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Geographic Distribution of Maternal Group B *Streptococcus* Colonization and Infant Death During Birth Hospitalization: Eastern Wisconsin

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Purpose Maternal group B *Streptococcus* (GBS) can be transmitted from a colonized mother to newborn during vaginal delivery and may or may not contribute to infant death. This study aimed to explore the geographic distribution and risk factors of maternal GBS colonization and infant death during birth hospitalization.

Methods We retrospectively studied mothers with live birth(s) in a large eastern Wisconsin hospital system from 2007 through 2013. Associations between maternal and neonatal variables, GBS colonization and infant death were examined using chi-squared, Mann-Whitney U and t-tests. Multivariable logistic regression models also were developed.

Results Study population (N=99,305) had a mean age of 28.1 years and prepregnancy body mass index (BMI) of 26.7 kg/m^2; 64.0% were white, 59.2% married, 39.3% nulliparous and 25.7% cesarean delivery. Mean gestational age was 39.0 weeks. Rate of maternal GBS colonization (22.3% overall) was greater in blacks (34.1% vs. 20.1% in whites, P<0.0001), unmarried women (25.5% vs. 20.0% married, P<0.0001), women with sexually transmitted or other genital infections (P<0.0001) and residents of ZIP code group 532XX (P<0.0001), and was associated with increasing BMI (P<0.0001). All predictors of colonization were significant on multivariable analysis. Rate of infant death was 5.7 deaths/1,000 live births (n=558 excluding lethal anomalies and stillbirths) and was negatively associated with maternal GBS colonization (P<0.0001). On multivariable analysis, 532XX ZIP code group, lower gestational age, preterm labor, hyaline membrane disease, normal spontaneous vaginal delivery, hydramnios, oligohydramnios and absence of maternal GBS were associated with infant death.

Conclusions Geographic characteristics were associated with infant death and maternal GBS colonization. Further research is needed to determine if increased surveillance or treatment of mothers colonized with GBS decreases the risk of infant demise at birth. (*J Patient Cent Res Rev.* 2016;3:66-78.)

Keywords group B *Streptococcus*; infant death; pregnancy complications, infectious; infant, newborn disease

Group B *Streptococcus* (GBS) infections are a leading cause of maternal and neonatal morbidity, often associated with pregnancy complications (e.g. endometritis) as well as maternal and neonatal infections (e.g. urinary tract infections and sepsis, respectively).[1-3] GBS significantly contributes to numerous systemic and focal neonatal diseases during the first several weeks of life.[1] Early-onset GBS occurs within the first week of life and frequently presents as sepsis, pneumonia or meningitis.[1-3] Late-onset GBS occurs when the infant is at least 1 week old or up to 3 months old (most cases occur between 3 and 4 weeks of age) and commonly presents as occult bacteremia or meningitis.[1,3] Both early-onset and late-onset GBS disease can be fatal.[1,2]

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Perinatal GBS is usually transmitted to a newborn during a vaginal delivery from a colonized mother. Generally recognized risk factors for early-onset neonatal GBS disease include infant birth at less than 37 weeks, birth after membranes ruptured for more than 18 hours, high concentration of GBS bacterium in mother, previous infant with invasive GBS, limited prenatal care, maternal age less than 20 years and peripartum fever/chorioamnionitis.[1,3] While factors contributing to late-onset disease are poorly understood, infants born prematurely or whose mother tested positive for GBS may incur higher risk.[4] Infants of black (non-Hispanic) race/ethnicity also are more likely to acquire both early-onset and late-onset GBS disease.[1,3]

In recent years, universal screenings at 35–37 weeks of gestation and protocols for GBS treatment at delivery have substantially reduced the incidence of early-onset GBS disease. However, despite these measures, cases of GBS disease still occur at a rate of 0.3 cases/1,000 live births.[2] *Streptococcus agalactiae* represents the dominant species of GBS, but all 10 known serotypes are associated with morbidity in the United States and Canada.[1,3] Rates of maternal GBS colonization for pregnant women and women of childbearing age are highly variable (2.8–28%) within and among geographic regions both nationwide and globally.[5-8] To our knowledge, the geographic distribution of colonization has not been investigated by postal code.

Reducing neonatal and infant death is a major global health priority, and further investigations regarding risk factors for maternal GBS colonization and links to infant death are needed. Among developed nations, the United States has relatively high neonatal and infant death rates — 4.0 deaths/1,000 live births and 5.9 deaths/1,000 live births, respectively — ranking 26th in infant mortality.[9,10] Major causes of neonatal death (defined as death within the first 28 days of life) include prematurity/low birth weight (25.9%), congenital abnormalities (21.2%) and maternal complications (10.0%).[11] Similar to neonatal death, major causes of infant death (defined as death within the first year of life) include congenital abnormalities (20.3%), prematurity/low birth weight (17.9%) and maternal complications (6.8%).[11]

In Wisconsin, the geographic focus of our study, the 2013 infant mortality rate (IMR) was 6.2 deaths/1,000 live births, slightly higher than the national average. ZIP codes within the city of Milwaukee experienced even higher IMR (~10 deaths/1,000 live births) in 2013 and demonstrated strong associations between lower socioeconomic status (SES) and black race (14.1 deaths/1,000 live births per 2010–2012 rolling-average of IMR) as well as higher rates of premature birth, low-birth-weight infants and infant mortality.[12]

Place matters. Studies have revealed ZIP code and census track level differences in other diseases such as obesity and diabetes.[13] Additionally, it has been suggested that "ZIP code is more predicative of health in general than (one's) genetic code" (David Williams, North American Primary Care Research Group Annual Meeting, 2011, Ottawa, Canada). The geographic distribution of GBS colonization as a single outcome, or in conjunction with infant death during the birth hospitalization, has not been studied. We explored the geographic distribution and risk factors associated with maternal GBS colonization and infant death during birth hospitalization (i.e. infant born alive but died before discharge) in a large eastern Wisconsin hospital system.

METHODS

Study Population

We conducted an exploratory retrospective study (approved by the Institutional Review Board) of GBS colonization and infant death associated with mothers who had a live birth(s) at an Aurora Health Care facility from 2007 to 2013. Headquartered in Milwaukee, Wisconsin, Aurora Health Care is a large, integrated medical system in eastern Wisconsin and a portion of northern Illinois consisting of 15 hospitals and 159 outpatient clinics. Data records abstracted for the system were retrieved from PeriData.Net, a comprehensive birth registry capturing most Wisconsin birthing hospitals.

All births were included in the analysis of GBS except those of unknown maternal GBS colonization status. Generally, test cultures for GBS were performed by prenatal providers using established guidelines or antepartum when patients were admitted to the hospital for labor or obstetrical complications and a recent culture result was unavailable.

To examine infant death during the birth hospitalization, we further excluded stillbirths (APGAR score of 0

at 1 and 5 minutes) and, using the definition reported by Wilkinson and colleagues,[14] infants with lethal anomalies.[14] (For example, newborns with Trisomy 13 or 18 were excluded from our analysis, but those with Trisomy 21 were not.) Similarly, we did not otherwise exclude newborns at any level of prematurity. Omitting stillbirths and newborns with lethal anomalies eliminated confounders that could potentially influence any associations related to infant death, specifically associations between peripartum and neonatal GBS treatment.

Statistical Analysis

Several variables of interest (defined prior to study commencement) were obtained and explored regarding our primary outcome, maternal GBS colonization, and our secondary outcome, infant death during birth hospitalization (Table 1). All analyses were performed using Minitab® statistical software (Version 13, State College, PA). To describe characteristics of our study population, we computed frequencies with percentages and means with 95% confidence intervals. To examine associations between maternal or neonatal variables and maternal GBS colonization or infant death, we used the Pearson chi-squared test of independence, Fisher's exact test, Mann-Whitney U test and two-sample t-test, as appropriate. Test results of P-value less than 0.05 were deemed statistically significant. Variables demonstrating significance in univariate analyses were included in multivariable logistic regression models; variables most strongly predictive of outcomes were identified using stepwise variable selection (entry P=0.15, removal P=0.05). Adjusted R-squared values were calculated to determine model fit.

Using similar methods, we performed subgroup analyses to determine if full study population patterns in GBS colonization and infant death were evident in select low- or high-risk populations, including singleton births, nulliparous women, neonates of gestational age < 32 weeks, and births within the ZIP code group 532XX. Subgroup analyses related to SES for ZIP codes within the 532XX group were determined based on the 2013 Milwaukee Health Report.[12] Geographic patterns in outcomes relating to Aurora Health Care patients with Wisconsin ZIP codes (Illinois and other state ZIP codes were excluded from maps) were examined using ArcGIS software (Version

Table 1. List of variables explored

Maternal	
Demographic characteristics	Age, race, ethnicity, prepregnancy BMI, education level, marital status, ZIP code, principal source of payment
Comorbidities	Prepregnancy diabetes, gestational diabetes, hypertension
Previous history	Low birth weight, small for gestation age, intrauterine growth restriction, fetal death/stillbirth, postpartum depression, prior uterine surgery
Sexually transmitted or genital infections	Hepatitis B, hepatitis C, genital herpes/HSV, genital herpes/HSV (active), human papilloma virus, chlamydia, gonorrhea, syphilis, bacterial vaginosis, yeast, trichomoniasis
Substance use	Tobacco use, alcohol use during pregnancy, cocaine, methamphetamine, heroin, hallucinogens, rohypnol, marijuana
Pregnancy characteristics	Hospital location, length of labor, method of delivery, multiple gestations, prenatal care, total number of prenatal visits, history of preterm labor this pregnancy, incompetent cervix, prolonged preterm rupture of membranes, premature rupture of membranes (length), hydramnios, oligohydramnios, vaginal bleeding, placenta previa, moderate/heavy meconium staining, GBS-positive, GBS-treated, abnormal PAP during pregnancy, urinary tract infections, anemia, prepregnancy depression, depression, antibiotics, clinical chorioamnionitis, fever
Neonatal	
Birth characteristics	Sex, gestational age (estimate*), birth weight, 1-min APGAR, 5-min APGAR
Outcomes	NICU admission, infant external transfer, antibiotics for neonatal sepsis, hypoglycemia, hyaline membrane disease/RDS, meconium aspiration syndrome, congenital abnormalities, discharged with mother, neonatal death

**For gestational age we used the best obstetric estimate, consistent with current guidelines.[15]*

BMI, body mass index; GBS, group B Streptococcus*; HSV, herpes simplex virus; NICU, neonatal intensive care unit; PAP, pulmonary arterial pressure; RDS, respiratory distress syndrome.*

10.2.1, Esri, Redlands, CA). Only ZIP codes with > 100 births over the study period were included on the maps. To further evaluate the association between GBS colonization and geography, ZIP codes were grouped by the first three numbers, i.e. 530XX, 531XX, 532XX … (Figure 1).

RESULTS

In total, 99,305 births were identified; 2,264 were excluded from GBS colonization analysis (N=97,041), and 2,523 were excluded from infant death analysis (N=96,782). Across all births, mothers (mean age 28.1 years, prepregnancy body mass index [BMI] 26.7 kg/m^2) were predominantly of white race (64.0%), married (59.2%) and on nongovernment insurance (57.7%), and 39.3% were nulliparous. Neonates (51.3% male) had a mean gestational age of 39.0 weeks and were born by either spontaneous vaginal delivery (67.6%), operative vaginal delivery (6.7%) or cesarean section (25.7%).

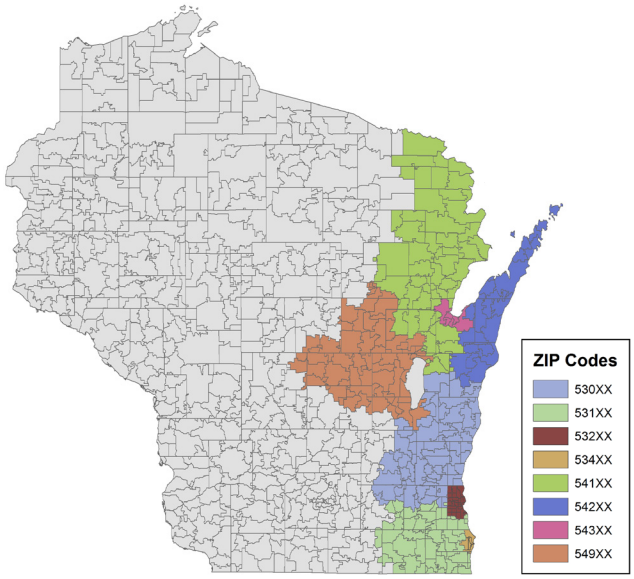

Figure 1. *Study target area by ZIP code groups.*

Maternal GBS Colonization

The overall maternal GBS colonization rate was 22.3%. Among Wisconsin ZIP codes with > 100 births, colonization rates varied from 9.8% to 38.0% (Figure 2). Nine ZIP codes had a GBS-positive rate > 30% (eight within the city of Milwaukee [range 30.6–38.0%] and one suburban village in eastern Wisconsin [34.3%]). Despite such variability, the colonization rate of ZIP code group 532XX (Milwaukee and surrounding cities) was significantly greater than all other groups, and no other groups demonstrated differences in rates (Table 2).

Univariable analyses revealed maternal GBS colonization was significantly associated with black (non-Hispanic) race, unmarried status, higher prepregnancy BMI, evidence of sexually transmitted infections, and antibiotic use for neonatal sepsis (Table 3). Multivariable analysis revealed that the odds of maternal GBS colonization were greater for unmarried status, for each 10 kg/m^2 increase in BMI, for those with a sexually transmitted infection and for those in the 532XX ZIP code group.

Table 2. Maternal GBS colonization and infant death rates by ZIP code group

	Maternal GBS colonization		Infant death	
ZIP code group	Rate*	Odds ratio (95% CI)	Rate†	Odds ratio (95% CI)
530XX (n=14,408)	20.02	0.66 (0.63–0.69)	4.53	0.54 (0.41–0.71)
531XX (n=24,591)	19.11	0.62 (0.60–0.65)	3.40	0.41 (0.32–0.52)
532XX (n=36,031)	27.48	Reference	8.35	Reference
534XX (n=1,755)	20.40	0.68 (0.60–0.76)	3.41	0.41 (0.18–0.92)
541XX (n=3,840)	18.26	0.59 (0.54–0.64)	3.37	0.40 (0.23–0.70)
542XX (n=3,485)	18.11	0.58 (0.53–0.64)	3.31	0.40 (0.23–0.69)
543XX (n=5,947)	17.89	0.57 (0.54–0.62)	4.37	0.52 (0.35–0.78)
549XX (n=5,416)	19.72	0.65 (0.60–0.70)	6.12	0.73 (0.51–1.05)

**Expressed as number of maternal GBS-positive cases/100 live births.*

†Expressed as number of infant deaths during birth hospitalization/1,000 live births.

CI, confidence interval; GBS, group B Streptococcus.

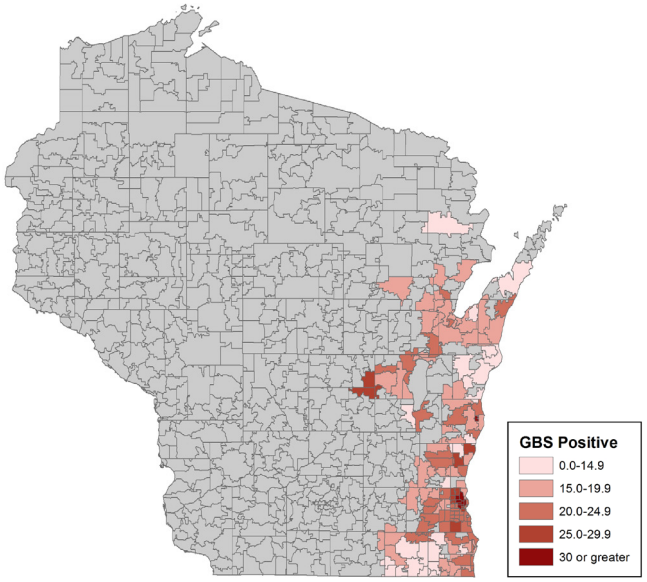

Figure 2. *Percentage of GBS-positive cases by ZIP code. Any ZIP codes that had < 100 births were omitted from the graph.*

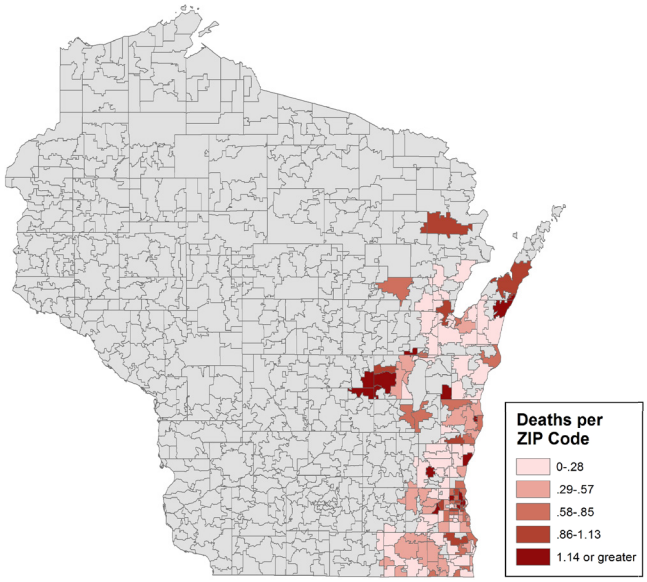

Figure 3. *Percentage of deaths during hospitalization per ZIP code. Any ZIP codes that had < 100 births were omitted from the graph.*

Additionally, maternal GBS colonization was 65% more likely for black (non-Hispanic) and 15% less likely for Hispanic women than non-Hispanic women. Stepwise variable selection identified 532XX ZIP code group, yeast vaginitis, prepregnancy BMI and unmarried status as the most significant predictors of GBS colonization.

Infant Death During Birth Hospitalization

The overall rate of infant death during birth hospitalization was 5.7 deaths/1,000 live births. Of the 558 total deaths (mean gestational age 26.5 weeks), 446 deaths (80%) occurred within the infant's first day of life. Complications of prematurity, specific and unspecified fetal causes and unknown/unlisted causes comprised 65.2% of infant deaths. Placental abruption/abnormalities accounted for 14.0% of deaths, maternal factors (including hypertensive disorders) 8.4%, congenital anomalies 5.4%, infection 5.2% and placental insufficiency 1.8%.

Among Wisconsin ZIP codes with > 100 births, mortality rates varied from 0 to 28.8/1,000. Range of mortality rates varied in part due to some ZIP codes having relatively few births. For example, one ZIP code with a mortality rate of 28.8/1,000 had four deaths out of 139 births. Across all ZIP code groups, the highest infant death rates corresponded to Milwaukee-area ZIP codes (532XX), encompassing only 37% of all study births but 55% of all infant deaths (Table 2, Figure 3). Among subjects in the 532XX ZIP code group, infant death rates were highest among mothers of black (non-Hispanic) race (11.9/1,000, 56.8% of deaths in this group).

From univariable analysis (Table 4), infant death during birth hospitalization was negatively associated with GBS colonization (54/21,529 deaths among those with GBS vs. 497/75,253 deaths among those without GBS, P<0.0001; GBS status for remaining 7 deaths was unknown). Infant death was associated with black (non-Hispanic) race, which revealed a significantly higher death rate than all other racial/ethnic groups. The infant death rate also was significantly higher for Asian than white (non-Hispanic) mothers (P=0.037). Univariable tests further identified unmarried status, prepregancy BMI, prepregnancy diabetes, chronic hypertension, maternal complications, male sex and prematurity/low birth weight as strongly associated with infant death (Table 4).

Multivariable analysis revealed the odds of infant death were greater for ZIP code group 532XX, lower gestational age, infant hyaline membrane disease, amniotic fluid volume abnormalities, spontaneous vaginal delivery and

Table 3. Predictors of maternal GBS colonization on univariable, multivariable analysis

	Maternal GBS colonization			
Predictor	**Percentage**	**Univariable *P***	**Multivariable *P***	**Multivariable odds ratio**
Marriage status				
Unmarried	25.5	<0.0001	**0.029**	**1.04**
Married	20.0			
Race				
White non-Hispanic	20.1	Reference	Reference	Reference
Black non-Hispanic	34.1	<0.0001	**<0.0001**	**1.50**
Hispanic	18.8	0.002	**<0.0001**	**0.83**
Prepregnancy BMI*		<0.0001	**<0.0001**	**1.01**
Resides in 532XX ZIP code group				
Yes	27.5	<0.0001	**<0.0001**	**1.21**
No	19.2			
Bacterial vaginosis				
Yes	31.7	<0.0001	**<0.0001**	**1.15**
No	21.5			
Yeast vaginitis				
Yes	33.3	<0.0001	**<0.0001**	**1.49**
No	21.2			
Trichomoniasis				
Yes	37.8	<0.0001	**<0.0001**	**1.19**
No	21.9			
Human papilloma virus				
Yes	26.0	<0.0001	**<0.0001**	**1.15**
No	22.1			
Chlamydial infection				
Yes	31.5	<0.0001	**<0.0001**	**1.17**
No	21.8			
Gonorrhea				
Yes	35.7	<0.0001	0.135	1.11
No	22.1			
History of genital herpes				
Yes	27.1	<0.0001	0.222	1.05
No	22.0			
Gestational age, weeks†		<0.02	**<0.0001**	**1.03** (per week)

Median BMI was 26.0 kg/m^2 in mothers colonized with GBS versus 25.0 kg/m^2.

†Median gestational age was 39.0 weeks for both positive and negative maternal GBS colonization.

BMI, body mass index; GBS, Group B Streptococcus.

absence of maternal GBS colonization. Race/ethnicity was not predictive of infant death, whether in dichotomous form (white non-Hispanic vs. all other) or comprising all five groups (Table 4). Gestational age accounted for 17.3% of the variation in infant death; all remaining associations accounted for less than 2% of variation. Stepwise variable selection identified gestational age, hyaline membrane disease, prematurity and spontaneous vaginal delivery as the most significant predictors of infant death.

Subgroup analysis revealed that previously described patterns in prediction of infant death remained even when multiparous women were excluded from analysis. When analyzing the births of nulliparous women only,

Table 4. Predictors of infant death on univariable, multivariable analysis

	Infant death			
Predictor	**Univariable rate***	**Univariable *P***	**Multivariable *P***	**Multivariable odds ratio**
Maternal characteristics				
Marriage status				
Unmarried	7.6	<0.0001	**0.112**	**1.28**
Married	4.3			
Race				
White	4.4	<0.0001	0.258	1.20
Non-white	8.8			
Prepregnancy BMI*		<0.0001	0.253	1.01
Resides in 532XX ZIP code group				
Yes	8.3	<0.0001	**0.004**	**1.57**
No	4.0			
Tobacco use				
Yes	7.3	0.002	0.851	1.03
No	5.3			
Nulliparous				
Yes	6.4	0.019	0.142	1.22
No	5.2			
Prenatal care				
Yes	5.2	<0.0001	0.082	1.78
No	71.3			
Prepregnancy diabetes				
Yes	16.0	<0.0001	0.827	1.11
No	5.6			
Chronic hypertension				
Yes	12.6	<0.0001	0.944	1.02
No	5.5			
Maternal GBS				
Yes	2.5	<0.0001	**<0.0001**	**1.96**
No	6.6			
Gonorrhea				
Yes	15.4	<0.0001	0.717	1.17
No	5.6			
Bacterial vaginosis				
Yes	10.5	<0.0001	0.068	1.42
No	5.3			
Urinary tract infection				
Yes	7.7	0.004	0.330	1.20
No	5.5			
Incompetent cervix				
Yes	95.0	<0.0001	0.207	1.38
No	5.0			
Hydramnios				
Yes	13.0	<0.0001	**<0.0001**	**2.98**
No	5.5			
Oligohydramnios				
Yes	53.0	<0.0001	**0.001**	**2.41**
No	5.2	<0.0001	**0.001**	**2.41**

Table 4 (cont). Predictors of infant death on univariable, multivariable analysis

	Infant death			
Predictor	**Univariable rate***	**Univariable *P***	**Multivariable *P***	**Multivariable odds ratio**
Maternal characteristics				
Prolonged ROM				
Yes	54.7	<0.0001	0.162	1.67
No	5.4			
Vaginal bleeding this pregnancy				
Yes	34.2	<0.0001	0.076	1.38
No	4.4			
Multiple gestations this pregnancy				
Yes	27.6	<0.0001	0.862	1.03
No	4.9			
Preterm labor this pregnancy				
Yes	36.8	<0.0001	**0.010**	**1.54**
No	4.3			
Depression during pregnancy				
Yes	9.4	<0.0001	0.083	1.48
No	5.5			
Spontaneous vaginal delivery				
Yes	6.4	<0.0001	**0.008**	**1.47**
No	4.2			
Infant characteristics				
Infant sex				
Male	6.1	0.021	0.149	1.20
Female	5.0			
Median gestational age, weeks‡		<0.0001	**<0.0001**	**1.67** (per week)
Median birth weight§		<0.0001	#	#
Neonatal hypoglycemia				
Yes	11.1	0.002	0.171	1.43
No	5.6			
Hyaline membrane disease/RDS				
Yes	29.9	<0.0001	**<0.0001**	**3.45**
No	4.9			

**Infant death rates during birth hospitalization expressed as number per 1,000 live births.*

†Median BMI was 27.0 kg/m² in mothers with infant death versus 25.0 kg/m².

‡Comparison between infants who died during birth hospitalization and those who did not; median gestational age was 23.5 weeks versus 39.0 weeks.

§Comparison between infants who died during birth hospitalization and those who did not; median birth weight was 595.0 g versus 3345.0 g.

#Birth weight not included in multivariable model due to significant confounding with gestational age, the latter being the strongest predictor.

BMI, body mass index; GBS, group B Streptococcus*; RDS, respiratory distress syndrome; ROM, rupture of membranes.*

multivariable efforts revealed that significant predictors of infant death no longer included lack of prenatal care, hydramnios and oligohydramnios. Examining the population of neonates born at 32 weeks gestation or later only, all of the multivariable model relationships remained as noted in Table 4 except that vaginal bleeding and multiple gestations were now significantly associated with infant death, whereas spontaneous vaginal delivery, 532XX ZIP code group and infant hyaline membrane disease were no longer significant. In this ≥ 32 weeks population, the birth hospital infant death rate was 0.8/1,000 in those with maternal GBS colonization, compared to 1.7 in those without colonization (P<0.01 in univariable and multivariable models). Within the population of neonates with gestational age < 32 weeks, multivariable efforts revealed that mothers were more likely to be unmarried but did not differ in respect to maternal age or race/ethnicity.

Maternal GBS colonization also was negatively and significantly associated with infant death on univariable analyses within populations of neonates < 28 weeks, < 2,500 g and < 1,500 g (but not <24 weeks or <750 g). Significance remained in one multivariable model that included gestational age among neonates < 2,500 g. In all five ZIP code groups with at least 25 birth hospitalization infant deaths, mothers colonized with GBS had lower infant death rates than those not colonized. This difference was significant in three separate ZIP code groups: 530XX (1.4 vs. 5.2, P=0.004), 532XX (3.4 vs. 10.1, P<0.0001) and 549XX (0.9 vs. 7.4, P=0.028).

Inclusion of SES in the univariable analysis of births within ZIP code group 532XX showed the infant death rate to be significantly higher in low-SES ZIP codes (9.4 deaths/1,000 live births) than middle-SES (7.9/1,000, P=0.033) and high-SES (4.8/1,000, P=0.003) ZIP codes (as defined by 2013 Milwaukee Health Report[12]). SES was not a significant predictor in the multivariable model of infant death; only marital status and self-pay insurance demonstrated significance. Through stepwise variable selection, marital status was identified as the single significant predictor but explained only 7.4% of the variation in infant death.

DISCUSSION

The maternal GBS colonization rate among women giving birth in this study (22.3%) is within the range of 15–35% during pregnancy, and is consistent with previously reported rates.[1] Among more recent reports in the developing world, this rate closely approximates that reported from central Alabama (22.8%),[16] but is a bit lower than rates from Botacatu (São Paulo, Brazil), Sweden (25.4%)[17,18] and San Francisco (26.4%),[19] and higher than that from Taiwan (18.3%).[20] Similar to our results, older studies also have observed an increased GBS colonization rate among black pregnant women compared to their white counterparts.[21,22] Among recent studies, black woman in Alabama were significantly more likely to be colonized during pregnancy than white women,[16] however this was not true in San Francisco.[19] As in our study, GBS prenatal colonization rates have been observed to be lower among Hispanic women than whites.[19,22]

Our study revealed a significant association between increased BMI and maternal GBS colonization. Previous studies have reported an increased risk of GBS maternal colonization with maternal obesity[19] and with increased maternal BMI.[22] Similar to our findings, previous studies have shown no association with diabetes[19,22] or alcohol use[19,22] and minimal to no relationship with parity.[18,19,22] Unlike our study (which used type of insurance as a proxy), authors from Washington state found an association between maternal GBS colonization and both educational level and income.[22] We found no association with tobacco use and maternal age; however, these associations were inconsistently found in other studies.[17-19,22] A recent study from Brazil found associations between GBS colonization in pregnant women and spontaneous abortion, sexual intercourse frequency and the presence of candidiasis or cytolytic vaginosis.[17] Our data did not allow exploration of the former two predictor variables. We did find a statistical association between GBS colonization and bacterial vaginosis as well as genital infections with yeast, trichomonas, human papilloma virus and chlamydia. However, clinical significance appeared to be minimal and the relative timing of each entity could not be determined from the data.

We report an association between ZIP code groups, and individual ZIP codes of residents, and maternal GBS colonization. Investigators have compared colonization rates between study centers,[5-8] however postal zone level analysis has been only minimally explored. A Swedish

study revealed no significant differences in colonization rates between regions of the country or with respect to the population size of the municipality.[18] Geographic differences noted in our study were independent of other demographic variables such as age, race/ethnicity and insurance status. The increased colonization rate in one suburban village in eastern Wisconsin (34.3%) was surprising and without explanation. Whether this phenomenon relates to a particular strain of GBS or perhaps to an increased inherent risk of colonization among some very extended families is unknown. Individual serotypes of GBS are distributed worldwide, and the particular distribution of serotypes has remained fairly consistent recently in the United States.[6]

The secondary outcome of interest for this study, infant death during birth hospitalization, would be anticipated to yield a rate somewhat lower than the local IMR. Our outcome would not include sudden infant death syndrome, accidents, late-onset GBS disease and other entities that would normally occur following discharge after birth. The calculated rate of death during birth hospitalization for 2007–2013 (5.7/1,000 live births) compares well to 2010 figures (most recent available) for Wisconsin (5.84/1.000 live births) from the National Vital Statistics Reports.[23] For Wisconsin, 100% of infant death records were linked to birth records.[23] The 2010 rate for the entire United States was 6.14/1,000 (range among studies: 3.57–9.62/1,000).[23] Regarding our rates of death following birth hospitalization, all ratio of rates among offspring of black women versus non-Hispanic white women (2.63) are essentially identical to that of the infant death rate across the United States in 2010 (2.64).[23] Similarly, the ratio of death rates for unmarried versus married mothers was identical between our study and national IMRs (both 1.77) and for male versus female infants (1.22 vs. 1.21); our ratio for multiple versus single births was somewhat higher (5.63 vs. 4.66).[23]

Our calculated rates for death during birth hospitalization were higher than the overall national IMR for neonates born at < 32 weeks gestation (249.5/1,000 vs. 165.6/1,000), perhaps because 20% of the infants in this subset of our study were born at < 24 weeks gestation. Our rates for death during birth hospitalization for infants born at < 2,500 g was significantly lower than the overall national IMR (1.49 vs. 2.13), again noting that our rate does not include infants discharged following birth hospitalization that died later in infancy.[23]

Thus, in general, our rates and trends regarding death following birth hospitalization are consistent with national trends regarding infant death overall, and are driven by the problem of preterm birth (with minor contributions from a variety of prenatal complications). Certainly, the latter are well recognized and many contribute to preterm birth.[11,24] One recent concern, maternal obesity, was found in our study to be a significant univariable predictor of infant death during birth hospitalization; however, this factor did not remain significant on multivariable analysis. Two recent meta-analyses associated increasing BMI with risk of infant death,[25,26] however the possibility of residual confounding variables was acknowledged.[26] A recent study using data from a Belgian birth registry revealed an increased adjusted odds ratio for perinatal mortality among obese mothers, though this was not statistically significant.[27]

Racial and insurance disparities are recognized as significant predictors of perinatal mortality, preterm birth and death among low-birth-weight infants.[23,24,28,29] Recently, environmental epigenetics, nutritional deficiencies and stress have been suggested as etiologic factors in adverse perinatal outcomes, perhaps mediated by differential inflammatory responses.[28,30] Racial disparities were certainly seen in our study, however, race/ethnicity did not remain a significant predictor of infant death when ZIP code group was included on multivariable analysis of the entire data set nor in the subset representing the 532XX ZIP code group. While self-pay versus governmental private insurance was predictive of infant death within the 532XX ZIP code group, which is consistent with national reports,[24] insurance type was not generally predictive of infant death in our study and the vast majority of our births were insured. A similar finding was seen in Arkansas, where Medicaid versus non-Medicaid insurance (and white vs. nonwhite race) were not predictive of 1-year mortality of very low-birth-weight infants when adjusting for births that occurred in hospitals with or without a neonatal intensive care unit.[29]

Our study reinforced that place *does* matter. IMRs vary significantly among U.S. states.[23] Examining the Healthcare Cost and Utilization Project's 2006 Kids' Inpatient Database, hospitalized neonates were at a greater risk of death if their family resided in counties with lower population densities. This relationship was not found in our study. While preterm birth certainly

drives the rate of infant death during birth hospitalization, geographic differences are still seen in our study when controlling for gestational age at birth and a number of other variables. Specifically, infants from homes within the city of Milwaukee and portions of immediately adjacent municipalities are at increased risk of death following birth hospitalization than those from other ZIP code groups. This geographic variable supersedes the variables of race/ethnicity, insurance type or marital status. Within this ZIP code group, marital status and self-pay insurance status were significant predictor variables.

Likely a complex interplay between neighborhood, race, marital status and income/insurance status, an unmeasured variable that may be described as parental stress and other unmeasured factors contribute to both preterm birth and death following birth hospitalization. Vos et al. examined the relationship between adverse perinatal outcomes and deprived neighborhoods through a systematic review. The meta-analysis ultimately included five Canadian and two British studies that compared adverse perinatal outcomes in the most deprived neighborhood quintile with those in the least deprived quintile. While there were some differences in the standard used to define deprived neighborhoods among studies, maternal residence in a deprived neighborhood was associated with preterm birth, small-for-gestational age and stillbirths.[31] Collins et al. examined preterm birth among Chicago-born white and African-American mothers who did or did not migrate to the suburbs. Migration in both groups was associated with lower preterm birth compared to their nonmigrant counterparts. When neighborhood income was accounted for, the protective association of suburban migration disappeared among Chicago-born whites. Adjusted odds ratios of preterm birth, low birth weight and small-for-gestational age approximated unity between Chicago-born white and African-American migrants compared to their nonmigrant counterparts.[32] The authors concluded that residential income seems to explain the association of migration to the suburbs and reduced rates of adverse birth outcomes. Unfortunately, household income was not investigated in our study, and our only proxy, insurance type, was not significant in the overall study. Self-pay insurance, however, was associated with infant death among the residents of the 532XX ZIP code group.

A study utilizing an Illinois data set of African-American infants and their mothers, with linked U.S. Census income data, revealed an association with decreased risk of preterm birth among mothers with upward economic progress following poverty in early life. This favorable association was not found among mothers who themselves were born with low birth weight (suggesting the phenomenon of epigenetics).[33] We were unable to assess the latter variable in our study. Further, it has been suggested that environmental exposures be assessed with regard to preterm birth and deprived neighborhoods.[34] For example, one candidate for further exploration would be lead, a compound associated with significant prevalence and increased risk of hypertension-deficit/hyperactivity disorder diagnosis among children within this same health system of this same region.[35]

A retrospective cohort study from nearby Dane County, Wisconsin, which spanned 1990–2007 and included subject numbers similar to ours, examined IMR and birth rates ≤ 28 weeks gestation.[36] In that cohort, the gap in IMR between babies born of black mothers and white mothers was significantly lessened in the mid-2000s, only to reappear starting in 2008 (when black-white gaps in mean income by linked U.S. Census data and food stamp use increased).[36] The risk of delivery ≤ 28 weeks gestation decreased for black women receiving standard or intensive "prenatal care" from 1990–2000 to 2001–2007, while those receiving "less-than-standard" prenatal care did not show this improvement.[36] Our study did not quantify prenatal care utilization as did the Dane County study. Dane County's 2008–2010 black IMR of 15/1,000 compares to our rate of black infant death following birth hospitalization in the 532XX ZIP Code of 11.9. Again, our death rate does not include death at home or in hospital following discharge from the birth hospital.

Finally, the negative association of maternal GBS colonization with death following birth hospitalization observed in our study was completely unexpected. While the lack of association between maternal GBS colonization and preterm birth has been reported,[37] the relationship of the former with decreased infant death risk is apparently a novel finding. Further study is required to determine if this association is due to increased surveillance of infants of GBS colonized mothers during the newborn period, the use of antibiotics during labor of colonized mothers, and/or other unknown biologic factors.

Limitations

Our study has several limitations. Ultimately, PeriData.Net is a clinically generated birth registry, not a research

dataset. The retrospective study design may have introduced information or observer bias due to missing data points and potential errors in data entry. Details regarding how GBS cultures were collected in each subject and specific maternal treatment were lacking. This data set did not link subjects to their death certificates, thus cause of death information was limited. Data collected included fields related to neonatal conditions such as sepsis, hypoglycemia, lung disease and anomalies; however, specific details of neonatal care were lacking.

This data set is understandably biased toward inclusion of prenatal and perinatal factors. Because 80% of our infant deaths occurred during the first day of life, prenatal and perinatal factors indeed appeared to be paramount. Additionally, this study also focused on a single geographic region and hospital system (not a community survey), and may have limited generalizability. It is also unclear from this analysis if distance or time to tertiary care birth hospital (for rural areas) or other uncaptured variables (for all areas) contribute to the associations observed.

The "Neonatal Death" field obtained from PeriData.Net also was limited, as it did not include those who transferred from Aurora Health Care to another hospital and died. These neonates were dropped from PeriData.Net (i.e. they were not included in the numerator or the denominator). However, most transfers went to Children's Hospital of Wisconsin, which provides an update that is included in PeriData.Net. Therefore, the extent of lost deaths is unknown but believed to be relatively minor. The consistency of our death rates and ratios with those of overall infant death rates nationally and regionally suggests general integrity of our data. As with all such studies, the significant outcomes are epidemiologic associations; cause and effect is not proven.

CONCLUSIONS

Race/ethnicity, unmarried status, increasing prepregnancy BMI, diagnosis during pregnancy of bacterial vaginosis, yeast vaginitis, trichomoniasis, human papilloma virus and chlamydial infection, and ZIP code group were predictive of maternal GBS colonization. Maternal GBS colonization was negatively associated with infant death even when controlling for gestational age. Further research is needed to determine if increased surveillance or treatment of mothers colonized with GBS decreases the risk of infant demise. Infant death prior to discharge was driven by premature birth but also associated with one ZIP code group, preterm labor, vaginal bleeding, normal spontaneous vaginal delivery, hydramnios, oligohydramnios, lower gestational age and lack of prenatal care. Ultimately, geography was a significant predictor of both GBS colonization and infant death. Clinicians, and society, need to consider a family's neighborhood, in addition to traditional factors, when assessing risk for infant death and identifying or developing possible mitigating factors.

Patient-Friendly Recap

- Group B streptococci (GBS) are bacteria that can be transmitted from a colonized mother to her newborn at birth.
- The authors reviewed nearly 100,000 birth records to determine frequency of GBS and its possible connection to infant mortality in communities across eastern Wisconsin.
- They identified several geosociological factors that yielded higher rates of both GBS and infant death, including area of residence.
- Interestingly, infants of mothers with GBS actually died less frequently than those of colonized mothers, possibly due to antibiotic use or increased health surveillance.

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Conflicts of Interest

None.

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