MAJOR ARTICLE

Prematurity Is the Major Risk Factor for Late-Onset Group B Streptococcus Disease

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A case-control study was conducted in the greater Houston area to determine risk factors for late-onset group B streptococcus (GBS) disease (onset of disease or first positive culture between 7 and 180 days after birth). Characteristics of 122 case patients diagnosed during 1995–2000 were compared with control subjects matched for birth hospital and date of birth. Half the case patients were preterm infants, 84% of whom were born at <34 weeks of gestation. The risk for late-onset GBS disease increased by a factor of 1.34 (95% confidence interval [CI], 1.15–1.56) for each week of decreasing gestation, by 3.70 (95% CI, 1.35–10.1) for infants of black mothers, and by 4.15 (95% CI, 1.27–13.60) for infants of mothers with a positive GBS screening. These risk factors are similar to that of early-onset GBS disease. However, prematurity is the major risk factor for late-onset GBS disease.

Group B streptococcus (GBS) is the most common cause of neonatal sepsis and meningitis. Two forms of GBS disease are recognized: early-onset disease (onset at <7 days after birth) and late-onset disease (onset ⩾7 days after birth). The incidence of late-onset GBS disease ranged from 2 cases/1000 live births in Birmingham, Alabama [1] to ~0.5 cases/1000 in metropolitan Atlanta [2] and in a multistate surveillance [3]. The widespread use of intrapartum antibiotic prophylaxis has reduced early-onset GBS disease by 70%, from 1.7 cases/1000 live births in 1993 to 0.5 cases/1000 in 1999. During the same period, the incidence of late-onset GBS disease appeared to be unchanged [3]. Late-onset disease accounts for ~50% of GBS disease in neonates and infants.

The epidemiology of early-onset GBS disease has been well described; data on late-onset GBS disease are mostly from case reports or from descriptions of only a modest number of case patients. Maternal complications during labor play a less important role in late-onset disease, compared with that in early-onset disease [1]. Evidence supports nosocomial acquisition [4–9] or transmission of GBS through breast milk [10–13]. Others have reported hospitalization [14] or human immunodeficiency virus (HIV) infection [15] as risk factors for late-onset GBS disease. A study in Atlanta during 1982 and 1983 revealed that black race and a maternal age <20 years were independently associated with a risk for late-onset GBS disease [2].

As part of a multicenter GBS study sponsored by the National Institute of Child Health and Human Development [16], a prospective active surveillance of GBS disease in neonates and infants was conducted from July 1995 through June 2000 in all hospitals in a radius of 50 miles of the Texas Medical Center (Houston). Using a case-control design, we conducted chart reviews during 2000 and 2001 to evaluate maternal and infant risk factors associated with late-onset GBS disease.

SUBJECTS AND METHODS

Case and control subjects. Infants with late-onset GBS disease (case patients) were identified by active weekly surveillance of all microbiology laboratories ($n = 35$) serving the hospitals of the greater Houston area within a 50-mile radius of the Texas Medical Center. Laboratories that sent out cultures for processing

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were included. Case patients were diagnosed between July 1995 and June 2000 by isolation of GBS from the blood or cerebrospinal fluid (CSF) and onset of illness or the collection of the first positive culture between 7 and 180 days after birth. The study was approved by the institutional review board of each participating hospital and was exempted from the requirement of obtaining consent from parents, because it involved retrospective chart review and no personal identifiers were obtained.

Case-control study. A case-control design assessed risk factors associated with late-onset GBS disease. For each case patient, an infant without GBS disease was selected as a control subject by locating the case patient in the delivery log and searching records of infants above and below until finding one who had no GBS disease, and whose maternal and birth records were available for review. Stillbirths and infants born at <20 weeks of gestation or having a birth weight <500 g were ineligible for the study. When both twins had late-onset GBS disease, only the first-born infant was included in the analysis.

Statistical analysis. Medical records of 145 infants for the treatment of late-onset GBS disease were reviewed to confirm the disease status and to obtain clinical data. Maternal and newborn medical records at the birth hospitals were reviewed by chart abstractors who were unaware of the disease status of the infants to obtain demographic, clinical, and labor and delivery data. Maternal and infant characteristics of case patients were compared with those of control subjects by use of the χ^2 test for categorical variables and the Wilcoxon sign-rank test for continuous variables. Conditional logistic regression was used to account for the matching of case patients and control subjects by birth hospital, to assess the risk factors associated with late-onset GBS disease. Maternal and infant characteristics associated with case patients, at a significance level of $P < .10$ in univariate analyses, were considered to be potential confounding variables. For conditional regression analyses, we selected forwardly from all variables with a $P < .10$ and entered gestational age as a continuous variable. A trichotomous variable was used to account for a GBS screening that was positive or negative, or not being screened (including screened, but result was missing). Because the receipt of intrapartum antibiotics was strongly associated with a positive GBS culture of mothers, of these 2 variables, only a positive GBS culture was allowed in the final regression model. All statistical analyses were 2-tailed, and the threshold of statistical significance was $P < .05$.

RESULTS

A total of 145 infants, including 2 sets of twins with late-onset GBS disease, were identified with an estimated annual incidence of 0.38 cases/1000 live births. Twenty-three infants were ex-

Table 1. Maternal and infant characteristics of infants with late-onset group B streptococcus (GBS) disease (case patients) and infants without GBS disease (control subjects).

Characteristics	Case patients (n = 122)	Control subjects (n = 122)	P
Infants			
Male	67 (54.9)	58 (47.5)	.25
Gestational age <37 weeks	61 (50.0)	18 (14.8)	<.001
APGAR score			
1 min ≤6	36 (29.5)	9 (7.4)	<.001
5 min ≤6	13 (10.7)	3 (2.5)	.01
Multiple births	12 (9.8)	2 (1.6)	.006
Sepsis diagnosis <7 days of life	75 (61.5)	45 (36.9)	<.001
Antibiotics after birth	52 (42.6)	16 (13.1)	<.001
Mothers			
Age <20 years	31 (25.4)	27 (22.1)	.55
Race/ethnicity			
Black	49 (41.2)	28 (23.1)	.003
White	35 (29.4)	41 (33.9)	.46
Hispanic	33 (27.7)	48 (39.7)	.05
Gravida 1	54 (44.3)	46 (37.7)	.29
Para 0	74 (60.7)	58 (47.5)	.04
Single/never married	62 (50.8)	44 (36.4)	.02
Abortion ≥1	34 (27.9)	34 (27.9)	1.0
Prenatal care	119 (98.4)	121 (99.2)	.56
Medicaid/public assistance	53 (44.2)	56 (46.3)	.74
Prenatal conditions			
Antibiotics	40 (35.4)	20 (17.7)	.003
Any cultures performed	106 (95.5)	102 (94.4)	.72
GBS screening	68 (55.7)	77 (63.1)	.24
Positive GBS culture	26 (38.2)	13 (16.9)	.02
Amniocentesis	11 (9.2)	7 (5.9)	.34
Ever diagnosed with diabetes	8 (6.6)	7 (5.7)	.79
Diabetes during this pregnancy	8 (6.6)	6 (4.9)	.58
Hypertension	24 (19.7)	20 (16.4)	.51
Exposure to substance	12 (10.0)	10 (8.3)	.64
HIV infected	2 (1.6)	1 (0.8)	.56
Corticosteroid therapy	36 (29.8)	5 (4.1)	<.001
Labor			
No labor	20 (16.5)	7 (5.7)	.008
Spontaneous ROM	43 (35.3)	36 (29.5)	.34
ROM ≥18 h	19 (15.7)	8 (6.6)	.03
Any procedures	31 (25.8)	54 (44.3)	.005
Maternal fever	7 (5.9)	10 (8.3)	.47
Antibiotics	46 (37.7)	25 (20.7)	.003
Any cultures performed	22 (18.3)	15 (12.4)	.20
Positive GBS culture	4 (3.3)	0 (0)	.04
Corticosteroid therapy	8 (6.6)	1 (0.8)	.02
Cesarean delivery	52 (42.6)	29 (23.8)	.002

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Percentages were calculated based on nonmissing data. HIV, human immunodeficiency virus; ROM, rupture of membrane.

Table 2. Conditional logistic regression analysis of risk factors associated with late-onset disease caused by group B streptococcus (GBS) in 122 case patients vs. 122 control subjects, matched by birth hospitals and date of birth.

Risk factor	OR (95% CI)
Prematurity by decreasing week of gestation	1.34 (1.15–1.56)
Mother who is black	3.70 (1.36–10.1)
Mother with positive GBS culture	4.15 (1.27–13.60)

NOTE. CI, confidence interval; OR, odds ratio.

cluded from the analysis because of home birth ($n = 3$), unavailable medical records ($n = 9$), unknown birth hospitals ($n = 9$), or second-born twin if both twins had late-onset GBS disease ($n = 2$). Therefore, this analysis included 122 case patients and 122 control subjects (table 1).

Characteristics of infants with late-onset GBS disease. Blood samples for culture were obtained from all 122 case patients, and CSF samples were obtained from 117 case patients; 85 had GBS isolated from blood, 10 from CSF, and 27 from both CSF and blood. Sixty-seven (54.9%) case patients were male, and 61 (50%) were born at <37 weeks of gestation. Of the 61 preterm case patients, 51 (83.6%) were born at <34 weeks of gestation. The onset of disease ranged from 7 to 137 days (median, 38.5 days).

In univariate analysis, compared with control subjects, case patients were more likely to have been born at <37 weeks of gestation ($P < .001$), to have an APGAR score at 1 min ≤6 ($P < .001$), to have been a product of multiple births ($P = .006$), to have a diagnosis of sepsis during the first 7 days after birth ($P < .001$), or to have been treated with antibiotics after birth ($P < .001$).

Characteristics of mothers of case patients. Maternal age, gravidity, history of abortion, and receipt of Medicaid or public assistance were comparable between mothers of case patients and control subjects (table 1). Prenatal care was recorded for >98% of mothers of case patients and control subjects. Prenatal GBS screening was recorded for 56% of case patients and in 63% of control subjects ($P = .24$). Characteristics that occurred more frequently among mothers of case patients, compared with those of mothers of control subjects, included being black ($P = .003$), being single or unmarried ($P = .02$), nulliparity ($P = .04$), having a positive prenatal GBS screening ($P = .004$), receipt of corticosteroid therapy ($P < .001$) or antibiotic treatment ($P = .003$) during the index pregnancy, no labor onset ($P = .008$), rupture of membranes at ≥18 h ($P = .03$), receipt of intrapartum antibiotics ($P = .003$), receipt of corticosteroid therapy during the index labor ($P = .02$), and Cesarean delivery for the index pregnancy ($P = .002$). During the index pregnancy and labor, 80 (65.6%) mothers of case patients, compared with 40 (32.8%) mothers of control subjects, had at least 1 risk factor for early-onset GBS disease (e.g., positive GBS screening, maternal fever [temperature >38.0°C], rupture of membranes at ≥18 h, having previously delivered infants with GBS disease, or delivered at <37 weeks of gestation) ($P < .001$). However, mothers of case patients were less likely than mothers of control subjects to have had intrapartum procedures (e.g., fetal scalp electrode, fetal scalp sampling, amniocentesis, or intrauterine pressure catheter; $P = .005$).

Multivariate analyses. After adjusting for variables with P values ≤.10 in univariate analyses shown in table 1, the results indicate that preterm birth, mother who is black, and mother with positive GBS culture were significantly related to the risk for late-onset GBS disease. The risk of late-onset GBS disease increased by a factor of 1.34 (95% confidence interval [CI], 1.15–1.56) for each week of decreasing gestation, by 3.70 (95% CI, 1.36–10.1) for infants born to mothers who are black, and by 4.15 (95% CI, 1.27–13.60) for infants born to mothers with a culture positive for GBS (table 2).

Analyses of infants born at ≥37 weeks of gestation. Of the 122 case patients, 61 were born full term; of these 61 full-term infants, 52 were matched to 52 control subjects by gestational age and birth hospital (table 3). In univariate analyses, case patients were more likely to be male (53.9% vs. 34.6%; $P = .05$). Mothers of case patients were more likely to be single/unmarried (50.0% vs. 33.3%; $P = .09$) or black (38.0% vs. 17.3%; $P = .02$), to have had a positive prenatal GBS screening (23.1% vs. 5.8%; $P = .01$), or to have received intrapartum antibiotics during the index pregnancy (32.7% vs. 17.3%; $P = .07$). In conditional logistic regression analyses, after adjusting for these variables, the results indicate that black mothers or mothers with a positive GBS culture remained significant as risk factors. The risk for late-onset GBS disease increased by a factor of 3.83 (95% CI, 1.00–14.60) for infants born to black mothers and by a factor of 5.37 (95% CI, 1.11–26.00) for infants born to mothers with a positive GBS culture. Furthermore, the risk for late-onset GBS disease increased by a factor of 2.81 for male infants (95% CI, 0.99–7.94; $P = .05$).

DISCUSSION

Investigators have previously reported that preterm birth, mothers who are black, or mothers with positive GBS culture

Table 3. Conditional logistic regression analysis of risk factors associated with late-onset disease caused by group B streptococcus (GBS) in 52 full-term case patients vs. 52 full-term control subjects matched by birth hospital.

Risk factor	OR (95% CI)
Male infant	2.81 (0.99–7.94)
Mother who is black	3.83 (1.00–14.60)
Mother with positive GBS culture	5.37 (1.11–26.00)

NOTE. CI, confidence interval; OR, odds ratio.

are risk factors for early-onset GBS disease [2, 17]. This study also demonstrated that these risk factors are associated with late-onset GBS disease.

The result of our analyses showed that prematurity is the major risk factor for late-onset GBS disease. Each week of decreasing gestation incurs an increased risk by a factor of 1.34 for late-onset GBS disease. The factor of 1.34 is multiplicative, so that the risk of a 30-week-old infant to develop late-onset GBS disease, compared with that of a 37-week-old infant, is multiplied by a factor of 7.76 $(1.34)^7$. Other risk factors also can be combined with that from gestation in a multiplicative manner, so that the risk of a 30-week-old infant born to a black mother who tested positive for GBS is increased by a factor of 119.15 ($7.76 \times 3.70 \times 4.15$), compared with a 37-week-old infant born to a nonblack mother who tested negative for GBS. The linear model does not assume any particular reference gestational age. The effect of gestation applies equally across all gestational ages.

The effect of gestational age on the risk of GBS disease could be explained by the amount of maternal IgG antibodies received by the infant, because susceptibility to invasive GBS disease has been correlated with deficiency in levels of maternal type-specific serum IgG antibodies [18–20]. Neonates whose mothers had levels of IgG GBS type Ia antibody ≥ 5 μg/mL had an 88% lower risk, compared with those whose mothers had levels <0.5 μg/mL [16]. The transfer of maternal IgG antibodies is age related; in infants born at >34 weeks of gestation, cord serum GBS type-specific IgG antibody levels were ~75%–80% of maternal level [16, 21], whereas, in infants born at <34 weeks of gestation, the cord serum GBS type-specific IgG antibody levels were 20% of maternal level [16]. Infants born prematurely, especially those at <34 weeks of gestation, receive low maternal IgG antibody and are at increased risk of early-onset GBS disease [16].

We showed that a mother with positive GBS culture has significant risk for having an infant with late-onset GBS disease. Maternal GBS carriage has been shown to persist for weeks to months [15, 22–23]. It is plausible that mothers with a positive prenatal GBS culture continue to carry the organism after delivery and thereby infect their infants. Baker et al. [24] found that 39.4% of genital cultures from mothers of infants having late-onset GBS disease yielded a GBS type identical to that isolated from infant's blood or CSF. Dillon et al. [1] reported that 10 of 21 infants with late-onset GBS disease were colonized at birth with a GBS type that caused their disease.

GBS colonization of the throat or genital-rectal area is common in infants, children, and adults [25, 26]. Household members and nursery health staff could potentially be the source of infection for late-onset GBS disease. Some evidence of nosocomial infant-to-infant horizontal transmission of GBS, presumably via the contaminated hands of nursery personnel [4, 27, 28], has been shown. Some case reports have suggested that breast milk is a source of late-onset GBS disease [10–13]. Because our study involved only a review of records, we were unable to assess the role of nosocomial acquisition of GBS, such as breast milk or other nonmaternal source, as the cause of late-onset infection.

Our observation of mothers of black race as a risk factor is consistent with reports on racial disparity in late-onset GBS disease [2, 29]. Black women have been reported to have higher GBS colonization rates than do women of other races or ethnic groups [4, 30–34], which could pose a higher risk for GBS disease in their offspring. Although a study has suggested that race or ethnicity did not influence antibody levels to GBS capsular polysaccharides [33], the basis for this racial disparity in GBS disease remains unexplained.

Investigators have stated that intrapartum antibiotic prophylaxis is not expected to prevent late-onset GBS disease [17]. Active immunization of mothers with GBS vaccines, although regarded as a desirable prevention strategy, may not prevent ~40% of late-onset GBS disease that occurred in infants born at <34 weeks of gestation, because transplacental transfer of IgG antibodies is inefficient at this age. Preterm infants could benefit from prevention strategies that reduce maternal GBS colonization. On the basis of observations of inhibition of colonization of pneumococci, meningococci, and *Hemophilus influenzae* type b by vaccine-induced serum antibodies, Robbins et al. [35] suggested that immunization of childbearing women might inhibit GBS colonization of the genitourinary tract. Hillier et al. [36] showed that GBS type-specific serum antibodies could protect against vaginal GBS colonization. GBS vaccination of women of childbearing age may, therefore, prevent infants from late-onset disease. An additional approach would be passive immunization of preterm neonates. Weisman et al. [37] reported that neonates infused with intravenous hyperimmunoglobulin to types Ia and III GBS polysaccharides maintain high antibody titers in serum for over 6 weeks. The effectiveness of these hyperimmune preparations for preventing late-onset GBS disease in neonates and infants should be determined.

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