Invasive Disease Due to Group B Streptococcus in Pregnant Women and Neonates from Diverse Population Groups

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From 1993 through 1996, surveillance for invasive disease due to group B Streptococcus (GBS) in neonates aged <7 days and in peripartum pregnant women was performed in a racially and ethnically diverse cohort in 4 cities in the United States. In a birth population of 157,184, 130 neonatal cases (0.8 per 1000) and 54 maternal cases (0.3 per 1000) were identified. Significant correlates with neonatal disease were black or Hispanic race and a birth weight <2500 g. The attack rate for peripartum maternal infection varied widely by city and may have been influenced by the frequency of administration of intrapartum antibiotics or of evaluating febrile women by performance of blood cultures. Pregnancy loss or GBS disease in the infant occurred in 28% of these maternal cases. Among neonatal and maternal GBS isolates, serotypes Ia (34%–37%) and III (25%–26%) predominated, and type V was frequent (14%–23%). These results provide a description of invasive GBS perinatal infection during the period in which guidelines for prevention were actively disseminated.

Since the 1970s, group B Streptococcus (GBS) or Streptococcus agalactiae has been appreciated as a leading cause of perinatal infection. In neonates aged <7 days, manifestations of GBS infection frequently include septicemia or pneumonia and, less often, meningitis. In infants aged from 7 days to 3 months, bacteremia with or without a focus is often the major clinical feature of infection, but meningitis is frequent [1]. In peripartum women, GBS is thought to contribute to urinary tract infection, chorioamnionitis, endometritis, and sepsis, as well as to preterm labor and premature birth [1–4].

In 1990 the attack rate for early-onset GBS infection in the United States was 1.8 per 1000 live births, with a mortality rate of 6% [5]. More recent surveillance documents a decrease in incidence to 0.8 per 1000 live births, a reflection of increased use of intrapartum maternal antibiotic prophylaxis [6, 7]. Comparable information regarding attack rates for GBS disease in pregnant women is not available.

This study was designed with 3 aims: (1) to determine attack rates for invasive GBS infection in neonates during the first week of life (early-onset disease) and among parturient women admitted for anticipated delivery; (2) to assess risk factors for early-onset disease; and (3) to define the serotype distribution of GBS isolates associated with invasive perinatal infections. After this study was designed in 1992, several recommendations were advanced outlining methods to reduce early-onset neonatal infection through administration of maternal intrapartum antibiotics, based either on antenatal culture screening or on the presence of maternal risk factors [8–10].

The Centers for Disease Control and Prevention issued guidelines for prevention of early-onset GBS infection in the spring of 1996 [11]. These recommendations were endorsed by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics [12, 13]. Since our study took place during this period of evolving GBS-prevention recommendations, we had an opportunity to assess whether the attack rates for perinatal GBS disease in our surveillance hospitals were changing over time.

Methods

This was a multicenter, prospective, active surveillance study in 12 hospitals in 4 cities during January 1993 through December 1996. In Houston, participating facilities included Ben Taub General Hospital, a county facility for indigent and some Medicaid patients; and the Methodist Hospital, St. Luke’s Episcopal Hospital, and Texas Children’s Hospital, facilities for self- and third-
party payors. In Minneapolis/St. Paul, 1 facility for indigent care (Hennepin County Hospital) and 5 for self- and third-party payors (Abbott Northwestern, Fairview Southdale, North Memorial, and United and University Medical Center hospitals) participated. In Seattle, patients were enrolled at Swedish Hospital, a private facility, and the University of Washington Medical Center, a hospital providing private and indigent care. In Pittsburgh, the Magee-Women’s Hospital, a county facility, participated in the active surveillance program. These hospitals were selected to represent ethnically and economically diverse populations.

Neonatal and maternal cases were identified by weekly review of the microbiology laboratory records of each participating hospital by study personnel, to identify recovery of GBS from specimens from otherwise sterile body sites (excluding urine) collected during routine care. Neonatal early-onset disease was defined by isolation of GBS from blood, CSF, or other usually sterile body sites (i.e., lung, liver, or spleen) during the first 6 days of life. Among pregnant women, a case was defined by isolation of GBS from blood or another usually sterile site (except urine) during hospitalization, 7 days before or after delivery.

In order to determine attack rates of infection, the total number of births and deliveries at participating hospitals was obtained from each hospital or the relevant department of public health. Total births by racial/ethnic group and birth weight also were ascertained.

Table 1. Occurrence of early-onset neonatal disease due to group B streptococci, by year, city, race/ethnicity, and birth weight.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of cases</th>
<th>No. of births</th>
<th>Attack rate/100 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>38</td>
<td>38,890</td>
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</tr>
<tr>
<td>1994</td>
<td>24</td>
<td>37,519</td>
<td>0.64</td>
</tr>
<tr>
<td>1995</td>
<td>39</td>
<td>40,084</td>
<td>0.97</td>
</tr>
<tr>
<td>1996</td>
<td>29</td>
<td>40,691</td>
<td>0.71</td>
</tr>
<tr>
<td>City</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Houston</td>
<td>62</td>
<td>47,252</td>
<td>1.31</td>
</tr>
<tr>
<td>Minneapolis/St. Paul</td>
<td>46</td>
<td>81,805</td>
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<td>Seattle</td>
<td>7</td>
<td>10,850</td>
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</tr>
<tr>
<td>Pittsburgh</td>
<td>15</td>
<td>17,277</td>
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</tr>
<tr>
<td>Race/ethnicity</td>
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<td></td>
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<tr>
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<td>49</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Asian</td>
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<tr>
<td>Other/unknown</td>
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<td>Birth weight, g</td>
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<tr>
<td>&lt;2500</td>
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<td>15,059</td>
<td>2.06</td>
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<tr>
<td>≥2,500</td>
<td>97</td>
<td>142,052</td>
<td>0.70</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>82</td>
<td></td>
</tr>
</tbody>
</table>

Results

From January 1993 through December 1996, 130 neonatal and 54 maternal cases were identified. The distribution of cases by year, birth weight, city, and race/ethnic origin is summarized in table 1. Among infant cases, the onset of illness occurred at or within 24 h of birth in 78 (61%), at 24–48 h in 42 (32%), and after 48 h in 10 (8%). Seventy-five (58%) of the infants were male and 55 were female; 91 (70%) were delivered vaginally and 41 by cesarean section. Most infants (111 [85%]) had GBS isolated only from blood; a few (9 [7%]) had bacteremia and isolation of GBS from the CSF; and 4 (3%) had GBS isolated from CSF but not blood. For 6 infants, only the lung, spleen, or liver cultures were positive. Meningitis was documented in 13 infants (10% of cases).

The overall attack rate for early-onset neonatal disease was 0.8 per 1000 births but ranged from 0.6 per 1000 births in Minneapolis/St. Paul to 1.3 per 1000 in Houston. The Minneapolis/St. Paul attack rate was significantly lower than the Houston rate after adjustment by logistic regression for maternal racial/ethnic origin and year of birth (relative risk [RR], 0.57; 95% CI, 0.35–0.93; P < .025). None of the other cities’ rates were significantly lower than the rate in Houston.

In each year studied, the attack rate for early-onset disease was lower than it was in 1993; however, this trend was not statistically significant. This observed decrease resulted in large part from the progressive and extensive decline in the attack rate for such disease in Houston (1993, 1.6 per 1000; 1994, 1.0 per 1000; 1995, 0.4 per 1000; and 1996, 0.4 per 1000; P = .07, Cochran-Mantel-Haenszel trend test).

The race/ethnicity of the active-surveillance obstetrical populations was diverse, varying between cities and between hospitals within the same city. Whites accounted for 27% of parturients in Houston, 78% in Minneapolis/St. Paul, 69% in
Seattle, and 81% in Pittsburgh. Black women accounted for 18% of study participants in Houston, 12% in Minneapolis/St. Paul, 13% in Seattle, and 16% in Pittsburgh. Although 51% of patients in Houston patients were Hispanic, this ethnic group accounted for only 0.1%–6% of women in the 3 other cities. Asian participants were few in Pittsburgh (0.1%) but accounted for 3%–6% of women in the 3 other cities.

Maternal race/ethnicity was a significant correlate of risk for early-onset GBS disease after adjustment for city and year. Attack rates for infants born to black and Hispanic mothers were higher than those for infants born to white mothers. Adjusted relative risks for race/ethnicity were 2.1 for blacks (95% CI, 1.29–3.44; \( P = .003 \)) and 2.0 for Hispanics (95% CI, 1.13–3.56; \( P = .02 \)). The attack rate among infants born to Asian mothers was also higher than that among infants born to white mothers (RR, 1.7; 95% CI, 0.67–4.30; \( P = .26 \)), but closer examination of the data indicated that this ambiguous result was produced by a high attack rate among Asian infants born in Houston in 1993 (3/289), in contrast to uniformly lower attack rates in other cities and in Houston for other years.

Birth weight was also a significant correlate of neonatal early-onset GBS disease. Among neonates weighing >2500 g at birth, the attack rate was 2.1 per 1000 births (31 cases among 15,050 births), compared with 0.7 per 1000 births (97 cases among 142,052 births) among infants with birth weights >2500 g. The birth weight of 2 affected neonates was not available. The RR of early-onset GBS disease among low-birth-weight neonates, after adjustment for city and year of birth, was 3.0 (95% CI, 2.00–4.49; \( P < .001 \)).

Twenty deaths occurred in 127 infant cases for which the outcome was available, resulting in a case-fatality ratio of 16%. Low birth weight was associated with higher mortality (\( P < .01 \) in test of trend). Thirteen (65%) of the deaths were among the 31 infants weighing >2500 g at birth, resulting in a case-fatality rate of 42%. Seven of the 94 infants who weighed >2500 g died, yielding a case-fatality rate of 7%.

The additional surveillance for early-onset GBS disease in neonates hospitalized at facilities in the catchment area of our 12 participating hospitals detected no affected infants who were born at a surveillance hospital and were then discharged and admitted to 1 of these facilities during 19 months of monitoring. Early-onset cases were reported among the birth populations of these catchment area hospitals, suggesting that this surveillance method was reasonably accurate.

There were 54 maternal cases of GBS infection, resulting in an attack rate of 0.3 per 1000 deliveries. The attack rates varied much more widely by city than did the rates for neonatal infection, ranging from 0.1 per 1000 in Pittsburgh (2 cases) and Minneapolis (8 cases) to 0.2 per 1000 in Seattle (2 cases) and 0.8 per 1000 in Houston (42 cases). Fifty-two women (96% of cases) were bacteremic, and 2 in Seattle had GBS isolated from amniotic fluid obtained by amniocentesis with intact membranes.

The racial/ethnic distribution of maternal cases was 8 whites, 12 blacks, 25 Hispanics, 3 Asians, and 6 other or unknown. Seven women (13%) were aged <20 years, 29 (54%) were aged 20–29 years, 14 (26%) were aged 30–39 years, and 4 were aged >40 years. The route of delivery was vaginal for 37 (78%), cesarean section for 16, and unknown for 1. There were no maternal deaths. The fetal outcome in the 54 maternal cases included 12 pregnancy losses (22%). Of these 12, 8 were classified as abortions because death occurred before 20 weeks of gestation, and 4 were stillbirths. The study population included 3 GBS-infected mother-neonate pairs. Thus, 28% of maternal cases were associated with pregnancy loss or birth of an infant who developed early-onset GBS disease.

Houston accounted for 78% of the maternal cases and 50% of the neonatal cases. This discrepancy, as well as the generally low observed attack rate for maternal peripartum GBS infection, may have resulted from the lack of uniform practices regarding the collection of blood culture specimens from febrile women and/or the use of intrapartum antibiotics in some of the surveillance institutions. It is not possible to distinguish the effect of these potential confounders from a true difference in attack rates within these populations.

Serotyping for capsular polysaccharide and C-protein antigens in GBS isolates from 129 infant and 53 maternal cases was performed. The capsular polysaccharide type distribution of GBS isolates from these cases is summarized in figure 1. For neonatal cases, serotypes Ia (37%), III (26%), and V (14%) predominated. These 3 serotypes were also the most prevalent among maternal isolates (81% of cases). No significant differences in serotype distribution by city or racial/ethnic origin were observed. One isolate from an infant was of serotype VII, a newly described serotype. There were 3 affected mother-neonate pairs, and the maternal and infant serotypes in each pair were concordant. Each infant isolate could be typed, and only 2 of 53 maternal strains were nontypable.

C-protein antigens were present in 98% of serotype Ia, 92% of serotype Ib, 47% of serotype II, and 11% of serotype V isolates from infants and pregnant women. \( \alpha \) protein was detected in each of the C-protein–containing strains, whereas \( \beta \) protein was found with \( \alpha \) protein only in type Ib strains. No serotype III isolate was found to contain a C-protein antigen.

Discussion

Our study provides a prospective appraisal of the epidemiology of neonatal and maternal GBS disease from 1993 through 1996. The results, while in many ways confirming previous studies that revealed that black race [5, 18] and low birth weight [5] were risk factors for early-onset GBS infection in neonates, extend these data into the mid-1990s in a large birth cohort that is geographically and racially/ethnically quite diverse. In addition, we have discovered enhanced risk for early-onset GBS disease among Hispanic infants. This result was surprising, be-
cause it has been reported that GBS colonization during pregnancy is significantly less frequent in Hispanics than in whites [19, 20].

However, a recent study in Houston demonstrated that colonization in pregnant Hispanic women exceeded that in whites [21]. The explanation for the increased risk for early-onset disease in infants born to Hispanic women will require additional studies.

We, like others [22, 23], have documented a shift in serotype prevalence, with the appearance of serotype V, which accounted for 14% and 23% of neonatal and maternal cases, respectively. In contrast to the report by Lin et al. [24] that showed geographic variability in the frequency of type V, in our population representing the southwestern, northwestern, midwestern, and northeastern United States, serotype V was consistently the third most frequent isolate. We also have demonstrated a corresponding increase in the prevalence of serotype Ia and decline in serotype II strains as a cause of perinatal GBS disease. Serotype III, the dominant serotype associated with neonatal GBS disease in the 1970s [25, 26], continues to be prominent, and less common serotypes or nontypable strains are rare.

These data regarding serotype distribution are crucial for formulation of an appropriate multivalent GBS polysaccharide-protein conjugate vaccine. A vaccine formulation containing GBS capsular types Ia, III, and V would be expected to cover ~80% of invasive infant and maternal disease, whereas the addition of type II would increase this to ~90%. Because nontypable and rare GBS serotypes (IV, VI, VII, and VIII) remain uncommon in invasive perinatal disease, an efficacious pentavalent GBS vaccine potentially could provide protection against 96%–99% of infections.

Conclusions from 4 years of surveillance of early-onset GBS disease representing >150,000 births are that overall attack rates were less than the rate of ~2 per 1000 live births predicted from many prior years of surveillance at these same institutions. Attack rates decreased from their 1993 baseline, albeit not significantly, an occurrence which corresponded with the publication of guidelines for prevention of early-onset GBS disease through maternal intrapartum antibiotic administration [11–13]. Our inability to demonstrate a significant decline in the incidence of early-onset disease was probably related to the relatively small birth population in which we attempted to detect significant trends over time. A similar and significant decline during 1993–1995 was reported from other surveillance sites in the United States for a birth cohort of >190,000 [27].

Significant correlates with attack rates in our study were city (with Minneapolis/St. Paul having a significantly lower rate than Houston), racial/ethnic group (with blacks and Hispanics having the highest disease rates), and low birth weight. Although the attack rates were 3 times higher for infants weighing <2500 g at birth, it is important to note that >75% of cases continue to involve larger infants [1, 5, 6, 26]. The contribution of intrapartum antibiotic prophylaxis and the potential for further reduction in attack rates, with increased compliance with

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**Figure 1.** Distribution of serotypes among isolates from neonates aged ≤7 days (n = 129) and pregnant women (n = 53) with invasive group B streptococcal infections (NT, nontypable). For each patient group, percentage of strains of each serotype is indicated (except for type VII [0.7%] in neonates and type Ib [1.9%] in pregnant women).
recommended guidelines for antibiotic prophylaxis in defined groups of pregnant women, cannot be determined from these data.

The declines in attack rate for early-onset disease at our surveillance sites are likely to have been influenced by the introduction of guidelines for GBS screening and intrapartum antibiotic administration [9–11]. Institutions and practitioners at our surveillance hospitals adopted these standards in different ways and at different time points after the initial recommendations in 1992 [9] and then after the 1996 consensus guidelines were devised [11, 12]. For example, at the Houston hospital with the highest attack rate for early-onset GBS disease in 1993, guidelines were introduced late in 1994, followed by a precipitous drop in cases in 1995 and 1996.

Although we observed a trend toward decreasing neonatal cases in each year after 1993, it is difficult to point conclusively to an effect of the guidelines from this study because of the heterogeneity of obstetrical practice. Our surveillance would indicate that cases are still occurring, although at decreased frequency, and while preterm, low-birth-weight babies remain at highest risk, term neonates continue to account for the majority of cases.

McLaren et al. [28] focused on term deliveries in a study in Illinois and concluded that intrapartum antibiotic administration based on maternal obstetric factors—including rupture of membranes for ≥18 h, intrapartum fever (temperature ≥38°C), and a history of giving birth to an infant with GBS sepsis—prevented only 10% of the GBS infections in term infants. In their case-control study, longer duration of labor and rupture of membranes were significant risk factors, but rupture of membranes was for >18 h in only 2 of their 21 cases.

Our data also provide a contemporary assessment of maternal peripartum GBS disease, but interpretation of the results and calculation of attack rates had to be tempered by the case-finding method. This was not a study of all peripartum complications but rather an evaluation of maternal GBS bacteremia in febrile women. Although we did not attempt to document the frequency of performance of blood cultures for febrile parturients, we suspect substantial variability in this practice between and within surveillance hospitals. The dramatic difference in attack rates by city is consistent with this hypothesis.

Therefore, conclusions about differences in attack rates by racial/ethnic origin or maternal age suffer from ascertainment problems. However, invasive GBS infection in a mother was associated with a poorer outcome for the fetus, with a pregnancy loss rate of 22%, including stillbirths. Concomitant invasive GBS disease was detected in 3 mother-infant pairs (with no deaths), in which, not unexpectedly, the serotypes were concordant.

Although the observed trend toward decreasing numbers of cases of early-onset GBS disease in neonates probably reflects increasing compliance with GBS-prevention guidelines, early-onset cases are still occurring, especially among term infants. In spite of the progress achieved with this interim prevention strategy, there is concern that intrapartum antibiotic use for an estimated 25% of pregnant women may lead to the emergence of antibiotic-resistant GBS [26].

For these reasons, we believe that future prevention efforts should include development of a multivalent vaccine [22–24] that should, on the basis of our own data and those of others, contain at least 4 of the GBS capsular types (Ia, II, III, and V). Meanwhile, surveillance as performed in this and other studies [6, 23] needs to continue. We believe that ongoing analyses of risk factors and of the efficacy of maternal chemoprophylaxis will continue to support a vaccine-based prevention strategy for GBS disease in pregnant women and neonates [26].

References


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