



Pregnancy and Neonatal Outcomes of Group B Streptococcus Infection in Preterm Births

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Objective: This study examines whether maternal group B Streptococcus (*Streptococcus agalactiae*, GBS) infection was associated with preterm births and premature neonatal outcomes.

Methods: Maternal and neonatal outcomes were examined among singleton pregnant women with preterm birth (from 24⁺⁰ weeks to 36⁺⁶ weeks) who were tested for GBS (n=203) during the pregnancy. Data were collected retrospectively from the medical records of women who delivered at our hospital from January 2015 to February 2017. We compared obstetrical factors (causes of preterm birth) and neonatal (gestational age at delivery, birth weight, Apgar score 1 min/5 min, hospitalization period, duration of mechanical ventilation, neonatal C-reactive protein within three days, and other complication [respiratory distress syndrome, neonatal deaths]) outcomes between GBS-infected and non-infected pregnant women.

Results: There were 203 singleton pregnant women included in the study, 25 of whom were confirmed to have a GBS infection during the pregnancy. There was no difference in neonatal outcomes by GBS status. Preterm premature rupture of membranes (pPROM), as an obstetric factor, was associated with GBS infection ($P=0.022$). GBS infection raised the risk of pPROM by 3.6 times (odds ratio 3.648, 95% confidence interval 1.476-9.016, $P=0.005$).

Conclusion: GBS infection in preterm birth was associated with pPROM but did not result in adverse neonatal outcomes. Continuous attention and evaluation of GBS infection, a major cause of neonatal sepsis and pneumonia, are needed.

Key Words: Streptococcus agalactiae, Premature birth, Fetal membranes, Premature rupture

Introduction

Group B Streptococcus (*Streptococcus agalactiae*, GBS) is a Gram-positive coccus that frequently colonizes the human genital and gastrointestinal tracts, as well as the upper respiratory tract of young infants.¹⁻³ GBS infections in pregnant women include urinary tract infection, upper genital tract infection, intra-amniotic infection, endometritis, and bacteremia.^{4,5} Neonatal sepsis occurs in 80-85% of cases of early-onset GBS disease.⁶ The mortality rate is 4-6%, and in the case of preterm birth, up to 30%. GBS can be acquired during labor or in utero by transmission from maternal-vaginal or anorectal-colonized mucosa.⁷⁻⁹

In 2002, the US Centers for Disease Control and Prevention (CDC) recommended universal antenatal screening at 35 to 37 weeks of pregnancy and intrapartum chemoprophylaxis for women with GBS colonization.¹⁰ An additional reduction in invasive GBS-related disease was reported after publication of this guideline.^{6,11} Reported maternal colonization rates are quite variable but generally range from 20% to 30%.^{10,12} The differences in colonization rates depend on the particular population and on the laboratory method used to

identify GBS.

Korea has not established a guideline for GBS screening during pregnancy, and there are few reports indicating a Korean interest in perinatal complications related to GBS infection in pregnant women. This lack of concern is probably due to the low GBS infection rate in Korea. Before 2010, according to national reports, the rate of GBS infection in Korean pregnant women was 0.3–5.9%. However, two recent studies reported a 2010 GBS infection rate of 8.3% or 10.0%.^{13,14}

Despite major advances in perinatal care, preterm birth is still the predominant cause of perinatal mortality and a major cause of neurological morbidity in surviving infants. Although the causes of preterm birth are uncertain, evidence suggests that maternal genital tract colonization by specific organisms increases the risk of preterm rupture of membranes and preterm birth.¹⁵

The aim of this study was to examine the relationship between maternal GBS infection and preterm birth outcomes.

Methods

1. Patient population

The study was approved by the institutional review board of Gachon University Gil Medical Center. The medical records of the 1,201 women admitted to our hospital for delivery between January 2015 and February 2017 were reviewed. Of the 1,201 patients, only 395 patients underwent GBS culture. Two hundred three singleton pregnant women with preterm birth (from 24⁺⁰ weeks to 36⁺⁶ weeks) were enrolled. One hundred ninety-two were excluded based on exclusion criteria. The exclusion criteria were multiple pregnancies, term birth, and intrauterine fetal death of unknown cause. Cases in which the baby was transferred to another hospital were also excluded.

2. Data collection

Vaginal cultures were performed for all women who were admitted due to the risk of preterm birth. Indications at such admissions included spontaneous preterm labor (SPTL), preterm premature rupture of membrane (pPROM), incompetent internal os of cervix (IIOC), pregnancy-induced hypertension (PIH), preeclampsia, placenta previa with bleeding, placental

abruption, uterine rupture, sign of fetal distress, fetal growth restriction (FGR), and fetal anomaly. IIOC was diagnosed when cervical length shortening was observed on ultrasound imaging in the second trimester without contractions or labor and in the absence of other clear pathology. Women with pPROM received antibiotic treatment (intravenous cephalosporin 2 g injection) until the culture results were available. If the culture was confirmed positive for GBS before delivery, penicillin or cephalosporin treatment was administered. Women without evidence of pPROM were not treated with antibiotics until culture results were confirmed.

The culture method was changed during the study period. Between January 2015 and February 2016, we obtained specimens from the vagina and anus separately. From March 2016, we used a rectovaginal swab method in which a specimen was obtained from the vaginal entrance and anus sequentially. In the vagina/rectal separate method, if either the vagina or the rectal was positive in culture, it was defined as GBS infection. Included in our assessments were subgroup analyses to detect differences between the two culture methods. Subgroup analysis was performed on all women who underwent GBS analysis (n=395) to examine the effect on GBS detection rate according to the culture method used.

3. Outcome definitions

Maternal and neonatal medical records were analyzed to determine whether the following factors were associated with GBS infection: 1) Obstetric factors (causes of preterm birth) were categorized into five types: SPTL, pPROM, IIOC, maternal complications, and fetal complications. PIH, preeclampsia, placenta previa, placental abruption, and uterine rupture were included as maternal complications, while fetal distress, FGR, and fetal anomaly were included as fetal complications. And 2) Neonatal outcomes such as gestational age at delivery, birth weight, Apgar score at 1 min/5 min, hospitalization period, duration of mechanical ventilation, neonatal C-reactive protein (CRP) within three days, and other complications (respiratory distress syndrome [RDS] and neonatal death) were included.

4. Statistical analysis

To determine whether the presence of GBS statistically differed by pregnancy and neonatal outcome variables chi-

squared test was used for categorical variables and the Mann-Whitney *U* test was used for continuous variables. Univariate analysis and multivariate logistic regression analysis were performed to detect associations with factors and to calculate an odds ratio (OR). Statistical analyses were performed by using SPSS (released 2009, PASW Statistics for Windows, version 18.0; SPSS Inc., Chicago, IL, USA). Null hypotheses of no difference were rejected if *P* values were less than 0.05.

Results

During the study period, 1,201 deliveries had occurred. There were 732 term births and 469 preterm births. Two hundred three cases met the inclusion criteria of being a GBS carrier with a preterm birth (24⁺⁰ weeks to 36⁺⁶ weeks). Of the 203 women that underwent GBS culture analysis, 25 (12.3%) had a positive GBS culture result. Interestingly, the GBS detection rate from samples obtained via the separate vagina/rectal swab method was 6.3%, whereas that from the rectovaginal swab method was 13.2%.

Characteristics of GBS-infected and non-infected subjects were not statistically different. Neither were sexually transmitted disease (STD) infection status nor chorioamnionitis status, which was diagnosed according to pathologic observations, associated with the presence of GBS infection (*P*>0.05). Moreover, there were no differences in the results of blood tests (maternal white blood cell count [WBC] and CRP) that could indicate signs of infection (*P*>0.05) (Table 1).

The incidence of pPROM was significantly higher in the

Table 1. Study Subject Characteristics (n=203)

	GBS (+) (n=25, 12.3%)	GBS (-) (n=178, 87.7%)	<i>P</i> -value
Maternal age (years)	32.6±4.6	33.0±4.9	0.300*
STD infection (%)	4 (9.5)	38 (90.5)	0.610 [†]
Chorioamnionitis (%)	8 (15.1)	45 (84.9)	0.675 [†]
Maternal CRP	1.21±2.65	1.31±3.09	0.389*
Maternal WBC	11,125±3,581	10,923±3,581	0.445*

Values are presented as mean±standard deviation or number (%). Abbreviations: GBS, group B Streptococcus agalactiae; STD, sexually transmitted disease; CRP, C-reactive protein; WBC, white blood cell.

*Mann-Whitney test.

[†]Chi-squared test.

GBS-positive group than the GBS-negative group (*P*=0.022). Among the study subjects, pPROM was the most common cause of preterm birth (n=68, 56.0%). However, the incidence of SPTL was significantly higher in the GBS-negative group (*P*=0.005). IIOC and other causes of preterm birth were not associated with maternal GBS colonization (*P*>0.05) (Table 2).

Neonatal outcomes such as gestational age at delivery, birth weight, Apgar score 1 min/5 min, hospitalization period, duration of mechanical ventilation, neonatal CRP within 3 days, and other complications did not differ by GBS status (*P*>0.05). Two

Table 2. Obstetric Factors between GBS (+) and GBS (-) in Preterm Birth

	GBS (+) (n=25, 12.3%)	GBS (-) (n=178, 87.7%)	<i>P</i> -value*
Causes of preterm birth (%)			
SPTL	2 (8.0)	64 (36.0)	0.005
pPROM	14 (56.0)	54 (30.3)	0.022
IIOC	1 (4.0)	6 (3.4)	1.000
Maternal complications [†]	7 (28.0)	44 (24.7)	0.806
Fetal complications [‡]	1 (4.0)	10 (5.6)	1.000

Values are presented as mean±standard deviation or number (%).

Abbreviations: GBS, group B Streptococcus agalactiae; SPTL, spontaneous preterm labor; pPROM, preterm premature rupture of membrane; IIOC, incompetent internal os of cervix.

*Chi-squared test.

[†]Maternal complications: pregnancy-induced hypertension, preeclampsia, placenta previa, placental abruption, uterine rupture.

[‡]Fetal complications: fetal distress, fetal growth restriction, fetal anomaly.

Table 3. Neonatal Outcomes between GBS (+) and GBS (-) in Preterm Birth

	GBS (+) (n=25, 12.3%)	GBS (-) (n=178, 87.7%)	<i>P</i> -value
Gestational age at delivery (weeks)	32.7±3.3	32.3±3.3	0.154*
Birth weight (g)	2,126±851	1,894±676	0.114*
Apgar score 1 minute	7.6±1.7	7.6±1.9	0.295*
Apgar score 5 minutes	9.0±1.1	9.0±1.4	0.273*
Hospitalization period (days)	32.8±40.5	32.7±40.0	0.412*
Duration of mechanical ventilation (days)	15.6±33.1	13.9±29.9	0.494*
Neonatal CRP within three days	0.40±0.82	0.25±0.57	0.094*
RDS (%)	7 (11.7)	53 (88.3)	1.000 [†]
Neonatal deaths (%)	1 (12.5)	7 (87.5)	1.000 [†]

Values are presented as mean±standard deviation or number (%).

Abbreviations: GBS, group B Streptococcus agalactiae; CRP, C-reactive protein; RDS, respiratory distress syndrome.

*Mann-Whitney test.

[†]Chi-squared test.

Table 4. Logistic Regression-Derived ORs and 95% CIs for the Association between GBS and pPROM

	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Gestational age at delivery	1.020 (1.005-1.034)	0.007	0.987 (0.962-1.014)	0.353
Birth weight	1.001 (1.000-1.001)	<0.001	1.001 (1.000-1.002)	0.002
GBS infection	2.923 (1.247-6.851)	0.014	3.648 (1.476-9.016)	0.005

Abbreviations: GBS, group B *Streptococcus agalactiae*; pPROM, preterm premature rupture of membrane; OR, odds ratio; CI, confidence interval.

neonates from GBS-infected women experienced GBS sepsis, and one neonate died (Table 3).

Based on univariate logistic analysis, GBS infection (OR 2.923, 95% confidence interval [CI] 1.247–6.851, $P=0.014$) was associated with pPROM. Among the maternal factors (maternal age, STD infection, chorioamnionitis, maternal CRP, maternal WBC) and neonatal outcomes (gestational age at delivery, birth weight, Apgar score 1 min/5 min, hospitalization period, duration of mechanical ventilation, neonatal CRP within three days, RDS, neonatal deaths), only gestational age at delivery (OR 1.020, 95% CI 1.005–1.034, $P=0.007$) and birth weight (OR 1.001, 95% CI 1.000–1.001, $P<0.001$) were associated with pPROM, based on the univariate logistic analysis results. After adjustment for gestational age at delivery and birth weight, GBS infection increased the risk of pPROM by 3.6 times (OR 3.648, 95% CI 1.476–9.016, $P=0.005$) (Table 4).

Discussion

Since the rate of GBS infection in Korea is considered low, there has been little apparent interest in perinatal complications associated with GBS infection in pregnant women. For this reason, Korea has not established guidelines for performing GBS screening during pregnancy. We suggest that, if multi-center medical facilities increase their level of interest in GBS infection and routinely conduct GBS analyses, the GBS diagnosis rate in Korea may increase.

In our review, 395 of 1,201 patients underwent GBS infection assessment. Thirty-eight (38/395, 9.6%) of the swab culture-assessed patients were positive for GBS. The percentage of GBS-positive patients with preterm births in the study sample was 12.3% (25/203). This incidence is higher than the infection rate previously reported in Korea but lower than that of other countries.^{10,12–14,16}

GBS prevalence and GBS serotype distribution differ by study region and country. Early-onset neonatal GBS disease has a different distribution among pregnant women in Korea than among those in other countries.^{6,17,18} The apparent increase in GBS infection may be due to a change in serotype following changes in dietary habits and globalization. Further epidemiological studies that include large sample sizes are needed in Korea.

A CDC guideline recommends the use of rectovaginal sampling for GBS detection.³ Based on our swab culture analysis results, after changing the GBS culture method from the use of separate vagina/rectum swabs to using a combined rectovaginal swab, the GBS detection rate increased. Previous studies have also shown that rectovaginal sampling results in an increased GBS-positive rate.¹⁹ However, our study results have a limitation in that no comparisons were made between the two swabbing methods in the same patients.

In our study, the most common cause of preterm birth was pPROM. All patients diagnosed with pPROM were treated with antibiotics, and patients without evidence of pPROM were not treated with antibiotics. Until the vaginal culture results were available, intravenous cephalosporin injections were given to treat a broad spectrum of bacteria in pPROM patients. If the presence of GBS before delivery was confirmed, penicillin or cephalosporin treatment was applied. Treatment for GBS involves administration of penicillin intravenously every 4 hours until delivery, while cephalosporin treatment can be used for patients with a penicillin allergy. For most of our study subjects, delivery was complete before culture results were confirmed, and most patients with pPROM were treated with cephalosporin, which is not the optimal treatment for GBS infection. Failure to apply the most appropriate antibiotic for GBS is a weakness of the treatments reported in this study.

In this study, SPTL appeared to be related to GBS presence. However, the univariate logistic analysis calculated OR was

0.154 (95% CI 0.035–0.672, $P=0.13$). The causes of SPTL are various, and sometimes it is caused by an unknown factor. Our data suggest that maternal GBS infection is not a major cause of SPTL. However, the frequency of SPTL among GBS-infected women was too small (8.0%) to produce accurate results.

In our study, GBS infection was a risk factor for pPROM. We assume that when a maternal GBS infection occurs, it advances through an increasing abundance of GBS, eventually leading to amniotic membrane rupture.

Each of the maternal and fetal complication factors in this study was grouped and classified into two broad categories (maternal or fetal) because each of the individual factors had a small sample size and produced no statistically significant difference related to GBS infection status.

During the study period, there were 68 cases of pPROM in women with preterm births. According to the hospital protocol, all neonates born with pPROM are treated with antibiotics, usually amoxicillin. In this study, all of the neonates whose mothers were identified as GBS infected were observed for at least 24 hours for signs of sepsis and were treated with amoxicillin prophylactically. This protocol has been previously reported to prevent GBS infection and improve neonatal outcomes.²⁰ Perhaps this protocol was responsible for our results that GBS infection did not affect factors such as Apgar scores, hospitalization periods, duration of mechanical ventilation, RDS, and infant mortality rates in our study.

In the case of neonatal death in this study, the GBS-infected mother had a history of gestational diabetes mellitus and SPTL. She had been treated with tocolytics at 31⁺⁵ weeks for 1 week and delivered at 34⁺⁵ weeks. She did not receive antibiotic treatment because her GBS status was not confirmed before delivery. The newborn expired within 16 hours of birth. Blood culture after birth revealed the presence of GBS and the neonate was diagnosed as GBS sepsis.

Ganor-Paz et al.²¹ concluded that GBS carriers with pPROM do not have adverse outcomes. In Ganor-Paz's study²¹, all patients with pPROM were treated with appropriate antibiotics according to a hospital protocol. Those results suggest that complications related to GBS infection such as neonatal sepsis, neonatal infection, and a low 5 minutes Apgar score can be prevented. Based on the results of this and previous studies, further research examining pPROM in GBS carrier patients in

our medical center is needed.

In conclusion maternal GBS infection in preterm birth was associated with pPROM, but it did not affect neonatal outcome. Considering the prognosis of GBS, a major cause of neonatal sepsis and pneumonia, national GBS-related protocols are needed. Along with a GBS screening protocol, accurate screening methods and intrapartum prophylactic antibiotic administration are needed to prevent adverse neonatal outcomes in GBS-infected mothers.

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