Progress Toward Vaginal GBS Vaccine Is Seen

BY DIANA MAHONEY
New England Bureau

BOSTON — Women with increased levels of type-specific serum antibody against group B streptococci may be protected from vaginal colonization by those serotypes, a study has shown.

The findings support current efforts to develop a vaccine to decrease vaginal acquisition and fetal transmission of the bacteria, lead investigator Dr. Sharon Hillier said at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology.

It has long been recognized that vaginal colonization by group B streptococci (GBS) is probably the single most important risk factor for neonatal sepsis, and while wider use of prophylactic intrapartum antibiotics has led to a substantial decline in the incidence of GBS infection in newborns, "a lot of women do develop amniotic fluid infections, preterm delivery, or even pregnancy loss" due to the bacteria, said Dr. Hillier of the University of Pittsburgh's Magee–Women's Hospital. "We really haven't understood why women become vaginally colonized with GBS, and we have few options for interrupting vaginal colonization. Prophylactic antibiotic treatment has been useful as an interim strategy, but it is just that—an interim strategy."

The longer-term objective, she said, is to develop a vaccine against GBS that will reduce vaginal colonization, prevent transmission to the neonate, and reduce overall morbidity.

The testing of potential vaccines is a logistical challenge, however, "because the incidence of neonatal sepsis is so low," Dr. Hillier said. "Even if an effective vaccine is developed, it would require more than 100,000 participants to achieve an even modestly powered vaccine trial."

In an effort to uncover surrogate end points for measuring GBS vaccine efficacy, Dr. Hillier and her colleagues designed the current study to evaluate the impact of naturally acquired antibodies on GBS acquisition, based on data from *Haemophilus influenzae* type b (Hib) vaccine research demonstrating that the Hib vaccine not only decreases Hib infection, but also reduces nasopharyngeal Hib colonization. As with GBS, a crucial factor in Hib virulence is the production of an antigenically variable polysaccharide capsule, she noted.

To test their hypothesis, the investigators enrolled 1,248 sexually active nonpregnant women aged 18-30 years in the study. At quarterly visits during the course of the study year, serum was collected from each of the women for evaluation of type-specific IgG antibody against the most common GBS serotypes. In addition, vaginal cultures were performed using selective broth medium for GBS; demographic and behavioral information, and vaginal flora assessments were also obtained. Based on the results from 1,089 women who returned for the quarterly visits, 973 women-years of follow-up were collected, Dr. Hillier said.

The median age of the predominantly white (61% vs. 35% black) study population was 21 years. "We specifically targeted younger women because of their higher level of sexual activity and increased incidence of GBS sepsis," Dr. Hillier noted.

During the evaluation period, the investigators recorded 298 GBS acquisitions, including 111 of serotype Ia, 26 of serotype II, 116 of serotype III, and 45 of serotype V, Dr. Hillier reported. Within and across the serotypes, "there was a strong association between the concentration of humeral antibody and acquisition of GBS," said Dr. Hillier, noting that overall, 61% of the GBS acquisitions occurred among women with 0.5 mcg/mL or less serum antibody to the respective serotype, while only 5% occurred among women with 3.0-5.0 mcg/mL of serum antibody.

"There was a strong relationship between the concentration of humeral antibody in the visit before the acquisition of GBS and the protective effect against acquisition," Dr. Hillier explained. "In type Ia, for example, about 50% of the GBS acquisitions occurred in women who had less than 0.5 mcg/mL of humeral antibody against type Ia at the previous visit." Similar percentages were observed for the other serotypes, she said. The linear association between concentration of antibody and acquisition of GBS was especially robust in serotype III, which is one of the most common serotypes that colonize women, she said.

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DR. HILLIER

The results of an adjusted hazards ratio using a Cox proportional hazards model for vaginal type III GBS acquisition showed a 70% reduction in acquisition of type III GBS among women with high levels of type III antibodies, said Dr. Hillier, noting that the independent association was consistent across multiple models.

"This finding leads us to believe that vaccination to induce high levels of serum antibody to type III GBS may result in decreased vaginal colonization of that serotype," Dr. Hillier said. To test this, she and her colleagues are currently conducting a National Institutes of Health–funded phase II randomized, double-blind clinical trial called SPIN (Streptococcal Prevention in Nonpregnant Women) of 50-mcg type III GBS polysaccharide-tetanus toxoid conjugate vaccine.

"This will be the study to answer the question of whether or not induced antibody can provide colonization resistance to GBS," she said. "If the answer is yes, it may allow us to move forward in vaccine development in GBS because we can use colonization as a surrogate end point." ■

More Treatments Emerging to Fight Bacterial Vaginosis

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Oral tinidazole, single-dose clindamycin vaginal cream, and lactobacillus-containing products are among the newer therapies for the treatment of bacterial vaginosis, Dr. Paul Nyirjesy said at a conference on vulvovaginal diseases.

Many of the therapies have emerged since the Centers for Disease Control and Prevention's treatment guidelines for bacterial vaginosis (BV) were issued in 2006. Bacterial vaginosis is among the most common vaginal diseases, occurring in about 10% of American women of reproductive age.

Oral tinidazole was approved in the United States in May 2007 for the treatment of BV. A recently published randomized controlled study in 235 women with BV found no significant difference in cure rates when tinidazole was administered as 1 g daily for 5 days or 2 g daily for 2 days (Obstet. Gynecol. 2007;110:302-9).

With use of the very stringent Food and Drug Administration guidelines for cure, 32% of women using the 2-day regimen and 41% using the 5-day regimen were cured, compared with 5.7% receiving placebo, said Dr. Nyirjesy, an investigator for the study. Both tinidazole regimens were superior to placebo.

The CDC's recommended oral therapy for BV is metronidazole 500 mg taken twice a day for 7 days, with clindamycin 300 mg taken twice a day for 7 days listed as an alternative.

Although metronidazole can cause GI complaints in up to 52% of patients, it remains the cheapest therapy for BV, said Dr. Nyirjesy, professor of obstetrics and gynecology and medicine at Drexel University College of Medicine, in Philadelphia. Oral metronidazole 2 g as a single dose was dropped as an alternative oral therapy in the 2006 guidelines because it is clearly inadequate as a treatment for BV, he added.

Single-dose clindamycin 2% vaginal cream is a sustained-release preparation that uses similar technology as single-dose butoconazole-1 cream, which gynecologists may be familiar with, said Dr. Nyirjesy, who has received support from Mission Pharmacal and KV Pharmaceuticals/Ther-RX, which respectively manufacture tinidazole and single-dose clindamycin cream.

In a study of 251 women with BV, clinical cure rates were not significantly different between single-dose clindamycin (Clindesse) and clindamycin 7-day (Cleocin) vaginal creams (88% vs. 83%) (Infect. Dis. Obstet. Gynecol. 2005;13:155-60).

Lactobacillus products would seem to have a role in BV, as the goal of treatment is to reestablish naturally occurring lactobacillus flora in the vagina depleted by BV and to decrease the presence of other species, such as *Mobiluncus* and *G. vaginalis*. But study findings have been mixed.

Lactobacillus-impregnated tampons used after a course of clindamycin ovules did not improve cure rates at 2 months in one study (Acta Derm. Venereol. 2005; 85:42-6). Early results with the *Lactobacillus crispatus* CTV-05 strain have not shown a benefit, he said at the conference sponsored by the American Society for Colposcopy and Cervical Pathology.

However, a recent study did report high satisfaction rates for an intravaginal lactobacillus capsule (J. Womens Health 2006; 15:1053-60). In a separate study of 32 women with BV, 88% treated with yogurt douches for 7 days during the first trimester of pregnancy were cured, compared with 5% who were not treated (Acta Obstet. Gynecol. Scand. 1993;72:17-9).

"The bottom line is that there is no well-studied product available and no well-demonstrated benefits," said Dr. Nyirjesy, who noted that most of the lactobacillus products are not available in the U.S.

He suggests individualizing BV therapy based on a variety of variables including cost, convenience, compliance, efficacy, spectrum coverage, and patient preference.

As for whether one antibiotic is better than another, the question has taken on new relevance in light of increasing evidence that not all BV is the same. Research has shown that, compared with other pregnant women, women with BV who have *Mobiluncus* morphotypes on gram stain are more likely to be symptomatic, have higher numbers of clue cells and positive "whiff" tests, and have vaginal immune and hydrolytic enzyme profiles, which are associated with a greater risk of preterm birth, Dr. Nyirjesy said.

A recent study led by Dr. Nyirjesy (Sex. Transm. Dis. 2007;34:197-202) found that significantly more patients on single-dose 2% clindamycin cream cleared *Mobiluncus* morphotypes than did patients on multiple doses of 0.75% metronidazole gel (97.5% vs. 80%).

Among women with *Mobiluncus* at baseline, clinical cure rates were significantly higher in those who received clindamycin (57.5% vs. 27%), but were not significantly different between treatment groups in women with no *Mobiluncus* at baseline (61% vs. 53%).

That information prompted audience members to question whether they should identify species on wet mount for all of their BV patients.

"The answer is absolutely not," he said. "The study shows that not all bacterial vaginosis is the same and that there may be different responses to antibiotics in women with BV."

He stressed that this last was a retrospective study from pooled data, and that marketing efforts notwithstanding, it was a preliminary paper that calls for further investigation. ■