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Risk factors for Group B streptococcal disease in neonates of mothers with negative antenatal testing

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Abstract

Objective—The aim of this study was to identify risk factors for early-onset GBS (EOGBS) disease in neonates of mothers with negative antenatal screening.

Study Design—We performed a retrospective cohort study of neonates born to mothers with negative antenatal GBS screening between 2002–2012. Our primary outcome was EOGBS infection. We used multivariable logistic regression to assess factors associated with EOGBS.

Results—EOGBS was confirmed in 492 of the 179,818 neonates that met the study inclusion criteria. Risk factors for EOGBS included black race (reference: white, odds ratio [OR] =1.81 [95% confidence interval; 1.43, 2.31]), maternal age <18 years (reference: >35 years, OR=2.63 [1.54, 4.51]), and maternal age 18–35 years (reference: >35 years, OR=1.94 [1.30, 2.88]).

Conclusion—Maternal age <18 years and black race were the strongest predictors of EOGBS. Further research investigating contributors to the discordance between screening results and neonatal outcomes in these populations is needed.

Keywords

GBS; Universal Screening; Health Disparities; infant; early-onset sepsis

INTRODUCTION

Despite widespread implementation of strategies to prevent Group B *Streptococcus* (GBS) vertical transmission from mothers to neonates,(1, 2) GBS infection persists as the leading cause of infectious morbidity and mortality for neonates in the United States.(2–4) Term neonates with early-onset GBS (EOGBS) have a case-fatality of 4–6%, and in premature

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neonates, mortality may be as high as 30%.^(3, 5, 6) Given the potentially severe outcomes associated with infection, neonatal clinicians seek early identification and treatment of neonates with EOGBS to prevent disease progression and minimize disease burden.

Changing risk factors and demographics in the era of intrapartum antibiotic prophylaxis (IAP) for GBS challenge current strategies for prompt recognition and secondary prevention of GBS disease.^(7, 8) For example, while maternal GBS colonization was historically the strongest risk factor for disease development,^(9, 10) a recent study documented that up to 80% of cases of EOGBS in term neonates occur in neonates born to mothers with negative antenatal GBS screening (largely due to the success of universal screening and IAP).⁽⁴⁾

Neonates born to mothers with negative GBS antenatal testing are least likely to benefit from the Centers for Disease Control and Prevention (CDC) guidelines for living with intrapartum antibiotic prophylaxis (IAP), and thus may be the group for which improved risk stratification and early recognition of disease may be most important. The purpose of this study was to identify risk factors for EOGBS in neonates whose mothers had negative antenatal GBS screening in the era of universal screening and IAP.

SUBJECTS AND METHODS

Patient Selection

We identified a cohort of neonates born to mothers with negative antenatal GBS screening and admitted on the first day of life to 327 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group, and discharged from 2002–2012. We limited the study to these years to reflect the revised CDC guidelines published in 2002 that recommended universal screening and IAP. Data was collected prospectively from daily progress notes generated by clinicians, and then analyzed retrospectively. To prevent missing a positive culture from an outside facility not recorded in the database, we excluded neonates born at outside hospitals and transferred into one of the Pediatrix Medical Group's NICUs.

Definitions

Mothers were defined as having negative antenatal GBS screening if a GBS culture was obtained with a negative result. Mothers for whom GBS cultures were not obtained or had unknown or positive GBS cultures were excluded (Figure 1). EOGBS was defined as isolation of GBS from blood, urine, or CSF cultures obtained in the first 3 days of life. Samples were processed in local clinical microbiology laboratories according to their local hospital standards. The first day of life was defined as day of life (DOL) 0. Prolonged rupture of membranes (PROM) was defined as rupture of membranes >18 hours, and the use of intrapartum antibiotics was defined as administration of any antibiotic to a mother at any time prior to delivery during her birth admission.

Statistical Analysis

Univariable comparisons were performed with Fisher's exact tests to evaluate the association of neonatal and maternal risk factors (including gestational age, sex, maternal race, PROM, delivery type, maternal antibiotic exposure, and maternal age) and EOGBS. We then used

multivariable logistic regression and included all variables in the model. Using a conservative estimate of GBS incidence of 0.40 cases per 1,000 live births², a sample size of at least 175,000 infants would allow for 10 events per variable.⁽¹¹⁾ We reported odds ratios with 95% confidence intervals, and two-tailed P-values <0.05 were considered statistically significant. We performed a sensitivity analysis in which we repeated our multivariable logistic regression analysis including neonates of mothers with either GBS negative or GBS unknown antenatal screening. We performed this sensitivity analysis with neonates of GBS unknown mothers because they represent a group of women that may not benefit from universal screening because they deliver prior to routine GBS screening at 35 weeks. Statistical analyses were performed using STATA 13.1 (College Station, TX). The Duke University Institutional Review Board provided permission to conduct this investigation.

RESULTS

A total of 179,818 neonates met the inclusion criteria (figure 1). Of these, 144,284 (80%) had a blood, urine, or CSF culture obtained on DOL 0, 1, or 2. EOGBS was confirmed in 492 neonates (incidence: 2.7 per 1000). Blood cultures were positive in 490 neonates, and 3 neonates had a positive CSF culture (1 neonate had positive cultures from both blood and CSF). No neonates had a positive urine culture. Positive cultures were collected on DOL 0 for 423 neonates, DOL 1 for 68 neonates, and DOL 2 for 1 neonate. Of the 492 neonates with EOGBS, 457 (93%) neonates were discharged to home, 29 (6%) were transferred to another facility, 2 (0.4%) were missing discharge data, and 4 (0.8%) did not survive. All 4 neonates who died were premature (gestational ages of 28 weeks (3 neonates) and 32 weeks (1 neonate)). Intrapartum antibiotics were given to 46,220 mothers, of which 27,543 (59.6%) delivered a neonate at <36 weeks gestational age, 18,497 (40.0%) at 36–41 weeks, 180 (0.4%) at 42 weeks gestational age. The median length of stay of the neonates with EOGBS that were discharged to home was 11 days (range: 6–153 days).

The overall median gestational age was 37 weeks (range: 24–41) with median birth weight of 2800 g (range: 570–4586). In univariable analysis, neonates who developed EOGBS were more likely to be term with gestational age between 37–41 weeks ($p < 0.001$), more likely to be delivered vaginally compared to cesarean section ($p < 0.001$), more likely to have black maternal race ($p < 0.001$), and less likely to have a mother that received intrapartum antibiotics ($p < 0.001$) (Table 1). On multivariable analysis, statistically significant risk factors for GBS disease included black compared to white maternal race, maternal age <18 years compared to >35 years, maternal age 18–35 years compared to >35 years, lack of maternal intrapartum antibiotics, vaginal delivery compared to cesarean delivery, and gestational age of 42 weeks compared to 36 weeks (Table 2).

In our sensitivity analysis including neonates born to mothers with GBS unknown status in addition to GBS negative status, there were 408,827 total neonates and 835 cases of EOGBS. In multivariable regression we found black race compared to white race and maternal age < 18 years compared to > 35 years were still significant predictors of EOGBS (OR 1.53 [95%CI 1.30, 1.84] and OR 1.91 [1.29, 2.83], respectively). Additionally, we found PROM to be a predictor (OR 1.65 [1.32, 2.08]) and male sex to be protective (OR

0.80 [0.69,0.92]) of EOGBS. In the sensitivity analysis, gestational age was not a predictor of EOGBS.

DISCUSSION

We conducted a large retrospective cohort study to determine risk factors for EOGBS in the era of universal IAP for GBS. We included only neonates of mothers with negative antenatal GBS screens to investigate risk factors for EOGBS in this population, for which limited clinical guidance exists. Risk stratification in this population may be the most critical as these neonates are least likely to benefit from universal screening and IAP.(12)

In this study, maternal demographics, including maternal age and race/ethnicity, were the strongest predictors of EOGBS disease. These factors remained significant predictors of EOGBS in our sensitivity analysis that included neonates of both GBS negative and GBS unknown mothers. Consistent with prior studies, maternal age <18 years and black maternal race were significant risk factors for EOGBS.(2, 10, 13–15) The incidence of EOGBS in mothers <18 years was more than three times that in mothers >35 years (4.6 versus 1.3 per 1000 neonates, respectively). Additionally, neonates born to black or Hispanic mothers had a higher incidence of disease compared with white neonates (3.9 and 3.2 versus 2.4 per 1000, respectively). Maternal demographic factors were stronger predictors of disease than delivery characteristics including PROM.

We did not investigate the cause of differences in risk of EOGBS observed by different demographic groups. However, the incidence of GBS disease has not decreased for black neonates to the same extent as white neonates since the introduction of universal screening. (2, 3) While the overall incidence of GBS decreased from 0.52 per 1000 during 2000–2003 to 0.31 per 1000 during 2003–2006, the incidence in black neonates increased during these same time periods from 0.53 to 0.86 per 1000.(1, 2, 6) Provider non-compliance with current guidelines has been hypothesized to contribute to differences in the incidence of EOGBS according to race and maternal age.(16) However, in large observational studies, screening rates have been high among women of all races and have not been shown to be a significant contributor toward racial disparities in neonatal GBS.(1) In our study, differential screening cannot be attributed as a cause of unequal rates of EOGBS by race or age as all women included were screened, and tested negative. One possible explanation of our study findings is that young and non-white mothers had higher rates of GBS colonization and acquisition late in pregnancy, after GBS screening, which increased their neonate's risk of exposure and invasive disease.

GBS vaginal or rectal colonization during pregnancy can be transient, intermittent, or persistent, and may contribute to false negative screening and EOGBS disease in neonates of mothers with negative screening.(17, 18) Prospective studies of pregnant women demonstrate that approximately 9% of women who test negative at their antenatal screening between 35–37 weeks will have a positive test result if re-cultured shortly after delivery.(19) The change in GBS status late in pregnancy may be due to acquisition of GBS late in pregnancy or inadequate sampling and false negative results during the antenatal screening.

Differential rates of GBS acquisition and clearance by race, ethnicity, and age may contribute to disparities in neonatal EOGBS.

Epidemiologic studies of pregnant and non-pregnant women have suggested higher rates of GBS acquisition (and colonization) in black women compared to white women.(20–22) Indeed, a longitudinal study of non-pregnant women found that African-American women had a 50% increased risk of acquiring vaginal GBS colonization within 4–12 months of enrollment compared with Caucasian women(20). In the era of universal screening and IAP, increased rates of GBS colonization in black compared to white women should not translate into higher rates of EOGBS in black neonates, given that colonized women should test positive on antenatal screening and receive IAP. However, higher rates of GBS acquisition in black compared to white women may contribute to the racial disparities in EOGBS given that black women who have negative antenatal testing may be more likely to become colonized prior to delivery, and will not receive IAP. Further studies are needed to delineate if the higher representation of falsely-screened young and black women in our study are due to different rates of acquisition versus inadequate sampling and disparities in obstetrical care. Intrapartum polymerase chain reaction for GBS has been shown to be highly sensitive and specific, (23–26) and could increase sensitivity for detecting GBS that is acquired after typical prenatal screening.

GBS persistence, acquisition, or loss, and thus risk of change in colonization from screening to delivery may also be correlated to the pathogenic serotype with which a woman is colonized.(27, 28) For example, GBS serotype III has a longer median duration of colonization (around 6 weeks), is more likely to persist throughout a pregnancy, and is the most common invasive serotype in neonates less than 7 days of age.(28, 29) Neonatal risk for invasive disease is also likely dependent on the maternal and neonatal immune responses to the specific serotype with which the mother is colonized.(30)

Despite a high rate of neonatal exposure to maternal GBS colonization (approximately 25–30%), the incidence of EOGBS is relatively low (approximately 1% of those exposed) and may depend on maternal transfer of serotype-specific antibodies and neonatal host-organism interactions.(2) Supporting this theory, several studies have demonstrated an association between the risk of developing invasive EOGBS disease in the neonate and maternal anti-capsular GBS antibody levels.(31–33) Demographic differences in serotype distribution, antibody prevalence, and immunologic factors may all contribute to differences in EOGBS by race, ethnicity, and age.(27) Although large cross-sectional studies show no difference in serotype distribution by race,(34, 35) maternal age has been associated with lower levels of anti-GBS antibodies.(36) In theory, women are exposed to GBS and develop antibodies against different serotypes over time. Because young mothers may have less lifetime exposure to build serotype-specific antibodies, the higher incidence of EOGBS in neonates of young mothers may be due to lower levels of protective antibodies.(37, 38)

Our study strengths include the large sample size and diverse population with data obtained after the revised 2002 CDC guidelines recommending universal screening and IAP. The dataset did not include information on neonatal and maternal clinical presentation such as vital signs or physical exam. This hindered the ability to evaluate risk factors for EOGBS

based on labor and delivery hospital course, such as known risk factors of maternal fever or chorioamnionitis, as well as neonatal presentation. We also could not determine the timing or type of intrapartum antibiotic administration, and clinical details regarding indication for antibiotics in mothers of term infants with negative antenatal GBS testing were not available in the dataset. Additionally, information on timing of screening was not available in the dataset and thus we could not control for timing of screening. Given the transient nature of GBS colonization, if young or black women were screened earlier in their pregnancy this might impact the negative predictive value of the screening. Lastly, we were unable to control for another recognized risk factor for EOGBS, history of GBS in a sibling, as this was not available in the database. The incorporation of these results into clinical practice should be interpreted with caution, as this sample is not reflective of all births during this time period and only included neonates admitted to a neonatal intensive care unit.

Future investigations are needed to further identify contributors to the excess burden of EOGBS disease among young, non-white mothers, and to determine the cause of increased false negative screening in these populations. Prospective studies are needed to determine if the increased discordance between screening results and neonatal disease is due to inadequate sampling and disparities in obstetric care versus increased rates of acquisition in these groups of women. Although improving access to screening may aid in narrowing this gap, our study suggests that disease incidence is higher even among young black women who undergo screening and have negative results. Prospective studies are also needed that investigate potential etiologies contributing to higher false-negative rates or changes in GBS colonization status in these populations as well as GBS serotype and antibody distribution in a diverse group of pregnant women. Lastly, intrapartum polymerase chain reaction to detect maternal GBS colonization should be further evaluated as a screening tool that may better identify mothers who should receive IAP.

Among mothers with negative antenatal GBS screening in our sample, demographic characteristics such as age <18 years and black race are the strongest predictors of their neonates developing EOGBS. Further research investigating contributors to false negative tests or changes in colonization status in these populations is needed to guide interventions to reduce health disparities in patients with EOGBS.

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Conflict of Interest

D.K.B. Jr. receives support from the National Institutes of Health (NIH) (award 2K24HD058735-06, National Center for Advancing Translational Sciences award UL1TR001117, National Institute of Child Health and Human Development contract HHSN275201000003I, and National Institute of Allergy and Infectious Diseases contract HHSN272201500006I); he also receives research support from Cempra Pharmaceuticals (subaward to HHSO100201300009C) and industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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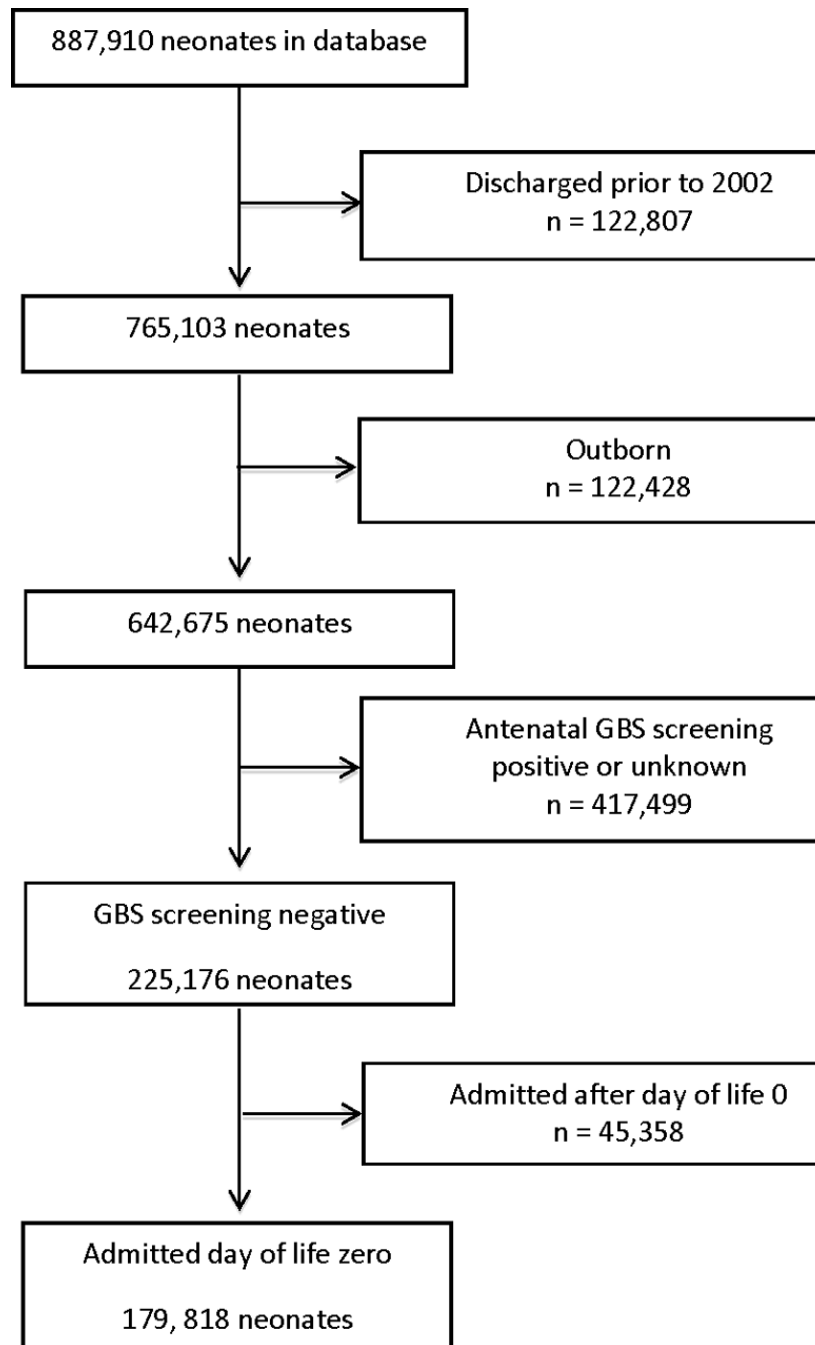


Figure 1.
Study Population

Table 1

Characteristics of infants with and without early-onset Group B Streptococcus infection

	EOGBS Positive n= 492, (%)	EOGBS Negative n=179,326, (%)
Birth weight, g		
<750	4 (0.8)	2152 (1)
750–1499	9 (2)	11,926 (7)
1500–2499	23 (5)	46,408 (26)
2500–3499	262 (53)	77,396 (43)
3500	194 (39)	41,338 (23)
Gestational age, weeks		
26	4 (0.8)	3442 (2)
27–29	5 (1)	5591 (3)
30–36	39 (8)	62,579 (35)
37–41	441 (90)	106,921 (60)
42	2 (0.4)	740 (0.4)
Male	272 (55)	101,458 (57)
Cesarean section	166 (34)	90,868 (52)
PROM	46 (10)	19,724 (11)
Intrapartum antibiotics	62 (13)	46,147 (26)
Race/ethnicity		
White	220 (46)	92,381 (54)
Black	103 (22)	26,381 (15)
Hispanic	133 (28)	41,733 (24)
Other	23 (5)	10,708 (6)
Maternal age, years		
< 18	30 (6)	6548 (4)
18–35	429 (88)	150,294 (84)
> 35	29 (6)	21,803 (12)

EOGBS: Early-onset Group B Streptococcus; PROM: Prolonged rupture of membranes

Table 2

Multivariable regression of predictors for early-onset Group B Streptococcus disease

	OR (95% CI)
Gestational Age, weeks	
36	0.24* (0.06, 0.98)
37–41	1.42 (0.35, 5.69)
42	REF
Sex	
Male	0.94 (0.78, 1.13)
Delivery Type	
C-section	0.56** (0.46, 0.68)
Labor Details	
PROM	1.38 (0.99, 1.91)
Intrapartum antibiotics	0.54** (0.40, 0.71)
Race or ethnicity	
White	REF
Black	1.81** (1.43, 2.31)
Hispanic	1.24 (0.99, 1.55)
Maternal Age, years	
<18	2.63** (1.54, 4.51)
18–35	1.94** (1.30, 2.88)
>35	REF

* p -value<0.05,** p -value <0.001

OR: Odds Ratio; CI: Confidence interval; PROM: Prolonged rupture of membranes