Progress Toward Vaginal GBS Vaccine Is Seen

Colonization by group B streptococci is probably the single most important risk factor for neonatal sepsis.

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, said Dr. Hillier.

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," noted Dr. Hillier.

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, noting that the linear association between concentration of antibody and acquisition of GBS was especially robust in serotype III, one of the most common serotypes that colonize women.

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," said Dr. Hillier. To test this, she and her colleagues are 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." ■

Phenazopyridine Can Sub For Dye in Patency Test

BY MITCHEL L. ZOLER
Philadelphia Bureau

OTTAWA — The topical urinary tract analgesic phenazopyridine is a good marker for confirming ureteric patency, based on experience in 124 women at one center.

By staining the urine orange or red, a dose of phenazopyridine makes it easy to see urine leak from the ureter and is a good alternative to the standard color marker for urine, indigo carmine, Jane Hui said at the annual clinical meeting of the Society of Obstetricians and Gynaecologists of Canada.

"Phenazopyridine is easy to use, effective, safe, and inexpensive. Phenazopyridine is the agent of choice," said Ms. Hui, a researcher in the department of ob.gyn. at Queens University in Kingston, Ont. It is now used routinely before urogynecologic surgery at Kingston General Hospital.

Physicians at Kingston General were forced to find a new way to assess ureteric patency and bladder mucosal integrity for women undergoing urogynecologic surgery when indigo carmine became temporarily unavailable in Canada in 2004. Phenazopyridine is an oral drug that has been marketed for many years as an analgesic for patients with urinary tract infection. It has a long history of safety when used short term at the recommended dose of 200 mg. It appears in the urine within about an hour after oral dosing and turns the urine a distinctive color. The drug is sold in the United States as a generic, over-the-counter agent.

Ms. Hui and her associates reviewed case records for 124 women who were treated with phenazopyridine as a urine marker during 127 surgeries performed at Kingston General Hospital from July 2004 to June 2005. All patients were scheduled to receive either 100 or 200 mg of phenazopyridine, although this treatment could be objectively confirmed in only 32 cases.

In all 32 cases, the records confirmed successful determination of bilateral ureteric patency and bladder mucosal integrity during cystoscopy. The treatment was also well tolerated by all patients, and there were no anaphylactic reactions. It was unlikely that any postoperative complications were caused by phenazopyridine use.

A major advantage of phenazopyridine is its cost. In Canada, a 200-mg dose costs $0.29 compared with a $34.50 for a single dose of indigo carmine, which is now again available to Canadian physicians. ■

Topical Estradiol Gel Approved to Reduce Menopause Hot Flushes

BY ELIZABETH MECHCATIE
Senior Writer

A topical estradiol gel formulation has been approved for treating moderate to severe vasomotor symptoms associated with menopause. The gel is available under the trade name Elestrin from BioSante Pharmaceuticals Inc.

A transdermal product that is invisible is a good option "for women not wanting an oral product or where there's reason not to prescribe an oral product, and [for women who] are not keen on a visible patch," said Dr. Wulf Utian, the executive director of the North American Menopause Society, and a consultant in women's health at the Cleveland Clinic. There are other estrogen gel products marketed; the 0.87-g dose of Elestrin is the lowest available dose of a gel product.

The Elestrin label contains contraindications, precautions, and warnings that are standard for the entire class of estrogen products.

In a 12-week study comparing different Elestrin doses with placebo in 484 symptomatic menopausal women with at least 60 moderate to severe hot flushes per week, the frequency and severity of hot flushes were significantly reduced by week 4 in the women on the 1.7-g daily dose and by week 5 in the women on 0.87-g daily dose, compared with those on placebo. The reductions in severity and frequency remained significant compared with placebo at 12 weeks of treatment, at which time the women on the higher dose had a mean of about three hot flushes per day, those on the lower dose had a mean of about five per day, and those on placebo had a mean of about eight per day.

Elestrin is applied in a thin layer to the upper arm once a day, starting at the lower approved dose, 0.87 g/day (0.52 mg of estradiol). If needed, dosage can be increased to 1.7 g/day (1.04 mg estradiol). (One pump actuation of the Elestrin applicator delivers 0.87 g; two actuations deliver 1.7 g.)

As in other dose-comparison studies of estrogen products, the Elestrin study showed that the lower dose takes a little more time to be effective but then is almost as effective as the higher dose, said Dr. Utian, an investigator in the study. "You get virtually the same level of efficacy, but it just takes a week or so longer to kick in, so the recommendation in practice is to advise the women that a low dose may take a little longer to reach efficacy, but don't start swapping doses too soon for higher doses because it's worth waiting."

The general belief is that the lower the estrogen dose, the less likely it is that there will be side effects, such as thromboembolism; this is "probably true," but there are still no long-term data confirming this, he said.

Dr. Utian said he has no financial ties to BioSante Pharmaceuticals. ■