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Group B *Streptococcus* Colonization is Associated with Early Term Births

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Group B *Streptococcus* Colonization is Associated with Early Term Births

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Bachelor of Science

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Abstract

Group B *Streptococcus* Colonization is Associated with Early Term Births

By Kelsey Mitchell

OBJECTIVE: To document if maternal *Group B Streptococcus* (GBS) colonization between 35 and 37 weeks of gestation is associated with increased early term birth (between 37 and 39 weeks gestation).

METHODS: In this cohort study of women delivering at term at Centennial Women's Hospital in Nashville, TN, GBS status and other clinical and demographic data were obtained from medical records. Exposed women were those testing positive for GBS (GBS positive [n=490]) and the unexposed tested negative for GBS (GBS negative [n=1,127]). Students t-tests and logistic regression determined association between GBS status and early term delivery. Breslow-day tests were used to assess heterogeneity across race strata.

RESULTS: The average gestational age was reduced to 271.1 (95% CI 270.4, 271.1) days for the exposed, GBS positive women compared to 274.7 (95% CI 274.4, 275.1) days for unexposed, GBS negative women ($p < 0.0001$). The adjusted odds of early term birth was increased by 3 fold in the exposed (OR 3.28; 95% CI 2.60 - 4.15; $p < 0.0001$). The mean birth weight of GBS positive women was 3285.3 (95% CI 3242.6, 3327.9) grams that was lower than the GBS negative women, 3373.8 (95% CI 3348.9, 3398.7) grams ($p = 0.0004$).

CONCLUSION: Colonization with GBS may have detrimental effects to the term infant through shortening of the gestational age contributing to infant morbidity and mortality warranting appropriate intervention and monitoring of GBS status during pregnancy.

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Chapter I: Literature Review

Group B *Streptococcus*

The bacterium, *Streptococcus agalactiae*, or more commonly known as Group B *Streptococcus* (GBS), normally resides in a women's intestines, vagina, or rectum. Approximately 10%-30% of women are asymptomatic carriers of GBS in the genital and gastrointestinal tracts (1-3). GBS is often not harmful to a women, however if passed to a child during pregnancy, labor, or delivery, GBS infection can be extremely harmful to an infant (1). GBS disease in infants is the leading cause of neonatal sepsis. Despite infants being most at risk, GBS infection has been found to be harmful to the elderly, and adults with chronic conditions such as diabetes and liver disease (4-6).

GBS can be acquired by the fetus during passage through the birth canal contributing to early and late onset diseases. Infants must be exposed to the bacteria at a mucus membrane site (7). In addition GBS infection can ascend vertically from the vaginal canal to the amniotic fluid after onset of labor or rupture of the membrane, however it can cross intact membranes as well (7, 8). If the bacterium crosses intact membranes it can lead to an intrauterine infection which has been associated with preterm birth (9). If the bacterium is aspirated it can lead to bacteremia in the infant.

Early onset disease

There are two types of GBS disease cases among infants: early onset disease and late onset disease. Early onset is classified as cases in which group B *Streptococcus* was isolated from infants younger than one week old (2, 10). Most early onset cases present within the first 48 hours after delivery (11). Early onset disease presents as respiratory

distress in infants, cardiovascular instability and apnea. The most common clinical symptoms observed are bacteremia, pneumonia, and meningitis found by one study to have be present in 83%, 9% and 7% of cases respectively (2). Early-onset disease usually results in rapid clinical deterioration and sepsis.

The Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance reported in 2008 approximately 1,200 cases of early-onset disease per year with almost 70% of cases born at term (≥ 37 weeks), (12). This is equivalent to 0.28 cases of early-onset GBS disease per 1,000 live births. In the early 1990's, prior to implementation of preventative measures, there was an annual incidence of 1.7 early-onset cases per 1,000 live births (13). In 2002 the CDC released revised guidelines for the prevention of early-onset disease causing the incidence of GBS early-onset in infants to decrease 27% from 0.47 cases per 1,000 live births in 2000 to 0.34 cases per 1,000 live births in 2004 with further decline by 2008. The case fatality rate for early onset disease has decreased from 50% in the 1970s to about 5% in 2009. The highest death rate was observed in infants with pneumonia (9%) and meningitis (4%) (2).

Late onset disease

Late onset-disease is cases that occur between one week and 3 months (2, 10). One study found 52% of infants with late-onset GBS disease were preterm births. Unlike early-onset disease, late-onset disease is not always acquired from the mother (11). One study found approximately 50% of cases of late onset disease were acquired from their colonized mother (14). Similar to early-onset disease, late-onset disease manifests as bacteremia (65%), meningitis (27%), and pneumonia (3%) (2).

The CDC Active Bacterial Core Surveillance reported in 2008 approximately 1,100 cases of late-onset GBS disease per year (12). This is equivalent to 0.25 cases of late-onset GBS disease per 1,000 live births. This number has decreased slightly from 2005 however appears to remain fairly stable with slight yearly fluctuations (2). The case fatality rate is about 5% for all late-onset disease with the highest death rate among infants presenting with bacteremia (18%).

Risk factors for GBS

Many risks factors of GBS disease have been identified in the research over the past decades. Maternal vaginal colonization is the primary risk factor associated with early onset GBS disease. The prevalence of GBS colonization in pregnant women in the United States is 10-30%. Some studies have shown that rates of colonization among black women are higher than among white women (15). Women who are more heavily colonized have an increased risk of having a child with early-onset disease than women who have light colonization (16, 17). Other factors that increase the risk for early-onset disease include gestational age of < 37 completed weeks (preterm birth), premature rupture of the fetal membranes lasting more than 18 hours, intra-amniotic infection, previous delivery of a newborn with early-onset disease, low levels of circulating antibodies against group B *Streptococcus*, young maternal age, and high intrapartum temperatures (18-21). A study found that if there is a rupture of the membrane prior to labor the odds of observing group B *Streptococcus* disease in a neonate is 11.1 times higher (21). Campbell et al found that younger maternal age is a risk factor for early-onset disease and hypothesized this is because of the lower levels of maternal anti-GBS antibody present at younger ages (22). Similarly, women who previously have had a

child with early-onset disease may have lower levels of antibodies and therefore have subsequent risks for early-onset disease in subsequent pregnancies (11, 13).

The etiology of late-onset disease is not well known and therefore risk factors are not as well characterized (11). Similarly to early-onset disease; prematurity, African American race, and maternal colonization all appear to increase the risk of late-onset disease in an infant. However, as stated earlier, maternal colonization is not necessary for late-onset disease to occur.

Racial disparities in acquisition of GBS

Racial disparity is evident in GBS-associated adverse outcome with African Americans more susceptible than other racial groups. The rate of early-onset GBS infection among African Americans was almost two times higher than among whites in 2005 (12). In addition a study in Atlanta found that thirty percent of early-onset disease could be attributed to black race, independent of other risks factors (23). The same study found black infants had 35 times the risk of late-onset GBS disease as non-black infants. However this study did not take into account the higher prevalence of GBS infection in mothers. Furthermore, there has been an increase in the incidence of GBS early-onset disease in African American infants from 0.53 per 1,000 in 2003 to 0.86 per 1,000 in 2006 ($p=0.005$) (12, 24). The majority of this increase was driven by term African American infants. These differences in GBS disease may be due to the higher rate of GBS colonization in African American women or some other unknown etiologic, socioeconomic or biological factors. African Americans have higher rates of preterm births compared to whites and the premature rupture of the membrane is a risk factor for

early-onset disease in infants, therefore this could play a role in the higher rates of disease observed in African American infants. Additionally, the susceptibility of African American infants to GBS related disease may be higher and could be contributing to the racial disparity observed in disease and adverse outcomes. The racial disparity has persisted despite the increased use of antibiotics and screening methods (11)

Prevention and treatment during pregnancy

The CDC developed guidelines in 2002 (updated in 2010) on screening for and prevention of adverse infant and maternal outcomes due to GBS (18). There are two primary strategies for determining if a pregnant woman is at risk of giving birth to a GBS positive infant. The first is a risk-based assessment technique. A woman who has the presence of any of the following is offered intrapartum antibiotic prophylaxis: delivery at less than 37 weeks, intrapartum temperature of greater than 100.4°F or rupture of membrane for more than 18 hours (18).

The second is a universal screening strategy which consists of all pregnant women having a recto-vaginal swab taken at 35-37 weeks. If a woman has a positive culture she is given intrapartum antibiotic prophylaxis. The positive predictive value of the culture taken within 5 weeks of delivery is 77-87% and the negative predictive value is 94-96% (25, 26). Colonization can be transient during the course of a pregnancy and therefore early colonization and positive swabs are not predictive of the risk of early-onset GBS disease in infants. The predictive value of the culture decreases if taken more than 5 weeks prior to delivery as well as one study found it decreased if specific culture procedures (recommended by the CDC) were not followed (26).

A large population based retrospective study in the United States following more than 600,000 live births and 5,000 infants with early-onset GBS, concluded that the screening approach is over 50% more effective at preventing early-onset GBS disease than the risk based approach (27). In the CDC guidelines in 2002 they adopted this conclusion and recommend culture-based screenings in the 35-37 gestational week to determine the women who should be offered intrapartum antibiotics (18). Women who have GBS bacteriuria (presence of bacteria in the urine) at any point during pregnancy and women with a history of a previous infant with early-onset GBS should be given intrapartum antibiotic prophylaxis (11, 18). In addition the CDC guidelines do not recommend antibiotics when a planned cesarean delivery before the onset of labor or rupture of membrane occurs.

Intrapartum antibiotic prophylaxis are antibiotics that are given during the period of labor or delivery (intrapartum) with the purpose to prevent infection (prophylaxis) (28). Some studies suggest this treatment reduces the risk to the neonate of early onset disease. However, a recent Cochrane review concluded that there was high risk of bias in study methodology in many of the major studies done on the subject and therefore more studies need to be done before a strong conclusion can be drawn (29). Studies found that even when using the maternal screening method and the appropriate antibiotic regime, early-onset group B streptococcal disease in infants still occurred (30, 31). This could partially be explained by women who have false negative screening results and therefore are not offered antibiotics, insufficient screening, suboptimal antibiotics given, and screening prior to the recommended time (31-34).

For preterm infants the CDC has developed an algorithm for physicians to follow (18). The algorithm suggests that if women do not have a previous GBS culture they obtain a culture immediately. The recommendations err on the safe side stating that women should start intrapartum antibiotic prophylaxis prior to results of the culture, subsequently discontinuing them if and when culture results return negative. There is a similar algorithm for the use of intrapartum antibiotic prophylaxis in women with preterm premature rupture of membranes (pPROM).

In addition to preventing the transmission of bacteria from the mother to the child (primary prevention), the CDC has recommended guidelines for preventing disease in the infant if he/she does acquire the bacteria (secondary prevention). As stated, studies have found that infants still acquire early-onset GBS disease despite the widespread use of the universal screening method (31, 33). In addition, with the implementation of universal screening, over 60% of early-onset GBS cases have been found in mothers who screen negative (31). Physicians must therefore be aware of the signs of sepsis and early-onset GBS disease. Signs of sepsis include: respiratory distress, apnea, fever or unstable temperature, acidosis, and pallor (35). If any of these early signs occur the CDC recommends performing blood and cerebrospinal fluid cultures (18). Some recommend giving the infant broad spectrum antibiotics prior to obtaining culture results (35). In addition, chorioamnionitis in the mother is a risk factor for early-onset GBS disease and can potentially cause intrapartum antibiotics to fail in preventing GBS disease in infants. Therefore the CDC recommends all children born to a mother with chorioamnionitis should undergo a diagnostic evaluation and receive antibiotics while waiting for the results.

In some situations mothers do not receive adequate intrapartum antibiotic prophylaxis because of the duration of exposure prior to delivery or use of an antibiotic with lower efficacy (18). It is recommended that these babies stay in the hospital to be observed for clinical signs of sepsis for 24 to 48 hours (35). Some studies suggest diagnostic testing be performed in this situation however, the latest CDC guidelines suggest simply observing “well-appearing” babies in the hospital (18, 36).

The antibiotic recommended by the CDC is penicillin. Women who are allergic to penicillin should receive cefazolin (if no history of anaphylaxis) or clindamycin (if high risk of anaphylaxis) (18, 37). Antimicrobial susceptibility testing should be done on the culture in cases with women who are allergic to penicillin. Intrapartum antibiotic prophylaxis should be given for at least 4 hours prior to delivery if possible.

The extensive use of intrapartum antibiotic prophylaxis in GBS positive women resulting in antibiotic resistance has been a major concern of experts in regards to the CDC guidelines. As of 2010 GBS is still susceptible to penicillin and ampicillin (11). However other gram negative bacterium such as *E. coli* has shown increasing levels of antibiotic resistance to penicillin and ampicillin (38). This raises concern in the future for women who are allergic to penicillin and GBS positive. In addition, GBS resistance to macrolides such as clindamycin appears to be rising. Various studies in the United States have found about 10-20% of GBS strands to be clindamycin resistant (39-41). Other studies report erythromycin resistance increasing. Although clindamycin and erythromycin should only be used in women who are allergic to penicillin, reports suggest penicillin is only being used 49% of the time (38). The increasing resistance of

GBS to erythromycin and clindamycin highlights the importance of choosing antibiotics carefully.

Many studies conclude that an effective vaccine against GBS is the only way to effectively eliminate early and late-onset GBS disease in infants (29, 32). A vaccine would decrease the concern over antimicrobial resistance as well as help to prevent late-onset GBS disease in infants, and GBS disease in non-pregnant adults (13, 42). Vaccines against GBS are being developed and researched, however no commercially available vaccine has been released yet. There are several phase II studies being done, however the differences in serotypes throughout the world has made it difficult to develop an effective vaccine (42). Analysis done on cost-effectiveness of prevention strategies found vaccines to be by far the most cost effective option if one were to be developed that was safe and effective (43, 44). Vaccine trials in pregnant woman are slow due to the added ethical and health issues associated with research on pregnant women. In addition to targeting pregnant women, some studies suggest targeting adolescent women in order to prevent GBS transmissions in pPROM or lack of second trimester prenatal visits (13, 45, 46). The main concern with adolescent vaccination is the duration of protection and persistence of antibodies in the blood (46).

Term Birth

Definition of terms

Gestational age can be described using two different nomenclatures. First physicians often describe gestational age by the week of gestation completed (47). The week of gestation completed is often reported as the number of completed weeks from

the first day of the last menstrual period. The second nomenclature used describes periods of gestational age thought to be based on clinical differences in morbidity and mortality of infants based on completed gestation (48). In 1970 a working party at the *Second European Congress of Perinatal Medicine* agreed on the following terms: preterm-gestation less than 259 days or 37 weeks; term-259-293 days or 37-41 weeks; and post term- greater than 294 days or 42 weeks.

Accuracy of gestational age determination

Gestational age can be measured in several ways, one of which is starting at the first day of a women's last menstrual period (LMP) (47). The estimated delivery date is 280 days from LMP. Determining gestational age using women's menstrual cycles and LMP can be unreliable as the LMP can be remembered inaccurately by a woman (49, 50). In addition the follicular phase, the time between menstruation and ovulation, can vary in women with irregular periods and may not be equal to the conventionally assigned 14 days. These inaccuracies can cause misclassification of infants as term when they are preterm.

Gestational age can also be determined clinically using ultrasound to measure the size of the head, abdomen and thigh bone of the growing fetus (51). Ultrasound measurement is more accurate if done earlier in pregnancy and not recommended past 20 weeks gestation (52). Studies have found gestational age determined by ultrasound and LMP to be similar; LMP estimates are 0.8 days longer on average than the estimates using the ultrasound method (49). However, some reports indicate agreement between methods in the term period and significant disagreement in preterm and postterm births (53).

Determinants of shortened gestational age

Some risk factors associated with preterm birth are: infection and inflammation, vascular disease, uterine over-distension, previous preterm birth, black race, low maternal body-mass index, and short cervical length (54, 55). Risk factors associated with preterm births could potentially be contributing to early term births as well. Maternal factors that have been associated with early term births include: advanced age (> 35 years), multiparity, and being single (56). Whether other maternal, environmental, and fetal factors differentiate early term birth from late term birth needs to be established. Elective early preterm delivery has also been identified as the most common modifiable cause.

Maternal and neonatal infection is one of the major factors associated with preterm birth. Certain vaginal/cervical colonizers during the latter half of the third trimester may induce an immune response that can potentially result in early term deliveries. Group B *Streptococcus* (GBS) is one bacterium that is normally screened between 35 – 37 weeks of pregnancy (11, 18) and has a high rate of infant mortality due to early onset disease leading to sepsis.

Outcomes based on gestational age

Gestational age is biologically continuous, however when considering the morbidity and mortality associated with gestational age at birth, most people think in terms of preterm, term and post-term categories. Recent research suggests that these categorizations may be misleading and may not portray the message most people believe they do (56, 57). Reddy et al. contends that the period known as “term” is not a homogenous period of time and that in fact there is variation in morbidity and mortality

associated with lower gestational week within the “term” period (56). The entire “term” period may not be a low risk period for all deliveries.

An analysis of the U.S. period-linked birth and infant death data of U.S singleton births from 1995 to 2001 found a 50% increased risk of infant death by 37 completed weeks compared to 39 weeks (0.66 per 1,000 live births at 37 weeks and 0.33 per 1,000 live births at 39 weeks) (58). More recently a similar study using data from 1995 to 2006 found a relative risk of 2.6 for white mothers and 2.9 for non-Hispanic African American mothers for neonatal death at 37 weeks compared to 40 weeks (56). This analysis did mention that the relative risk declined slightly when deaths related to birth defects were excluded. In a large population based survey of repeat caesarean sections the analysis found a risk of adverse outcomes (included: respiratory, admission to NICU, newborn sepsis or hospitalization) 2.1 times higher with a gestational age of 37 weeks compared to 39 weeks (59). Similarly an analysis done on all preterm and term births in an urban hospital found a two to three time higher risk of adverse outcomes when comparing 37 weeks to 39 weeks (60). The same analysis concluded that there was a 23% decrease in adverse outcomes with each additional week from 23 to 29 weeks.

The most common gestational age associated morbidity studied is respiratory morbidity and mortality. Early term births are at an increased risk for respiratory disorders and severe respiratory failures (60, 61). Some studies estimate as high as a two times higher risk of severe respiratory disorder at 38 weeks compared to 39+ weeks (61). In addition other studies have been done that conclude that there is an increased risk of respiratory disorders for late preterm births (35-36wks) compared to term births (62-64).

These studies combine all of term into one category and could potentially be inadvertently masking the heightened risk that still exists at and after 37 weeks.

In addition to respiratory disorders there is a decreased need for resuscitation in the delivery room as the gestational age increases from 34 to 42 weeks (65). The odds of serious neonatal pulmonary disease appear to be highest at 37 weeks in low-risk pregnancies and decreases with increased gestational age (64). The frequency of the need to use mechanical ventilation in neonates appears to decrease as gestational age increases; it appears to be higher in those who are 37-38 weeks (early term) compared to 39 weeks (61, 64, 66). Some of these studies similarly group gestational weeks into categories rather than leaving them as continuous and therefore fail to show the risks associated with each week of gestation.

Due to the heightened risk of adverse outcomes, the rate of hospital stays and length of hospital stays is shorter as gestational age increases (60, 64, 67, 68). Neonatal intensive care unit (NICU) admissions decrease with each additional gestational week until 39 in which the frequency plateaus (68). In addition, stays in the NICU longer than 7 days decreases with a gestational week, however the categorization of gestational age in this study does not allow us to conclude the level at which it plateaus (60).

Studies have shown that even small decreases in gestational age within the term period decreases gray matter density in children 6-10 years of age (69). Authors conclude that “small differences in gestational age can have lasting effects on neurodevelopment for both term and preterm infants and may contribute to long-term risk

for health and disease,” (69). This may relate to studies that show gradual increase in IQ scores from 37 to 40 week gestation (70).

There has been a plethora of studies that look at long term results of preterm birth in terms of educational achievement, economic burden to society, and behavioral and psychiatric issues (71-78). The majority of these studies analyze the data using the referent category as 37 weeks and beyond, in this way considering term as a homogenous group and the continuum of gestational age is lost. A handful of studies done by Lindström et al using a Swedish cohort categorizes gestational age into smaller groups and shows a moderate effect of gestational age on academic and professional achievement, psychiatric admission to hospitals, and attention-deficit/hyperactivity disorder (ADHD) (72, 73, 79). The Swedish cohort showed that infants born with a gestational age less than 39 weeks attended postsecondary education less, were employed less, and were more likely to receive social welfare benefits. Additionally Lindström et al concluded that 85% of the risk of psychiatric admissions to hospitals were attributable to preterm and early term births (73).

The risks associated with preterm birth seem to persist into the early term period (58). However, not enough studies treat gestational age as a continuum and treat the 5-week term period as one homogenous period of time in terms of risk. If studies were to break up term births into categories such as early term (37^{0/7}-38^{6/7}) and late term (39^{0/7}-41^{6/7}), as some of the studies have suggested, more of the risks thought to be associated with preterm birth may be seen in the early term period as well (56, 57).

GBS as a possible determinant of gestational age

Given the differences in neonatal outcomes in early term and late term births, defining the determinants that contribute to early term births is important. Some risk factors associated with preterm birth are: infection and inflammation, vascular disease, uterine over-distension, previous preterm birth, black race, low maternal body-mass index, and short cervical length (54, 55). Some maternal factors that are associated with early term births are: advanced age (> 35 years), multiparity, and being single (56). Whether other maternal, environmental and fetal factors differentiate early term birth from late term birth needs to be established.

Maternal and neonatal infection is one of the major factors associated with preterm birth. Certain vaginal/cervical colonizers during the latter half of third trimester may induce an immune response that can potentially result in early term deliveries. Group B *Streptococcus* (GBS) is one bacterium that is normally screened between 35 – 37 weeks of pregnancy and has the highest rate of infant mortality due to early onset disease leading to sepsis (11, 18). Studies to date have looked at GBS status in relation to preterm birth but none have studied the effects of GBS status on term births and gestational age (12, 16, 80). Understanding the association between GBS colonization during late third trimester and early birth outcomes at term could lead to better case management of GBS positive women and potential avoidance of adverse outcomes. We hypothesize that GBS colonization, in otherwise normal pregnancies, increases the incidence of early term delivery (37 – 39 weeks).

Chapter II: Manuscript

Title Page

Group B *Streptococcus* Colonization is Associated with Early Term Births

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KEY WORDS/ PHRASES: pregnancy, infection, preterm birth, vaginal colonization, GBS

Abstract

OBJECTIVE: To document if maternal *Group B Streptococcus* (GBS) colonization between 35 and 37 weeks of gestation is associated with increased early term birth (between 37 and 39 weeks gestation).

METHODS: In this cohort study of women delivering at term at Centennial Women's Hospital in Nashville, TN, GBS status and other clinical and demographic data were obtained from medical records. Exposed women were those testing positive for GBS (GBS positive [n=490]) and the unexposed tested negative for GBS (GBS negative [n=1,127]). Student's t-tests and logistic regression determined association between GBS status and early term delivery. Breslow-day tests were used to assess heterogeneity across race strata.

RESULTS: The average gestational age was reduced to 271.1 (95% CI 270.4, 271.1) days for the exposed, GBS positive women compared to 274.7 (95% CI 274.4, 275.1) days for unexposed, GBS negative women ($p < 0.0001$). The adjusted odds of early term birth was increased by 3 fold in the exposed (OR 3.28; 95% CI 2.60 - 4.15; $p < 0.0001$). The mean birth weight of GBS positive women was 3285.3 (95% CI 3242.6, 3327.9) grams that was lower than the GBS negative women, 3373.8 (95% CI 3348.9, 3398.7) grams ($p = 0.0004$).

CONCLUSION: Colonization with GBS may have detrimental effects to the term infant through shortening of the gestational age contributing to infant morbidity and mortality warranting appropriate intervention and monitoring of GBS status during pregnancy.

Introduction

The notion of term birth as a homogenous class has recently been challenged (56-58). Previously term birth, 37^{0/7} to 41^{6/7} weeks gestation, was considered clinically as a single period. However recent research has begun to examine the period referred to as “term birth,” and the variations in infant mortality rate within this period (56). When examined more closely, this period is non-uniform in the distribution of the risk of infant morbidity and mortality. Zhang et al reported the increased risk of infant mortality during the preterm period persists into the early term period of 37 through 38 weeks (58). Mortality rate for infants born at 37 week gestational age was 3.9 per 1,000 live births, 2.5 per 1,000 live births at 38 weeks and 1.9 per 1,000 live births for infants born at 40 weeks gestation in 2006 (56). In these reports “early term” birth is referred to as births occurring between 37^{0/7} and 38^{6/7} weeks gestation and “late term” birth is from 39^{0/7} to 41^{6/7} weeks gestation (56).

The disadvantage of early term birth may extend through childhood with infants born in the early term period showing increased rates of disability (69-71). Studies have shown that even small decreases in gestational age within the term period decreases gray matter density in children 6-10 years of age (69). This may relate to studies that show gradual increase in IQ scores from 37 to 40 week gestation (70).

Given the differences in neonatal outcomes in early term and late term births, defining the determinants that contribute to early term births is important. Some risk-factors associated with preterm birth are: infection and inflammation, vascular disease, uterine over-distension, previous preterm birth, black race, low maternal body-mass index, and short cervical length (54, 55). Risk factors associated with preterm births

could potentially be contributing to early term births as well. Maternal factors that have been associated with early term births include: advanced age (> 35 years), multiparity, and being single (56). Whether other maternal, environmental, and fetal factors differentiate early term birth from late term birth needs to be established. Elective early preterm delivery has also been identified as the most common modifiable cause.

Maternal and neonatal infection is one of the major factors associated with preterm birth. Certain vaginal/cervical colonizers during the latter half of the third trimester may induce an immune response that can potentially result in early term deliveries. Group B *Streptococcus* (GBS) is one bacterium that is normally screened between 35 – 37 weeks of pregnancy (11, 18) and has a high rate of infant mortality due to early onset disease leading to sepsis. GBS can be acquired by the fetus from a colonized mother mainly through two mechanisms. The fetus can be infected prior to the onset of labor by an infection that ascends vertically from the vaginal canal crossing intact membranes to establish intraamniotic infection (7, 8, 18). The infant can also be infected during delivery as it passes through the vagina. The major adverse neonatal outcome associated with Group B *Streptococcus* (GBS) colonization of the maternal genital tract is early neonatal sepsis. The Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance reported in 2008 approximately 1,200 cases of early onset disease per year with almost 70% of cases born at term (≥ 37 weeks) (2, 18). GBS disease in infants is associated with significant morbidity and mortality. An estimated 6.8% that are diagnosed with early onset disease due to GBS die (2).

Studies to date have looked at GBS status in relation to preterm birth (2, 12, 16, 80, 81), but none have studied the effects of GBS status on gestational age at term.

Understanding this association between GBS colonization during late third trimester and early birth outcome at term could lead to better case management of GBS positive women and potential avoidance of adverse outcomes. We hypothesize that GBS colonization, in otherwise normal pregnancies, increases the incidence of early term delivery (37 – 39 weeks).

Reports consistently indicate a racial disparity in GBS-associated adverse infant outcome where African Americans are shown to have a higher incidence than other racial groups. The rate of early onset GBS infection among African Americans was almost two times higher than among Caucasians in 2005 (2, 18). In addition, over time there has been an increase in the incidence of GBS early onset disease in African American infants from 0.52 per 1,000 in 2003 to 0.89 per 1,000 in 2005 ($p=0.005$) (2). The primary objective of this study is to document if maternal GBS colonization leads to early term birth and secondarily to determine any racial disparities associated with this condition. We also determined the effect of GBS colonization on birth weight in this study population.

Materials and Methods

Subject Recruitment

Data for this report was derived from two data resources at the Perinatal Research Center, Nashville, TN. Parent studies were designed to examine genetic and biomarker risk factors associated with spontaneous preterm birth for which extensive demographic and clinical data were collected from cases (preterm vaginal birth) and controls (term vaginal deliveries). These studies were approved by the Institutional Review Boards at

TriStar, the parent company of the Institutional Review Board for Centennial Women's Hospital in Nashville, TN and also by WIRB, Seattle, WA. The current study was determined by Emory IRB to not require IRB approval. Term controls from the parent study make up the study population for this report. Subjects were included in the study after informed consent was obtained. The Centennial Women's Hospital is a tertiary care hospital and receives many high-risk pregnancy referrals from Middle Tennessee. Pregnant women ages 18-40 were recruited from the Centennial Women's Hospital from September 2003 to December 2010.

Subjects included in this report had spontaneous onset of labor followed by vaginal delivery. All subjects with labor induction or cesarean sections at term (irrespective of GBS status) were excluded. Subjects with preterm labor, preterm prelabor rupture of the membranes, multiple gestations, preeclampsia, placenta previa, fetal anomalies, and/or medical (such as gestational diabetes mellitus)/ surgical complications of pregnancy and delivering at term were excluded. Gestational age was determined by date of last menstrual period. Participants without gestational age were excluded. Only patients who delivered at term (37^{0/7} weeks to 42^{0/7} weeks) were included in our study. Group B *Streptococcus* status was obtained from medical records and those who tested GBS positive when screened between 35-37 weeks gestation, were considered exposed and those who were GBS negative were unexposed. Race was determined by self-report from a set of provided choices and determined by the race of the mother and father of the fetus, their parents, and grandparents. Subjects of mixed race were excluded from this study. Only those who identified as non-Hispanic African American or non-Hispanic Caucasian were included in the study.

Statistical Analysis

Analyses were conducted to assess comparability of the unexposed group and exposed groups. For categorical variables χ^2 tests were used to assess statistical differences in the distribution of demographic and clinical characteristics between GBS positive and GBS negative women. Gestational age was analyzed as a continuous variable and dichotomized into early term (37^{0/7} - 38^{6/7} weeks) and late term (39^{0/7} - 41^{6/7} weeks) births. Student's t-tests were used to determine statistical differences for continuous variables. In addition, t-tests were performed to determine if racial disparities exist among GBS positive vs. negative women. Chi-squared Breslow-Day tests were used to assess heterogeneity between race stratum in the association between GBS status and early and late term births.

Logistic regression was performed to determine if GBS positive status was associated with shortened gestational age (early and late term births) and then stratified on race to observe possible disparities. Potential confounders adjusted for in logistic regression analysis included: marital status, continuous maternal age, education, employment status, gravidity, smoking status, income level, and insurance.

All analyses were performed with SAS 9.2 and p-values less than 0.05 were considered significant.

Results

A total of 1,617 subjects were included in the study. Of these 608 (37%) were African Americans and 1,039 were Caucasians. Data on the demographic and clinical characteristics of the GBS positive and negative groups are presented in Table 1. The

average age of mothers in our study was 27 years. Overall, thirty percent (n=490) of the women in our study were found to be positive for GBS, which is consistent with the national prevalence of GBS in pregnant women. The GBS positive and negative populations had certain similar characteristics. They did not differ significantly in marital status, income, insurance status, maternal education, smoking status, maternal age or gravidity. In our study population there was a significant difference between GBS status among race ($p = 0.0002$), gestational age ($= < 0.0001$), birth weight ($p = 0.0005$) and APGAR score at 5 minutes ($p = 0.02$).

The average gestational age was significantly reduced to 271.4 (95% CI 270.4, 271.7) for GBS positive women compared to 274.7 (95% CI 274.4, 275.1) days for GBS negative women ($p < 0.001$). In a racially stratified analysis there appears to be a significant mean reduction in gestational age between GBS positive and GBS negative women for both races (African American: $p < 0.001$; Caucasian: $p < 0.001$) (Table 2).

Overall, there was no difference in gestational age between African Americans and Caucasians ($p = 0.44$) (Table 4). However, in our study African American infants had an average birth weight of 3234.7 grams and Caucasian infants had on average a significantly higher birth weight of 3412.5 grams ($p < 0.001$).

Multivariable analysis indicated that the odds of early term birth was increased by 3 fold in GBS positive women (OR 3.28; 95% CI 2.60 - 4.15; $p < 0.0001$) adjusting for marital status, smoking status, income level and insurance. There appeared to be an interaction between GBS and race in early and late term births (Table 6) ($p = 0.033$). The crude odds of early term birth in Caucasian women is 4.06 (95% CI 3.04, 5.43) and for

African American women the odds ratio is 2.48 (95% CI 1.75, 3.51) when considering the interaction between race and GBS status. Moreover, when gestational age was considered as a continuous variable the interaction between GBS and race was also significant (Table 5) ($p=0.0245$). However, the significant interaction between race and GBS status disappears when adjusting for marital status, smoking status, income level, and insurance.

The mean birth weight for the GBS positive group was 3285.3 (95% CI 3242.6, 3327.9) grams while for the GBS negative group mean birth weight was 3373.8 (95% CI 3348.9, 3398.7) grams ($p = 0.0004$). Racial disparities were found in birth weight. Table 3 describes the birth weight differences in GBS status stratified by African Americans and Caucasians. Among African American women birth weight does not show a significant difference based on GBS status ($p=0.3213$). However, among Caucasian women GBS positive status does on average significantly lower birth weight compared to GBS negative status ($p<0.001$).

Discussion

Recent reports have described the period of “term birth” (delivery after the completion of 37 weeks of gestation) as non-uniform and have suggested that pregnancies should be managed in such a way as to prolong gestational age (56-58). The determinants of early term birth have not been extensively studied; although, lower gestational age can have a large impact on the health and development of the child. Early term birth (37 – 39 weeks) and late term births (39 to 42 weeks) have different impacts on neonatal outcome (69-71). However studies primarily examine impacts of preterm birth versus term birth rather than looking at early term versus late term births. Infants

born with a longer gestational age have lower neonatal and infant mortality rates (56). The physiologic reasons for early onset of labor at term have not been extensively studied in part because the pathologic consequences are largely unclear and not emphasized clinically. Since the causal factors for early term labor and delivery have not been clearly established, we examined one of the potential bacterial factors – cervical vaginal GBS colonization - screened between 35 – 37 weeks as a factor associated with this condition.

The results of our study, based on screening of 1,662 women from Nashville Birth Cohort in Tennessee, USA, illustrate that women who are GBS positive between 35-37 weeks gestation are more likely to have an early term birth and a child with a lower birth weight. In our population, GBS positive as compared to negative women are 3 times more likely to deliver between 37 and 39 weeks rather than delivering from 39 to 41 weeks. Our results suggest that women who are GBS positive have a greater risk of an early term birth and it is also associated with significant reduction in birth weight. Both of which can contribute to morbidities similar to that seen in infection associated with preterm birth.

In addition to its association with higher rates of infant morbidity and mortality (56, 57), early term birth can affect the development of the child, the cost of healthcare and may prolong hospital stays. Studies have shown associations between infants born during the early term period and lower cognitive development and in some cases lower IQ (69-71).

African American women historically have higher prevalence of colonization and adverse neonatal outcomes due to GBS colonization (2, 18). Our results showed lower

birth weights among African American women and lower birth weight among GBS positive women. These results indicate that GBS colonization could potentially be a contributing factor to the low birth weight we found among African American women.

More studies are required to determine how GBS positive pregnancies should be managed in order to prolong the gestational age of the child and to determine, if prolonged, is there better childhood outcomes. As suggested by Reddy et al, 40 weeks of gestation has the lowest infant mortality rates across all races and should be regarded as the optimal gestational age to use as a control group rather than analyzing infants born over the entire term period (56). The CDC currently recommends that women who are GBS positive should be treated with intrapartum antibiotic prophylaxis except in the instance of cesarean delivery (18). Some studies suggest this treatment reduces the risk to the neonate of early onset diseases. However, a recent Cochrane review concluded there was insufficient evidence to support a strong conclusion and that more studies need to be done (29). In addition, intrapartum antibiotic prophylaxis does not address the issue of prolonging the pregnancy because the recommended antibiotics are only given after the rupture of the membrane and/or initiation of labor.

There have been few studies conducted on the effectiveness of reducing maternal colonization with GBS by intravenous administration of prophylactic antibiotics antepartum. Studies that have considered treatment in the late third trimester have found its effectiveness in reducing maternal GBS colonization at delivery (82). This treatment option may reduce the risk of intrauterine infection, prolong gestation and prevent early onset neonatal diseases. The CDC does not recommend antepartum antibiotic because some studies indicate the risk of adverse neonatal outcomes (18). Recolonization after

early treatment is common, decreasing the effectiveness of antibiotic prophylaxis on neonatal disease in those patients treated before the onset of labor.

Our study has several innate strengths. There is little room for misclassification bias due to the clearly defined outcomes and recruitment methodology. The study results are also strengthened by the lack of missing data in the dataset especially within the outcome and predictor variables. In addition, the population was clearly stratified in terms of age, race, and other demographic data in this and previous studies (83-85).

Some limitations of the study should be noted. The study is limited to data drawn from one hospital in the South Eastern United States and is yet to be replicated elsewhere. The risk factors associated with early term can be multifactorial and therefore difficult to attribute to one single risk factor. There could be confounders that we have not yet considered or controlled for in our study. The fact that the Group B positive women had a higher incidence of smokers is a cause for concern. This finding could be unrelated, could be a contributing factor to early delivery or could be because of increased susceptibility to colonization due to smoking.

Once GBS colonization is confirmed as one of the risk factors for early term birth, future studies should consider the mechanistic factors leading to early term birth. These can include differences in either maternal or fetal immune response, resulting in early labor. A review of the association between GBS and preterm delivery suggest that bacterial products such as peptidoglycan polysaccharide and phospholipase, can induce a cytokine cascade that may result in labor by stimulation of the prostaglandin pathway (86). Previous studies have also shown that different bacteria produce unique biomarker

signatures and GBS provokes a unique inflammatory response from fetal tissues (9). Based on these studies and our own current findings reported here, in future studies we will examine biomarkers that are associated with GBS colonization in an attempt to elucidate the mechanistic factors associated with this condition.

Chapter III: Extended Conclusions

Further Racial Disparity Discussion

Our study found the average gestational age was significantly reduced in GBS positive women compared to GBS negative women ($p < 0.001$). In a racially stratified analysis gestational age does not appear to be significantly different between GBS positive and GBS negative women for either race, African American or Caucasian (African American: $p < 0.001$; Caucasian: $p < 0.001$) (Table 2). In addition, overall in our study, there was no difference in gestational age between African Americans and Caucasians ($p = 0.44$) (Table 4).

However, when Breslow-Day tests were performed on frequency tables of early and late term infants and GBS status stratified on race there appeared to be a significant difference between the crude odds ratios (Table 6) ($p = 0.033$). The frequency table showed higher crude odds of early term births when GBS positive in Caucasian women (OR=4.06). This could be due to the multifactorial processes at work in pregnancy and gestational age in African American women. The excess risk of preterm births and lower gestational age in African Americans has been studied with no decisive conclusion of the cause. The relative impact of a single factor, such as GBS, may alone have a relatively small impact in African Americans compared to Caucasians due to the other risk factors and processes in play.

Our analysis using interaction terms of GBS and race in models agreed with the conclusions of the Breslow-Day tests. There appeared to be an interaction between GBS and race in early and late term births (Table 6) ($p = 0.033$). The crude odds of early term birth in Caucasian women is 4.06 (95% CI 3.04, 5.43) and for African American women

the odds ratio is 2.48 (95% CI 1.75, 3.51) when considering the interaction between race and GBS status. Moreover, when gestational age was considered as a continuous variable the interaction between GBS and race was also significant (Table 5) ($p=0.0245$). However, the significant interaction between race and GBS status disappears when adjusting for marital status, smoking status, income level, and insurance.

Logistic regression was performed to determine if GBS positive status was associated with shortened gestational age (early and late term births) without considering effect measure modification. Potential confounders were determined based on previous knowledge and percent changes in odds ratios from the gold standard (Table 7). The model that had both small changes in odds ratios and included potential confounders we deemed important *a priori* were included in the final model. Potential confounders adjusted for in the logistic regression analyses included: marital status, continuous maternal age, education, employment status, gravidity, smoking status, income level, and insurance. Multivariable analysis indicated that the odds of early term birth was increased by 3 fold in GBS positive women (OR 3.28; 95%CI 2.60 - 4.15; $p < 0.0001$) adjusting for marital status, smoking status, income level and insurance.

In our study African American infants had an average birth weight of 3234.7 grams and Caucasian infants had on average a significantly higher birth weight of 3412.5 grams ($p < 0.001$). African American women historically have higher prevalence of colonization and adverse neonatal outcomes due to GBS colonization (2, 18). Our results showed lower birth weights among African American women and lower birth weight among GBS positive women. These results indicate that GBS colonization could potentially be a contributing factor to the low birth weight we found among African

American women. However, the pathway from GBS colonization to lower birth weight in African Americans may not be through decreased gestational age. Some researchers present gestational age as a mediating variable and believe controlling for gestational age in studies on the factors contributing to preterm birth will create bias (87).

Strengths and Limitations

Our study has several innate strengths. There is little room for misclassification bias due to the clearly defined outcomes and recruitment methodology. The study results are strengthened by the lack of missing data in the dataset especially within the outcome and predictor variables. In addition, the population was clearly stratified in terms of age, race, and other demographic data in this and previous studies (83-85).

Limitations of the study should be noted. The study is limited to data drawn from one hospital in the South Eastern United States and is yet to be replicated elsewhere.

In addition there appears to be a possible sampling bias that may make it hard to generalize to the larger population. Theoretically if during the parent study the preterm cases and term controls were selected without regard to race then the sample should reflect the racial distribution and disparities present in the source population. The distribution of our sample lead us to believe there may have been an oversampling of Caucasian preterm GBS positive women or African American term GBS negative women in the parent study. This resulted in a relatively equal proportion of GBS positive women in each race category among term births, with Caucasians having a slightly higher proportion of GBS positive results. Historically African American women have higher

prevalence of GBS colonization than Caucasian women, and this was not seen in our study.

The risk factors associated with early term can be multifactorial and therefore difficult to contribute to a single risk factor. There could be confounders that we have not yet considered or controlled for in our study. The fact that the Group B positive women had a higher incidence of smokers is a cause for concern. Smoking is known to be associated with lower birth weight and therefore should be considered further in future analysis. This finding could be unrelated, could be a contributing factor to early delivery, or could be because of increased susceptibility to colonization due to smoking.

Lastly, there could have been misclassification due to the differences in using last missed period or ultrasound dating to determine gestational age. Although studies have shown that there is little difference in the two methods, a difference in a day could have an impact on how a baby is classified. When grouping gestational age into preterm and term infants, or early term and late term, a single day can change the classification of a birth. However, this would not have as a strong an impact if gestational age was used as a continuous variable. Moreover, as stated earlier, on average LMP estimates gestational age 0.8 days longer than the ultrasound method and often there is agreement between the methods (49, 53).

Public Health Implications

Recent reports have described the period of “term birth” (delivery after the completion of 37 weeks of gestation) as non-uniform and have suggested that pregnancies should be managed in such a way as to prolong gestational age (56-58). The

determinants of early term birth have not been extensively studied; although lower gestational age can have a large impact on the health and development of the child. Early term birth (37 – 39 weeks) and late term births (39 to 42 weeks) have different impacts on neonatal outcome (69-71). Studies primarily examine impacts of preterm birth versus term birth rather than looking at early term versus late term births. Infants born with a longer gestational age have lower neonatal and infant mortality rates (56). The physiologic reasons for early onset of labor at term have not been extensively studied in part because the pathologic consequences are largely unclear and not emphasized clinically. Since the causal factors for early term labor and delivery have not been clearly established, we examined one of the potential bacterial factors – cervical vaginal GBS colonization - screened between 35 – 37 weeks as a factor associated with this condition.

The results of our study, based on screening of 1,662 women from Nashville Birth Cohort in Tennessee, USA, illustrate that women who are GBS positive between 35-37 weeks gestation are more likely to have an early term birth and a child with a lower birth weight. In our population, GBS positive women are 3 times more likely to deliver between 37 and 39 weeks compared to delivering 39 to 41 weeks. Our results suggest that women who are GBS positive have a greater risk of an early term birth and it is also associated with significant reduction in birth weight. Both of which can contribute to morbidities similar to that seen in infection associated with preterm birth.

In addition to its association with higher rates of infant morbidity and mortality early term birth can affect the development of the child, the cost of healthcare and may prolong hospital stays (56, 57). Studies have shown associations between infants born

during the early term period and lower cognitive development and in some cases lower IQ (69-71).

Future Directions

More studies are required to determine how GBS positive pregnancies should be managed in order to prolong the gestational age of the child and to determine, if prolonged, is there better childhood outcomes. As suggested by Reddy et al, 40 weeks of gestation has the lowest infant mortality rates across all races and should be regarded as the optimal gestational age to use as a control group rather than analyzing infants born over the entire term period (56). Future studies should begin with gestational age as a continuous variable or break the “term” period into smaller groups in order to better illustrate differences in outcomes based on gestational age. The few studies that have done this have been able to show that outcomes differ from 37 to 42 weeks gestation.

The CDC currently recommends that women who are GBS positive should be treated with intrapartum antibiotic prophylaxis except in the instance of cesarean delivery (18). Some studies suggest this treatment reduces the risk to the neonate of early onset diseases. However, a recent Cochrane review concluded that there was insufficient evidence and bias in the major studies done on the subject and therefore more studies need to be done before a strong conclusion can be drawn (29). Additionally, intrapartum antibiotic prophylaxis does not address the issue of prolonging the pregnancy because the recommended antibiotics are only given after the rupture of the membrane and/or initiation of labor. Physicians and future studies should begin to explore how to prolong

pregnancies of women who are GBS positive if this relationship is found to hold in other populations.

Once GBS colonization is confirmed as one of the risk factors for early term birth, future studies should consider the mechanistic factors leading to early term birth. These can include differences in either maternal or fetal immune response, resulting in early labor. A review of the association between GBS and preterm delivery suggest that bacterial products such as peptidoglycan polysaccharide and phospholipase, can induce a cytokine cascade that may result in labor by stimulation of the prostaglandin pathway (86). Previous studies have also shown that different bacteria produce unique biomarker signatures and GBS provokes a unique inflammatory response from fetal tissues (9). Based on these studies and our own current findings reported here, in future studies we will examine biomarkers that are associated with GBS colonization in an attempt to elucidate the mechanistic factors associated with this condition.

Currently there is no GBS vaccine available, however there are several phase II studies being done. An effective vaccine would prevent colonization in women and transplacental transfer of antibody to infants (11). A GBS vaccine could prevent early and late-onset GBS disease in infants and may have an effect on the racial disparities that exist in neonatal GBS disease. The uneven distribution of GBS serotype in the world has created barriers to producing effective vaccines (35). Although phase II trials of the vaccine are promising there continues to be issues with safety of testing on pregnant women and the durability of the vaccine over time (46).

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Tables

Table 1: Demographic and Clinical Data of Participants based on GBS status, Nashville, TN (2003-2010)

Characteristics	GBS Positive (n=490)	GBS Negative (n=1,127)	Two-tailed P	Total (n=1,617)
Marital Status, n (%)				
Single	219 (46.3)	447 (40.7)	0.12	666 (42.4)
Divorced	12 (2.5)	30 (2.7)		42 (2.7)
Married	242 (51.2)	622 (56.6)		864 (54.9)
Annual income, n (%)				
< \$50,000	364 (77.9)	871 (78.9)	0.65	1235 (78.7)
> \$50,000	103 (22.1)	232 (21.1)		335 (21.3)
Insurance, n (%)				
Insured	413 (87.3)	964 (86.5)	0.67	1377 (86.7)
Uninsured	60 (12.7)	150 (13.5)		210 (13.3)
Maternal Race, n (%)				
Caucasian	285 (56.4)	754 (66.0)	*0.0002	1039 (63.1)
African American	220 (43.6)	388 (34.0)		608 (36.9)
Years of education, mean (SD)	13.8 (2.3)	13.8 (2.4)	0.97	13.8 (2.3)
Maternal Smoking during pregnancy, n (%)				
Nonsmoker	412 (84.9)	989 (88.3)	0.07	1401 (87.2)
Smoker	73 (15.1)	132 (11.7)		205 (12.8)
Maternal Age in years, mean (SD)	26.9 (5.6)	27.1 (5.6)	0.64	27.1 (5.6)
Gestational age in days, mean (SD)	271.1 (6.9)	274.7 (6.2)	*<0.0001	273.6 (6.6)
Birth weight in grams, mean (SD)	3285.3 (480.4)	3373.8 (426.7)	*0.0005	3346.5 (445.4)
Gravidity, n (%)				
1	136 (28.9)	320 (29.4)	0.12	456 (29.3)
2 - 3	216 (46.0)	544 (50.0)		760 (48.8)
> 3	118 (24.1)	224 (20.6)		342 (21.9)
Apgar score, mean (SD)				
At 1 min	8.3 (1.0)	8.4 (0.9)	0.09	8.4 (0.9)
At 5 min	8.9 (0.4)	9.0 (0.3)	*0.02	8.9 (0.3)

*Significant at a 0.05 significance level

Table 2: Gestational age of African Americans and Caucasian newborns, Nashville, TN (2003-2010)

Gestational Age (days)	All Participants**			African American			Caucasian		
	GBS Positive (n= 487)	GBS Negative (n= 1,121)	P	GBS Positive (n= 209)	GBS Negative (n=383)	P	GBS Positive (n=278)	GBS Negative (n=738)	P
Mean \pm SD	271.1 \pm 6.9	274.7 \pm 6.2	*<0.0001	271.6 \pm 7.1	274.4 \pm 6.2	*<0.001	270.5 \pm 6.7	274.9 \pm 6.2	*<0.001
Median	270.2	274.4		272	274.4		270.0	274.8	
Minimum	259	259		259	259		259	259	
Maximum	291	292		289	290		291	292	
Interquartile Range	266-275	271-280		266-276	270-279		266-274	272-280	

*Significant at a 0.05 significance level

**excluded those with missing race information

Table 3: Gestational weight of African Americans and Caucasian newborns, Nashville, TN (2003-2010)

Birth weight (grams)	All Participants**			African Americans			Caucasian		
	GBS Positive (n= 487)	GBS Negative (n= 1,121)	P	GBS Positive (n= 209)	GBS Negative (n= 278)	P	GBS Positive (n= 383)	GBS Negative (n= 738)	P
Mean \pm SD	3284.1 \pm 480.5	3374.4 \pm 426.6	*0.0004	3210.2 \pm 496.2	3248.1 \pm 414.3	0.3213	3339.6 \pm 461.4	3439.9 \pm 418.4	*0.0010
Median	3249	3348		3212	3250		3300	3409	
Minimum	1952	2075		1952	2075		2020	2082	
Maximum	4896	5322		4554	5115		4896	5322	
Interquartile Range	2957-3604	3080-3656		2870-3560	2955-3515		3024-3670	3140-3719	

*Significant at a 0.05 significance level

** excluded those with missing race information

Table 4: Differences in mean gestational age and mean birth weight by race, Nashville TN (2003-2010)

	African Americans (n=608)	Caucasians (n=1039)	P
	Mean \pm SD	Mean \pm SD	
Gestational Age in days	273.7 \pm 6.7	273.6 \pm 6.6	0.440
Birth weight in grams	3234.7 \pm 444.9	3412.5 \pm 432.7	*<0.001

*Significant at a 0.05 significance level

Table 5: Number of gestational days difference between GBS positive and negative women among race based on linear regression, Nashville TN (2003-2010)*

Race	Difference in Days	Lower	Upper
African American Women	-0.39	-0.55	-0.24
Caucasian Women	-0.62	-0.75	-0.49

*interaction between GBS and race was found to be significant in linear regression model ($p=0.025$)

Table 6: Frequency and crude odds of early and late term birth by Group B *Streptococcus* status and stratified by race, Nashville TN (2003-2010)**

	All Participants (n=1,608)			African American (n=592)			Caucasian (n=1,016)			P _{BD} ***
	<u>GBS</u> Positive	<u>GBS</u> Negative	<u>OR</u>	<u>GBS</u> Positive	<u>GBS</u> Negative	<u>OR</u>	<u>GBS</u> Positive	<u>GBS</u> Negative	<u>OR</u>	
Early Term	275	313	*3.35	111	120	*2.48	164	193	4.06	*0.033
Late Term	212	808		98	263		114	545		

*Significant at a 0.05 significance level

**interaction between GBS and race was found to be significant in logistic regression model (p=0.033)

***P_{BD} – Breslow-Day test for odds ratio heterogeneity between races

Table 7. Logistic regression evaluation of confounding of the OR for the gestational age and GBS status, Nashville TN (2003-2010)

	Gold Standard (GS)			Model 1			Model 2		
	OR	Lower	Upper	OR	Lower	Upper	OR	Lower	Upper
Exposure									
GBS status	3.945	2.849	5.463	3.353	2.688	4.183	3.356	2.661	4.233
Potential Confounders									
Marital Status	1.056	0.849	1.313				1.008	0.877	1.159
Annual income	1.189	0.744	1.9				1.313	0.979	1.761
Insurance	1.148	0.492	2.676				0.917	0.655	1.284
Maternal Race	1.023	0.697	1.502				1.182	0.909	1.536
Years of education	0.972	0.889	1.063						
Maternal Smoking in pregnancy	1.082	0.658	1.780						
Maternal Age in years	1.032	0.995	1.071						
Birth weight in grams	0.999	0.914	1.243						
Gravidity	1.066	0.914	1.243						
Apgar score @ 1min	0.998	0.849	1.174						
Description	Adjusted for all potential confounders			Unadjusted			Adjusted for marital status, income (50K), insurance (y/n), and maternal race (b/w)		
Total N	865			1,617			1,511		
Early Term	290			589			545		
Precision of 95% CI for Early Term	1.92			1.56			1.59		
Compared to Model #	-			GS			GS		
%Change in Early Term RR	-			-15.01			-14.93		
Compared to Model #	GS w/o education			GS w/o education			GS w/o education		
%Change in Early Term RR	21.50			3.26			3.36		
Notes	lost many observations due to missing information								

	Model 3			Model 4			Model 5		
	OR	Lower	Upper	OR	Lower	Upper	OR	Lower	Upper
Exposure									
GBS status	4.191	3.072	5.717	3.287	2.603	4.151	3.271	2.589	4.133
Potential Confounders									
Marital Status	1.057	0.872	1.281	1.035	0.898	1.193	0.980	0.840	1.144
Annual income	1.328	849.000	2.078	1.333	0.992	1.791	1.287	0.951	1.740
Insurance	1.038	0.456	2.365	0.912	0.651	1.278	0.925	0.660	1.296
Maternal Race	1.167	0.814	1.674	1.221	0.937	1.591	1.214	0.931	1.583
Years of education	0.969	0.892	1.051						
Maternal Smoking in pregnancy				1.409	1.015	1.955	1.397	1.006	1.940
Maternal Age in years							1.022	0.998	1.046
Birth weight in grams									
Gravidity									
Apgar score @ 1min									
Description	Adjusted for marital status, income (50K), insurance (y/n),maternal race (b/w), education (years)			Adjusted for marital status, income (50K), insurance (y/n),maternal race (b/w), smoking during pregn (y/n)			Adjusted for marital status, income (50K), insurance (y/n),maternal race (b/w), smoking during pregn (y/n), maternal age (years)		
Total N		888			1,501			1,495	
Early Term		296			542			541	
Precision of 95% CI for Early Term		1.86			1.59			1.60	
Compared to Model #		GS			GS			GS	
%Change in Early Term RR		6.24			-16.68			-17.08	
Compared to Model #		GS w/o education			GS w/o education			GS w/o education	
%Change in Early Term RR		29.07			1.23			0.74	
Notes				Smallest % change from GS w/o education and few loses of obs			maternal age has little no effect; in demographics all were relatively the age (small range)		

	Model 6			GS w/o education		
	OR	Lower	Upper	OR	Lower	Upper
Exposure						
GBS status	4.268	3.104	5.868	3.25	2.53	4.16
Potential Confounders						
Marital Status	0.994	0.804	1.230	1.061	0.902	1.248
Annual income	1.261	0.767	1.994	1.211	0.882	1.665
Insurance	1.089	0.478	2.485	0.793	0.55	1.142
Maternal Race	1.166	0.803	1.695	0.983	0.74	1.305
Years of education	0.951	0.872	1.038			
Maternal Smoking in pregnancy	1.258	0.773	2.046	1.13	0.797	1.603
Maternal Age in years	1.036	0.999	1.074	1.017	0.991	1.045
Birth weight in grams				0.999	0.999	0.999
Gravidity	1.06	0.911	1.232	1.094	0.973	1.229
Apgar score @ 1min	0.992	0.847	1.162	0.994	0.872	1.133
Description	Adjusted for everything except birth weight			Adjusted for everything except educ		
Total N	865			1,432		
Early Term	290			519		
Precision of 95% CI for Early Term	1.89			1.64		
Compared to Model #	GS			GS		
%Change in Early Term RR	8.19			-17.69		
Compared to Model #	GS w/o education			GS w/o education		
%Change in Early Term RR	31.44			0.00		
Notes	education is missing in many observations and should not be included as confounder b/c lose too much information			use this as GS model since it has everything except education, and education changes the number of observations dramatically		