reported on a BV double blind-randomized study of treatment with flagyl (7 d) and erythromycin (14 d) given at 24 weeks EGA, with a repeat treatment in 2–4 weeks PRN in high-risk pregnant women, those with a past medical history of PTD. Those treated had fewer PTDs than the placebo group. The benefit was shown only in those with BV present at the first exam. It is believed that benefit may be due to eradication of early upper genital tract colonization (U. urealyticum/chlamydia). Of note, women with BV had higher rates of PTD in all groups, regardless of the treatment regimen.

Hauth et al made a somewhat disconcerting observation when they discovered that antibiotic therapy in pregnant women without BV led to a 3-fold increase in spontaneous preterm birth prior to 34 weeks EGA, vs placebo-treated women. This was identified in the Hauth et al evaluation of NICHD MFMU Network BV Treatment trial. Bacterial vaginosis (BV) was diagnosed using a Nugent score of 7–10, and pH≥4.7. Women with the lower Nugent scores (7–8) and treated with flagyl had a greater risk of PTD.

In conclusion, there are several infections which may contribute to the Black-White gap in preterm and LBW deliveries. These somewhat consistently include the occurrence of BV, which has been found to be associated with a 3-fold increase in PROM with patients with a vaginal pH>4.5. Additional research must be conducted to further evaluate the contribution of this and other infections in this area of health disparity.

Final recommendations include the suggestion that, for "Improved Access, Effectiveness, and Primary Care for All Americans" we should consider written office policies for the screening and treatment of those maternal infections which may impact pregnancy outcomes. One must be diligent, but prudent, in the translation of research to practice to improve clinical outcomes. Finally, attentively follow the guidelines of the CDC, ACOG, and the US Preventive Services Task Force regarding screenings and management of clinical conditions.

REFERENCES

1. Meis PH, Goldenberg RL, Mercer B, et al. The preterm prediction study: significance of vaginal infections. *Am J Obstet Gynecol.* 1995; 173(4):1231–1235.
2. Fiscella K. Racial disparities in preterm births: the role of urogenital infections. *Public Health Rep.* 1996;111:104–113.
3. Iyasu S, Tomashek K, Barfield W. Infant mortality and low birth weight among Black and White infants—United States, 1980–2000. *JAMA.* 2002;288(7):825–826.
4. Morales WJ, Schorr S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study. *Am J Obstet Gynecol.* 1994;171(2): 345–349.
5. Hauth JC, Goldenberg RL, Andrews WW, et al. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *N Engl J Med.* 1995;333(26):1732–1736.
6. Fiscella K, Franks P, Kendrick JS, et al. Risk of preterm birth that is associated with vaginal douching. *Am J Obstet Gynecol.* 2002; 186(6):1345–1350.
7. Martin Q. Vaginitis: meeting the clinical challenge. *Clin Cornerstone.* 2000;3(1):36–47.
8. Demissie, Kitaw, Rhoads, et al. Trends in preterm birth and neonatal mortality among Blacks and Whites in the United States from 1989 to 1997. *Am J Epidemiol.* 2001;154(4): 307–315.
9. Elliott B, Brunham RC, Laga M, et al. Maternal gonococcal infection as a preventable risk factor for low birth weight. *J Infect Dis.* 1990;161:531–536.
10. Cram LF, Zapata M-I, Toy EC, et al. Genitourinary infections and their association with preterm labor. *Am Fam Physician.* 2002; 65(2):241–248.
11. Secor R, Clark M. Bacterial vaginosis: common, subtle, and more serious than ever. *Clin Rev.* 2001;11(11):59–68.
12. Workowski KA, Levine WC, Wasserheit JN. US Centers for Disease Control and Prevention Guidelines for the Treatment of Sexually Transmitted Diseases: an opportunity to unify clinical and public health practice. *Ann Intern Med.* 2002;137(4):E255–E262.
13. Brocklehurst P, Hannah M, McDonald H. Interventions for treating bacterial vaginosis in pregnancy. *Cochrane Database System Review.* 2000;(2):CD000262.
14. Delzell JE, Lefevre ML. Urinary tract infections during pregnancy. *Am Fam Physician.* 2000;61:713–721.
15. Hillebrand L, Harmanli OH, Whiteman V, et al. Urinary tract infections in pregnant women with bacterial vaginosis. *Am J Obstet Gynecol.* 2002;186(5):916–917.
16. Berg AO. Screening for bacterial vaginosis in pregnancy. Recommendations and rationale. *Am J Prev Med.* 2001;20(suppl 3):59–61.

17. Batteiger BE. STDs: progress! *Medscape Infect Dis.* 2001;3(2).
18. Goldenberg RL, Klebanoff MA, Nugent R, et al. Bacterial colonization of the vagina during pregnancy in four ethnic groups. *Am J Obstet Gynecol.* 1996;174(5):1618–1621.
19. Ness RB, Hillier SL, Richter HE, et al. Douching in relation to bacterial vaginosis, lactobacilli, and facultative bacteria in the vagina. *Am Coll Obstetricians Gynecologists.* 2002;100(4):765–772.
20. Andrews WW, Hauth JC, Goldenberg RL. Infection and preterm birth. *Am J Perinatol.* 2000;17:357–365.
21. Weisbord JS, Koumans EH, Toomey KE, et al. Sexually transmitted diseases during pregnancy: screening, diagnostic, and treatment practices among prenatal care providers in Georgia. *South Med J.* 2001;94(1):47–53.
22. Obata-Yasuoka M, Ba-Thein W, Hamada H, et al. A multiplex polymerase chain reaction-based diagnostic method for bacterial vaginosis. *Am Coll Obstet Gynecol.* 2002;100(4): 759–764.