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# Reduction of Morbidity and Mortality Rates for Neonatal Group B Streptococcal Disease through Early Diagnosis and Chemoprophylaxis

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**Pregnant women, part of the term service population at Orlando Regional Medical Center, were screened for group B streptococci (GBS), using Lim Group B Strep Broth (GIBCO Laboratories, Madison, Wis.) and the Phadebact Strep B Test (Pharmacia Diagnostics, Piscataway, N.J.). Of the 803 women screened, 173 were confirmed as colonized with GBS at the time of admission in labor. Eighty of these women were treated with ampicillin at least 6 h prior to delivery. The remaining 93 women received no ampicillin. None of the infants born to the treated women was colonized with GBS at surface culture sites. Forty-three of the infants born to untreated women were colonized. Rapid identification of GBS colonization in women, combined with ampicillin chemoprophylaxis, significantly reduced vertical transmission of GBS.**

Group B streptococci (GBS) are a leading cause of serious bacterial disease in the newborn. Approximately 10 to 30% of all pregnant women are colonized with GBS (1, 4, 20). Although the incidence of serious infection in neonates is 0.2 to 0.4% (24), it is estimated that as many as 12,000 to 15,000 infants develop symptoms of early-onset (respiratory distress, sepsis) or late-onset (meningitis) GBS disease annually in the United States, with a mortality rate of 50% (3).

Current laboratory procedures for diagnosis of GBS disease fall into two major categories: procedures that identify bacteria from patient culture and procedures that identify antigens from body fluids. Conventional procedures for identification of bacteria from patient culture include the CAMP test (8), sodium hippurate hydrolysis (2), coagglutination (7, 11, 18, 21), latex agglutination (19, 22), and the precipitin test (16). Such procedures, which require initial growth and isolation of bacteria on primary blood agar plates followed by additional tests, in many cases are labor intensive and can result in diagnosis delayed by as much as 48 to 72 h after patient culture. These tests, furthermore, do not differentiate between infants who are asymptomatically colonized and those who are at risk of developing symptomatic GBS disease. As a consequence of such limitations, these procedures are more frequently used to confirm GBS colonization in infants than as aids for early diagnosis and clinical mangement of disease.

In recent years the sensitivities of coagglutination (9), latex agglutination (6, 10), and counterimmunoelectrophoresis (12, 23) have been refined to permit direct detection of GBS antigen in the body fluids of infected infants. Such procedures are rapid and accurate, but unfortunately are sensitive only in infants who already are diseased and have sufficient quantities of antigen in their body fluids for detection. The detection of body fluid antigen, while valuable in rapid confirmation of a diseased state, is of limited use in early diagnosis and prophylactic intervention of disease in newborn infants.

Recently we described a new procedure to rapidly and selectively identify maternity patients heavily colonized with GBS and considered to be at high risk of delivering infants symptomatic for early-onset GBS disease (13–15, 17). It was hypothesized in these previous reports that rapid identification of such high-risk women could be used to initiate early chemoprophylactic therapy. This paper presents results from a clinical study in which term pregnant women were rapidly diagnosed for GBS and either treated or not treated with ampicillin. The data show that early diagnosis of GBS infection combined with chemoprophylaxis is effective in interrrupting vertical transmission of GBS and in reducing the morbidity and mortality rates of GBS disease in newborn infants.

## MATERIALS AND METHODS

**Patient cultures.** A total of 803 term maternity patients, randomly selected from the service population at Orlando Regional Medical Center (ORMC) in Orlando (Orange County), Fla., were cultured for GBS as part of a screening study conducted from May 1984 to May 1985. Vaginal cultures were collected with sterile cotton-tipped applicators and transported in Port-A-Cul tubes (BBL Microbiology Systems, Cockeysville, Md.). Cultures were taken at one of six Orange County Health Department clinics at 36 weeks gestation and weekly thereafter until the women were admitted in labor to ORMC. Clinic cultures were processed at the Orlando Branch Laboratory, Florida Department of Health and Rehabilitative Services. GBS culture-positive women were recultured at the time of admission to ORMC and prior to delivery. Infants delivered from these women were cultured for GBS at two sites: oropharynx and umbilicus. Urines of all infants also were screened for GBS antigen by latex agglutination (Wellcogen Strep B Test; Wellcome Diagnostics, Research Triangle Park, N.C.). All hospital cultures were processed by the ORMC laboratory.

**Processing of cultures.** Maternal and infant culture swabs were processed as previously described (13–15, 17). Culture swabs were inoculated into 5 ml of Lim Group B Strep Broth (GIBCO Laboratories, Madison, Wis.), incubated at 36°C in 5% $CO_2$, and tested for the presence of GBS by coaggluti-

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nation (Phadebact Strep B Test; Pharmacia Diagnostics, Piscataway, N.J.) after 5 and 20 h of incubation. Maternal culture broths were heated to 90°C for 10 min in a dry bath prior to coagglutination testing to eliminate multiple coagglutination reactions caused by blood on culture swabs (14).

Coagglutination test results were interpreted as recommended by Pharmacia Diagnostics. Tests in which coagglutination was observed with the Strep B reagent but not the control reagent were considered positive for GBS. Negative tests were those in which no coagglutination was observed with either the Strep B reagent or the control reagent.

**Treatment of maternity patients.** Maternity patients found to be colonized with GBS at the time of admission to ORMC were randomly divided into two groups: test group and control group. Women in the test group were administered 1 g of ampicillin intravenously every 6 h until delivery. In no instance was ampicillin given less than 6 h before delivery. Women in the control group were not given ampicillin.

**Statistical analysis.** Statistical analysis of the data was performed by using chi square for contingency tables and Fisher's exact test.

## RESULTS

**Colonization rates and magnitudes.** Of the 803 pregnant women screened at the Orange County Health Department clinics in this study, 204 (25.4%) were found to be colonized with GBS. Of these 204 women, 173 remained GBS positive at the time of admission in labor at ORMC. Forty-eight of these 173 GBS-positive women had 5-h positive vaginal cultures and could be considered heavily colonized as observed in previous studies (13, 15); the remaining 125 women had 20-h positive vaginal cultures and were lightly colonized.

**Prophylactic efficacy.** Twenty-seven of the 48 heavily colonized women and 53 of the lightly colonized women received ampicillin chemoprophylaxis in this clinical study (Table 1). None of the infants born to these treated women had GBS detectable at either of the infant culture sites. In comparison, 16 (76%) of the infants born to the 21 untreated heavily colonized women had GBS detectable at one or more sites. Twenty-seven (38%) of the infants born to the 72 lightly colonized women were colonized with GBS. Ampicillin significantly ($P < 0.001$; chi square analysis) reduced the vertical transmission of GBS in treated patients.

**Characteristics of maternal and infant subjects.** Two of the women in the untreated heavily colonized control group developed chorioamnionitis. These two women delivered two infants who were urinary GBS antigen positive. One untreated heavily colonized woman developed both chorioamnionitis and endometritis. This woman gave birth to an infant with a GBS antigen-positive urine and GBS sepsis, confirmed by a GBS-positive blood culture. There were two other infants with GBS antigen-positive urines delivered from women in the untreated heavily colonized control group. One of these infants had symptoms of respiratory distress and a GBS-positive oropharyngeal culture.

Only one infant with a GBS antigen-positive urine was born to a woman in the untreated lightly colonized group. This infant was delivered from a woman who had chorioamnionitis. All women with chorioamnionitis or endometritis or both were treated after diagnosis and delivery with double-antibiotic (ampicillin and gentamicin) therapy.

None of the women in either of the treated subject populations (heavily colonized or lightly colonized) had chorioamnionitis or endometritis. No evidence of early-onset GBS disease (sepsis, respiratory distress) or GBS antigen-positive urine was documented among infants born to women in the treated groups. Infants delivered from ampicillin-treated women, furthermore, were monitored for late-onset GBS disease for at least 4 weeks after birth. None of these infants developed late-onset disease.

**Relevance of prophylaxis** A total of 803 term maternity patients were screened in this study. There was no evidence of early-onset GBS disease (sepsis, respiratory distress, GBS antigen-positive urine) among the 710 infants born during the study period to the 80 GBS-positive women treated with ampicillin and the 630 women who were screened, found to be GBS negative, and not treated. In comparison, six infants with GBS antigen-positive urines (two of these infants developed GBS sepsis or respiratory distress) were born to the 93 screened, untreated GBS-positive women. The difference in morbidity between these two groups (untreated GBS-positive women versus treated GBS-positive women and untreated GBS-negative women) is significant (6 of 93 versus 0 of 710; $P < 0.001$; Fisher's exact test, one-tailed).

The 803 women screened in this study constituted part of the 1,979 term service maternity patients admitted in labor to ORMC from May 1984 to May 1985. These participants were randomly selected from the term service population and there was no difference in socioeconomic status of screened and unscreened patients. During this period there were also 3,095 term private maternity patients admitted to ORMC.

There were no cases of early-onset GBS sepsis (as determined by GBS-positive blood cultures) among the 710 in-

TABLE 1. Effect of ampicillin prophylaxis on vertical transmission of GBS

| Group | No. of colonized infants/no. of colonized women | |
|---|---|---|
| | 5-h positive | 20-h positive |
| Test (treated) | 0/27 | 0/53 |
| Control (untreated) | 16/21[a] | 27/72[b] |

[a] This group of untreated 5-h positive women and infants included three women with chorioamnionitis, including one with endometritis, and five infants with GBS antigen-positive urines, including one with GBS respiratory distress and one with GBS sepsis.

[b] This group of untreated 20-h positive women and infants included one woman with chorioamnionitis who delivered an infant with a GBS antigen-positive urine.

TABLE 2. Incidence of neonatal GBS sepsis in infants delivered from term maternity patients at ORMC

| Neonatal GBS sepsis | | No. of births | Maternity population | |
|---|---|---|---|---|
| No. of cases (incidence)[a] | No. of deaths (incidence) | | No. | Group |
| 0 (0.00) | 0 (0.00) | 710 | 710 | Term service patients screened and found negative or positive and treated with ampicillin |
| 7 (5.49) | 3 (2.35) | 1,274 | 1,269 | Term service patients screened and found positive but not treated with ampicillin or not screened |
| 7 (2.25) | 1 (0.32) | 3,110 | 3,095 | Term private patients not screened or treated with ampicillin |

[a] Incidence is expressed as number of cases or deaths per 1,000 births.

fants born during the study period to the 80 GBS-positive women treated with ampicillin and the 630 women who were screened and found to be GBS negative (Table 2). In comparison, seven cases of neonatal GBS sepsis (incidence rate, 5.49 per 1,000 births) and three deaths resulting from such disease (incidence rate, 2.35 per 1,000 births) were recorded among the 1,274 infants born from the remaining 1,269 term service patients. These 1,269 service patients included the 93 women in the untreated study groups and 1,176 term service patients who were not participants in the screening for GBS.

Seven cases of neonatal GBS sepsis and one death were recorded among 3,110 infants born during the study period to the 3,095 term private maternity patients at ORMC. The incidence of GBS sepsis in this population was 2.25 cases per 1,000 births and the incidence of death from GBS sepsis was 0.32 death per 1,000 births.

## DISCUSSION

It has been shown in previous studies (5, 25) that ampicillin administered during labor to pregnant women successfully interrupts vertical transmission of GBS. However, it is neither practical nor necessarily desirable to nonselectively treat all pregnant women or even the large population of GBS-positive women with ampicillin prior to delivery. Although such blanket treatment may reduce the incidence of early-onset GBS disease in newborn infants, it also can lead to increased antibiotic resistance of bacterial pathogens, adverse maternal drug reactions, and other complications. Until recently only clinical criteria (premature labor or prolonged rupture of membranes or both, history of maternal fever, maternal intrapartum infection, etc.) could be used to identify high-risk women for chemoprophylaxis before delivery. These clinical criteria unfortunately are not highly selective. As a consequence, patients having these high-risk factors and not colonized with GBS are needlessly treated. Furthermore, such selection excludes from prophylaxis those women who have uncomplicated deliveries.

Conventional laboratory tests for identification of GBS are not useful in rapid and selective diagnosis of women at high risk of delivering infants with early-onset GBS disease. These laboratory tests are labor intensive and results generally are not available until 24 to 72 h after patient culture. The tests also do not differentiate between women at low risk and those at high risk of delivering infants symptomatic for GBS disease. Laboratory procedures that directly detect antigens in infant body fluids provide immediate results, but are of limited use in chemoprophylaxis.

Recently we reported a laboratory procedure to rapidly diagnose GBS colonization in women and infants (13–15, 17). This procedure uses an enriched, selective broth (Lim Group B Strep Broth) in combination with coagglutination to identify within 5 to 20 h women and infants colonized with GBS. In the current study the procedure was used to rapidly screen women in their last trimester and up to the time of hospital admission for GBS colonization. This information was used to treat colonized women before delivery. The results of this clinical study provide strong evidence that such confirmatory diagnosis of maternal GBS colonization combined with chemoprophylaxis successfully interrupts vertical transmission of GBS. Furthermore, it is important to note that in the study population a large proportion of infants with GBS antigen-positive urines or early-onset GBS disease or both was born to heavily colonized women. The women's vaginal cultures were identified within 5 h of inoculation into Lim Group B Strep Broth. Although 21.5% (173 of 803) of the women were GBS positive at the time of admission to ORMC, only 6.0% (48 of 803) of all admitted women were heavily colonized. These heavily colonized women could be considered to be a high-risk group for delivering infants with symptomatic GBS disease. Only one infant with a GBS antigen-positive urine was born in the group of lightly colonized women. Because this infant was delivered from a woman who had chorioamnionitis, it may be recommended that selective treatment be extended to include lightly colonized women who present complications in pregnancy.

The ability to rapidly identify GBS colonization levels in women prior to delivery and the significance of this finding are supported in this study. Such a predictive ability, with early treatment when indicated, plays an important role in the prevention of early-onset GBS disease in the newborn.

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