Journal of Microbiology, Immunology and Infection (2019) 52, 265–272

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Group B Streptococcal infection in neonates and colonization in pregnant women: An epidemiological retrospective analysis

Ching-Yi Cho [a,d,e], Yi-Hsuan Tang [a,d], Yu-Hsuan Chen [a,d], Szu-Yao Wang [d], Yi-Hsin Yang [f], Ting-Hao Wang [a,d], Chang-Ching Yeh [b], Keh-Gong Wu [a,d,e,**], Mei-Jy Jeng [a,c,d,*]

[a] *Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan*
[b] *Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan*
[c] *Institute of Emergency and Critical Care Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[d] *Department of Pediatrics, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[e] *Division of Pediatric Infectious Disease, Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan*
[f] *School of Medicine, Fu Jen Catholic University, New Taipei, Taiwan*

Received 26 April 2017; received in revised form 3 August 2017; accepted 17 August 2017
Available online 23 August 2017

KEYWORDS
Group B Streptococcus;
Universal screening;
Early-onset disease;
Late-onset disease;
Intrapartum antibiotic prophylaxis

Abstract *Background:* Group B Streptococcus (GBS) infection is one of the major causes of neonatal morbidity and mortality. Universal GBS screening with intrapartum antibiotic prophylaxis (IAP) in pregnant women were initiated in 2012 in Taiwan. This study aimed to analyze the most recent maternal GBS colonization rate and the changes in neonatal GBS infection rate from 2011 to 2016.

Methods: All pregnant women and their live born neonates between January 2011 and June 2016 were retrospectively reviewed. Whether GBS screening was done, screening results, presence of risk factors, the use of antibiotics, and neonatal outcome were analyzed. In addition, hospitalized neonates diagnosed with GBS infections were retrieved for comparison of early onset disease (EOD) (<7 days) and late onset disease (LOD) (≥7 days).

Results: A total of 9535 women delivered babies during the study period. The maternal GBS screening rate was 71.0% and the colonization rate was 22.6%. The overall neonatal invasive GBS infection rate was 0.81 per 1000 live births and the vertical transmission rate was 1.2%. After 2012, the invasive neonatal GBS infection rate declined from 1.1–1.6‰ to 0.6–0.7‰

* Corresponding author. Department of Pediatrics, Taipei Veterans General Hospital, 201, Section 2, Shih-PaiRoad, Taipei 112, Taiwan. Fax: +886 02 28739019.
** Corresponding author. Department of Pediatrics, Taipei Veterans General Hospital, 201, Section 2, Shih-PaiRoad, Taipei 112, Taiwan. Fax: +886 02 28739019.
E-mail addresses: kgwu@vghtpe.gov.tw (K.-G. Wu), mjjeng@vghtpe.gov.tw (M.-J. Jeng).

http://dx.doi.org/10.1016/j.jmii.2017.08.004

in 2014 and thereafter, the GBS EOD incidence rate declined from 2.8‰ to 0.0—0.6‰, but the LOD incidence rate remained approximately 0.7‰. Infants with EOD had strong association with obstetric risk factors.
Conclusions: Taiwan's universal GBS screening with IAP program reduced the incidence rate of neonatal GBS EOD to be lower than 1‰ after 2012. Pediatricians still should pay attention to infants with GBS LOD since its incidence rate remained unchanged.

Background and introduction

Group B Streptococcus (*Streptococcus agalactiae*, GBS) is an encapsulated gram-positive diplococcus frequently found in the human gastrointestinal or lower genital tract.[1,2] GBS colonization of the vagina or rectum has been reported in approximately 25% of all healthy adult women of childbearing age,[3,4] and in pregnant women it can cause asymptomatic bacteriuria, urinary tract infection, chorioamnionitis, postpartum endometritis, and bacteremia. According to a surveillance study by the United States Centers for Disease Control and Prevention (CDC) during 1999—2005, the rate of invasive infection in pregnant women was 0.12 per 1000 live births.[5] In addition, it is a major risk factor for preterm labor, infection in neonates and young infants and subsequent sepsis or sequelae.[6—8] Up to 50% of neonates born to these women will become infected, and 1—2% will develop disease.[9—12]

Vertical transmission most often occurs after the onset of labor or rupture of the fetal membrane, especially when GBS colonization in the vagina is high ($>10^5$ cfu/mL).[13—15] Young infants may also acquire GBS from contact with colonized individuals after discharge and develop late-onset GBS disease (LOD). Several maternal obstetrical factors are associated with an increased risk of developing early-onset GBS disease (EOD). The clinical risk factors include delivery at less than 37 weeks of gestation, premature rupture of the membrane (PROM), rupture of the membrane for 18 h or more before delivery, chorioamnionitis, GBS bacteriuria during the current pregnancy ($>10^4$ cfu/mL), temperature $\geq$ 38 °C during labor, and prior delivery of an infant with GBS disease.[13,16,17] In the US, the incidence of GBS disease has also been reported to be higher among neonates born to African-American mothers and mothers less than 20 years of age.[18—20]

Invasive GBS disease, defined as isolation of GBS from a sterile site, emerged in the 1970s as the leading cause of neonatal morbidity and mortality, of affected newborns were reported to have died from the infection in 1990s.[19,21] To prevent the EOD, consensus guidelines were published in 1996 and recommended either a risk or screening-based approach to identify candidates for intrapartum antibiotic prophylaxis (IAP). This policy resulted in a significant decline in the incidence of invasive GBS disease in newborns, from 1.7 cases per 1000 live births in the early 1990s to 0.34—0.37 cases per 1000 live births in recent years.[13,22—24] Therefore, universal screening at 35—37 weeks of gestation for maternal GBS colonization and the wider use of IAP were promoted by the CDC in 2010, as well as American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the American College of Nurse-Midwives, the American Academy of Family Physicians, and the American Society for Microbiology.[13]

Table 1 shows the trend of GBS disease from 1988 to 2006 Taiwan, which included a GBS colonization rate of around 20% and an incidence rate of GBS disease of 0—2 cases/1000 live births.[25—29,31] On April 15th, 2012, the Ministry of Health and Welfare formally initiated a universal GBS screening program that offered all pregnant women free examinations at 35—37 weeks' gestation. In our hospital, the obstetric physicians follow the CDC guidelines to provide GBS and to determine the candidates for IAP. Women with unknown GBS colonization status at the time of delivery are managed according to the presence of intrapartum risk factors. In addition, the pediatricians manage the neonates based on the algorithm for secondary prevention of EOD among newborns according to the CDC recommendations.[13]

Few reports have investigated GBS colonization in pregnant women and related neonatal infections in Taiwan.[12,26—31] Furthermore, no published studies has investigated the neonatal GBS infection rate after the initiation of the universal GBS screening program and IAP for high-risk pregnancies in Taiwan. Therefore, this study aimed to determine the most recent maternal GBS carrier rate and the related neonatal GBS infection rate before and after the implementation of the universal maternal GBS screening program, and to compare factors related to the early and late onset of neonatal GBS disease.

Methods

This retrospective study was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB), Taipei, Taiwan (number 2016-12-006CC).

Maternal GBS colonization and neonatal GBS infection rates

We conducted a retrospective chart audit of pregnant mothers who gave birth at Taipei Veterans General Hospital between January 1st, 2011 and June 30th, 2016 to obtain complete records of skin-to-skin contact between the mothers and their live neonates. The medical records were reviewed for maternal age, gestational age, whether or not

Table 1 Recent trend of GBS disease in Taiwan.

Authors	Year	Design	Multicenter	Study period	Age (month)	GBS incidence (no./1000 live births)	EOD (%)	LOD (%)	Maternal colonization rate (%)
Yang et al.[28]	1998	Retrospective	−	1988−1996	0−3	NA	9.0	82.0	NA
Ho et al.[27]	1999	Retrospective	−	1985−1995	0−3	0.11−1.39	74.0	26.0	NA
Liao et al.[26]	2002	Retrospective	−	1980−2000	0−3	NA	42.9	57.1	NA
Chung et al.[31]	2004	Retrospective	−	1996−2002	0−3	0−1.83 (EOD)	48.0	52.0	NA
Yu et al.[32]	2011	Retrospective + Prospective	+	2001−2005	0−3	1.1	64.3	35.7	20 (11−29)
Yang et al.[25]	2012	Cohort	−	2005−2006	0	NA	NA	NA	6.2*

*GBS colonization rate of asymptomatic pregnant women at more than 37 weeks' gestation who were planning to undergo vaginal delivery; GBS = Group B Streptococcus; no. = numbers; EOD = early-onset disease; LOD = late-onset disease; NA = not applicable.

GBS screening was performed, screening results, presence or absence of prenatal risk factors for neonatal GBS infection, comorbidities, the use of intrapartum antibiotics and if the treatment was adequate (adequate IAP treatment was defined as receiving $\geq$ 4 h of intravenous penicillin, ampicillin, or cefazolin before delivery), and basic neonatal information including body weight, body height, Apgar scores, and the presence of skin-to-skin contact. The clinical risk factors were defined as followings: presence of the symptoms/signs of infection (any of the following: intrapartum temperature $\geq$ 38 °C, urinary tract infection with more than 10 white cells per high power field or $> 10^4$ cfu/mL bacteria in a urine culture, C-reactive protein level $>$ 1 mg/dl, serum white cell count $>$ 11,000/cumm, differential count with segments $>$ 75%), infectious signs in any of the multiparities, GBS bacteriuria at any time during pregnancy, prior delivery of an infant with GBS disease, preterm premature rupture of the membrane (PPROM), rupture of the membrane 18 h or more before delivery, fetal distress (poor heart rate variation, fetal heart beat $>$180 or $<$100 bpm), dysfunctional labor, presence of meconium in the amniotic fluid, use of an internal fetal monitor, and birth asphyxia (Apgar score $<$5 within 5 min after birth).

All records of the neonates born to the enrolled pregnant mothers were reviewed for microbiological laboratory data and the age at onset of GBS infection. Invasive GBS infection was defined as the laboratory isolation of GBS from a normally sterile site (in our study, blood, cerebrospinal fluid, and urine) with any signs of clinical disease (e,g. sepsis, pneumonia, or meningitis). Non-invasive GBS disease indicated that the GBS culture was identified from a non-sterile site with the signs of clinical disease. The incidence of GBS infection was calculated as the number of cases per 1000 live births during the study period.

Early and late onset of neonatal GBS diseases

To compare the associated clinical factors between the early and late onset of neonatal GBS disease, we further analyzed the records of hospitalized infants aged 0−90 days between January 2009 and June 2016, and enrolled the sick neonates admitted to intermediate nursery or neonatal intensive care units due to neonatal infections for further analysis. The neonates with positive GBS cultures from various sites were recruited, and their sex, gestational age, body weight, age at the onset of symptoms (EOD, defined as disease onset before 7 days of life, and LOD, defined as the development of symptoms after 7 days or more), delivery method (vaginal delivery, or cesarean section, C/S), the need for admission to an intensive care unit, oxygen demand, ventilator use, neurologic sequelae, and the long-term condition at outpatient clinics. We also traced back the clinical data of the mothers of these enrolled sick neonates.

Statistical analysis

SPSS (version 22.0, SPSS Inc., Chicago, IL, USA) was used for data analysis, and SigmaPlot 12.3 (Systat Software Inc., San Jose, CA, USA) was used to create graphical representations. The chi-squared test (goodness-of-fit) for continuity was used for categorical variables and analysis of variations among group means. The Student's *t* test was used to compare patients' data with normal distribution between two groups. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated to compare associated factors among the neonates with no disease, EOD, and LOD. A *p* value less than 0.05 was considered to be statistically significant.

Results

Maternal GBS colonization and neonatal GBS infection rates

A total of 9535 pregnant women who gave birth to 9845 babies were enrolled. The mean age of the mothers was 32.8 $\pm$ 6.2 years, and their mean gestational age was 38.1 $\pm$ 2.2 weeks. Overall, 71.0% of the mothers received GBS screening from 35 to 37 weeks of gestation, and 1532 had positive results for GBS, with 22.6% colonization rate.

The maternal GBS colonization rate ranged from 17.5% to 25.0% during the study period (Fig. 1A), and the overall GBS colonization rate was 22.6%. As shown in Fig. 1A, there were slight fluctuations but no significant changes during past the past 6 years in the maternal GBS colonization rate. Of all women colonized with GBS, 47.6% presented with any one of the clinical risk factors for neonatal GBS transmission.

Regarding IAP, more than 94.1% of the GBS-colonized women received IAP, however only 63.6% received adequate IAP. Among the women with inadequate IAP

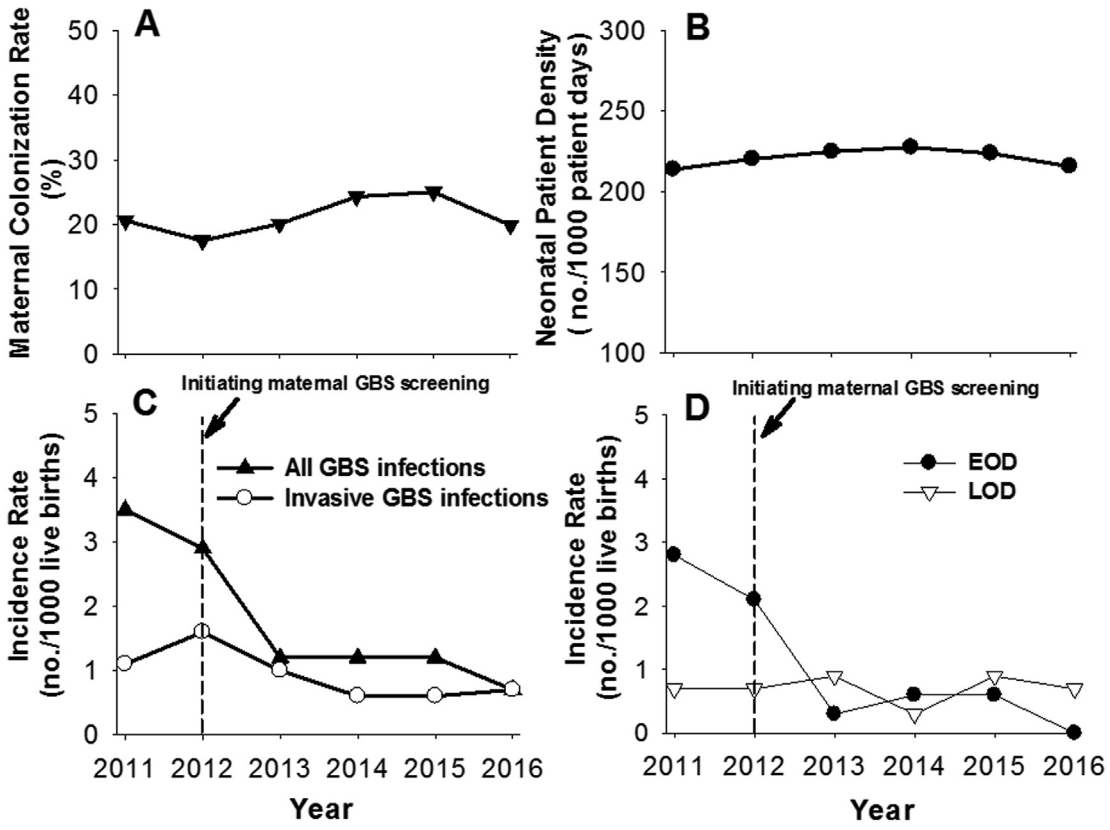

Figure 1. (A) Maternal GBS colonization rate (%), (B) neonatal patient density (numbers/1000 patient-days), (C) incidence rate of GBS disease (numbers/1000 live births), and (D) incidence rate of early onset disease (EOD) and late onset disease (LOD) (numbers/1000 live births) from January 2011 to June 2016. The dotted line in graphs C and D indicates the year maternal universal GBS screening program and adequate IAP were initiated. GBS = Group B Streptococcus; IAP = intrapartum antibiotic prophylaxis.

treatment, one third underwent a C/S procedure. About half of the mothers (51.3%) received IAP before membrane rupture, while the other half was treated after membrane ruptured.

The general neonatal GBS infection rates were 3.5 and 2.9 cases per 1000 live births (‰) in 2011 and 2012, respectively, which fell to 1.2‰ in 2013 and 0.7‰ in 2016 (Fig. 1C). However, the invasive neonatal GBS infection rate declined from 1.1 to 1.6‰ in 2012 and before to 0.6—0.7‰ in 2014 and thereafter (Fig. 1C), although the general neonatal patient densities were similar during the study period (Fig. 1B). Fig. 1 also shows that the incidence rate of EOD declined from 2.8 cases per 1000 live births (‰) to 0 during the study period, while the incidence rate of LOD remained unchanged (Fig. 1D). The top three maternal factors associated with positive neonatal GBS infections were the presence of symptoms/signs of maternal infection, dysfunctional labor, and fetal distress (Fig. 2). Among the 1532 maternal GBS carriers, 18 gave birth to infants with early-onset GBS disease which occurred within 1 day after birth, resulting in a vertical transmission rate of 1.2%.

Early and late onset of neonatal GBS disease

The overall number of hospitalized neonates was 22,413 (mean: 249 cases/month) during the study period, and the total number of patient-days was 101,774 (mean: 1130.8/month), resulting in an average patient density of 220.2 cases/1000 patient-days. A total of 43 infants aged 0—90 days had GBS infections identified by positive culture results from different sites. Thirty-four infants were inborn and the others were outborn, for an average incidence of GBS infection of 3.45 per 1000 live births. When focusing on the infants with to invasive GBS disease (a total of eight infants were delivered at Taipei Veterans General Hospital

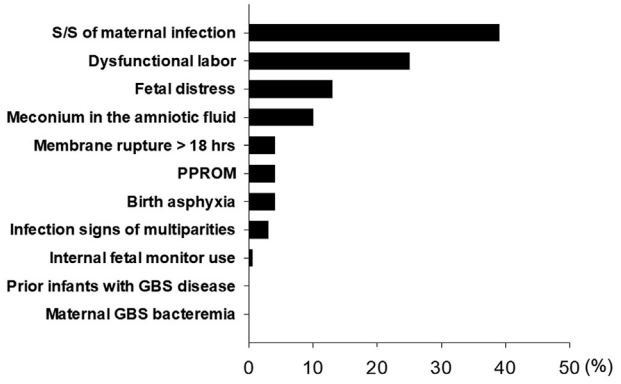

Figure 2. The distribution of risk factors for neonatal transmission among the GBS-colonized mothers. GBS = Group B Streptococcus; S/S = symptoms and signs; PPROM = preterm and premature rupture of membrane.

Table 2 Culture sites of early- and late-onset GBS infection.

Culture sites	EOD N = 31 (%)	LOD N = 12 (%)
Blood	4 (12.9)	8 (66.6)
CSF	0 (0)	2 (16.6)
Urine	0 (0)	4 (33.3)
Ear swab	29 (93.5)	0 (0)
Total	31	12

GBS = Group B Streptococcus; EOD = early-onset disease; LOD = late-onset disease; CSF = cerebrospinal fluid.

with GBS found in the bloodstream, cerebrospinal fluid, and urine), the incidence was 0.81 per 1000 live births.

Among the infants suffering from GBS infection, 31 (72.1%) had EOD, and 12 (27.9%) had LOD. With regards to the culture sites, positive blood cultures were found in 12 of the neonates, cerebrospinal fluid in two, urine in four, and ear swabs in 29. Two neonates had GBS identified both from blood and cerebrospinal fluid, and the other two had GBS in both blood and urine. All of these four patients were in the LOD group. GBS meningitis and urosepsis occurred exclusively in the LOD group. All of the positive ear swab results were identified in the neonates with EOD (Table 2).

The most common presentations of infants with GBS infection were fever, respiratory distress, poor activity, muscle tone, and appetite. For two meningitis cases, seizure and cerebral infarction were found. For babies having positive GBS from ear swab, two of them had GBS bacteremia as well. These two cases required ventilator support (nasal cannula and nasal prong) and even needed to be admitted to the neonatal intensive care unit (NICU) for intensive management. Six out of nine cases with only positive GBS ear swab were admitted to NICU and received ventilator support for the respiratory distress and poor activity. One of them had generalized seizure.

The average gestational age of the GBS-infected babies was 37.6 ± 1.8 weeks, and 69.8% were term babies while 30.2% were premature. One premature infant had a very low birth weight (<1500 g), and there were 29 male infants and 14 female infants. The majority of the infants with EOD had disease onset in the first 24 h of life. The babies with LOD were brought to our hospital at a mean age of 47.25 days (from 9 days to 3 months).

Table 3 shows the neonatal characteristics of the infants without GBS disease, those with EOD, and those with LOD. Among the GBS-infected babies, 29 (67.4%) were delivered vaginally and the others (32.6%) by C/S. The babies delivered vaginally were more prone to develop EOD, with an OR of 5.83 (95% CI 1.36–29.94) compared to those with LOD. There were significantly more premature infants among EOD group, with OR 4.22 (95% CI 2.04–8.73), compared to the healthy infants. Fourteen babies had skin-to-skin contact with their mother immediately after delivery, ten of whom had EOD with positive cultures from ear swabs.

The mean hospital stay of the sick babies was 8.7 days (ranged 3–31 days). Sixteen (37.2%) cases were admitted to the NICU for intensive monitoring and treatment (ranged 3–13 days). Most of these cases were in EOD group, and they had a longer intensive ward stay compared to those in LOD group. Sixteen infants required ventilator support during the hospital stay. The majority of these infants required only nasal cannula or nasal prong assistance, and only four babies were intubated (three in the EOD group and one in the LOD group). The requirement of oxygen assistance was significantly greater in the EOD group. Six babies had central nervous system involvement including meningitis, intraventricular or intracranial hemorrhage, and seizures. Two of these babies suffered from neurologic sequelae including epileptic events, speech delay, and brain infarction that required rehabilitation therapy. No cases of mortality were identified during the study period (Table 4).

Table 5 lists the obstetric characteristics of the infants without GBS disease, those with EOD, and those with LOD. Of the infected infants, 31 (72.1%) of their mothers received GBS screening, which is higher than the average screening rate (71.0%); the other mothers either had unknown GBS status or did not receive screening examinations. Twenty-one of the 31 mothers who received GBS screening had positive results, and there were significant effects of having a positive GBS screening results among the infants with EOD and LOD compared to those without GBS disease. (EOD/no disease: OR 5.05, 95% CI 2.49–10.26; LOD/no disease: OR 3.85, 95% CI 1.22–12.16). Among the mothers of the sick babies, only seven (14.3%) with positive GBS colonization results received adequate IAP. The absence of adequate IAP for maternal colonization had a stronger association with EOD than with no disease (OR 25.68, 95% CI 3.32–198.91). The maternal presentation of symptoms or signs of infection was an important risk factor for GBS transmission, especially in the EOD group. (OR 2.99, 95% CI 1.46–6.11 compared with no disease, OR 4.15, 95% CI 0.39–44.57 compared with LOD). PROM or PPROM also played a significant role in increasing the disease burden in

Table 3 Neonatal characteristics of infants without GBS disease, those with EOD, and those with LOD.

Neonatal characteristics	ND N (%)	EOD N (%)	LOD N (%)	OR (95% CI) EOD/ND	OR (95% CI) LOD/ND	OR (95% CI) EOD/LOD
Prematurity (GA<37 weeks)	1274 (13.0)	12 (38.7)	1 (8.3)	4.22 (2.04–8.73)*	0.61 (0.08–4.71)	6.95 (0.79–60.91)
Vaginal delivery	3354 (69.8)	25 (80.6)	5 (41.7)	1.80 (0.74–4.40)	0.31 (0.10–0.98)*	5.83 (1.36–29.94)*
BBW < 1500 g	196 (2.0)	1 (3.2)	0 (0.0)	1.64 (0.2–12.11)	NA	NA
Sex (male)	5038 (51.4)	16 (51.6)	6 (50.0)	1.01 (0.49–2.05)	0.94 (0.30–2.94)	1.07 (0.28–4.05)
Skin-to-skin contact	5694 (58.1)	12 (38.7)	1 (8.3)	0.46 (0.22–0.94)*	0.07 (0.01–0.51)*	6.95 (0.79–60.91)

*$p < 0.05$. EOD = early-onset disease; GA = gestational age; LOD = late-onset disease; ND = infants without GBS disease; OR = odds ratio (95% confidence interval); BBW = birth body weight; NA = not applicable.

Table 4 Differences in clinical presentations between the EOD and LOD groups.

Clinical findings	EOD N = 31 (%)	LOD N = 12 (%)	*p*
Oxygen support	15 (48.4)	1 (8.3)	0.015
Nasal cannula/ NCPAP	12	0	
Intubation	3	1	
ICU stay	11 (35.5)	5 (41.7)	0.707
Bacteremia	4 (12.9)	8 (66.7)	0.000
CNS involvement/ neurologic sequelae	1 (3.2)	5 (41.7)	0.001
Mortality	0	0	

NCPAP = nasal prong continuous positive airway pressure; EOD = early-onset disease; LOD = late-onset disease; ICU = intensive care unit; CNS = central nervous system.

both EOD (EOD/no disease: OR 6.70, 95% CI 3.13–14.34) and LOD (LOD/no disease: OR 14.06, 95% CI 1.97–100.14). Fetal distress had a greater impact on the EOD group (OR 4.14, 95% CI 1.94–8.85).

Discussion

The present study is the most recent retrospective report of GBS epidemiology among neonates and pregnant women in Taiwan. The results showed a relatively high screening rate (71.0%) since the launch of the universal screening program for all pregnant women. Unexpected preterm labor was the main reason for not undergoing GBS screening, and some women may have received prenatal examinations at local clinics or other hospitals and thus had an unknown or uncertain GBS status. The maternal GBS colonization rate was 22.6% from 2011 to 2016, which is similar to previous studies in Taiwan but slightly higher than in studies from other countries.[3,4] This may be due to the relatively easy access to medical care, and good compliance of the patients and physicians to perform GBS screening.[3,4,9] A prior multicenter study in southern Taiwan reported a colonization rate of 20%, which is very close to our result in a medical center in northern Taiwan, and indicates that the GBS carrier rate is approximately 20% for Taiwanese women of childbearing age.

Our study disclosed an incidence rate of 0.81 per 1000 live births for invasive GBS disease, with a maternal GBS colonization rate of 22.6%. The average maternal colonization rate and incidence of GBS disease were relatively consistent over the past 30 years, even after the implantation of universal screening and IAP. This may be due to increased rate of screening and advances in the techniques used to detect pathogens. However, in our study, the number of identified GBS cases peaked in 2011 and fell gradually thereafter, especially EOD, even though the patient density was slightly higher in 2014. The success of the universal GBS screening program and adequate IAP may have contributed to this finding.

The mean age at delivery of the mothers with GBS-infected infants was 32.5 ± 3.8 years, which is different to earlier research from the U.S. in which neonates born to younger mothers had a higher risk of GBS disease.[19,20] Differences in culture and medical habits may explain this inconsistency. In addition, our study was performed in a tertiary medical center and this may have led to selection bias. That is, the women having babies in our study may had a higher prevalence of risk factors such as older age, more comorbidities and gestation-related illnesses. In addition, women with a higher socioeconomic status or older age tend to choose medical centers instead of local clinics for neonatal delivery in Taiwan.

Neonatal factors

We identified 43 cases with GBS disease during the study period. As in previous studies, the majority of the cases (more than 70%) with EOD developed symptoms or signs of infection within the first 48–72 h of life.[32,33] The 2010 CDC consensus guidelines and previous studies have indicated that the highest incidence of invasive GBS disease occurs in young infants. However, these studies have only reported the burden of disease and the availability of effective interventions for EOD. The reported incidence rate of EOD in infants in Taiwan ranges from 0.11 to 1.8 per 1000 live

Table 5 Obstetric characteristics between the infants without GBS disease, those with EOD and those with LOD.

Obstetric risk factors	ND N (%)	EOD N (%)	LOD N (%)	OR (95% CI) EOD/ND	OR (95% CI) LOD/ND	OR (95% CI) EOD/LOD
No adequate IAP	3117 (31.8)	28 (90.3)	0 (0)	25.68 (3.32–198.91)*	NA	NA
PROM or PPROM	646 (6.6)	9 (29.0)	6 (50.0)	6.70 (3.13–14.34)*	14.06 (1.97–100.14)*	0.48 (0.06–3.89)
Positive GBS screening result	1538 (15.7)	15 (48.4)	6 (41.7)	5.05 (2.49–10.26)*	3.85 (1.22–12.16)*	1.31 (0.34–5.05)
Fetal distress	1009 (10.3)	10 (32.3)	0 (0.0)	4.14 (1.94–8.85)*	NA	NA
S/S of maternal infection	3107 (31.7)	18 (58.1)	3 (25.0)	2.99 (1.46–6.11)*	0.72 (0.07–6.92)	4.15 (0.39–44.57)
Meconium in the amniotic fluid	833 (8.5)	3 (9.7)	0 (0.0)	1.59 (0.56–4.58)	NA	NA
GBS screening	6743 (68.8)	24 (77.4)	7 (50.0)	1.56 (0.67–3.62)	0.45 (0.15–1.41)	3.43 (0.84–14.05)
Dysfunctional labor	2019 (20.6)	2 (6.5)	0 (0.0)	0.41 (0.13–1.36)	NA	NA

*$p < 0.05$. GBS = Group B Streptococcus, EOD = early-onset disease, LOD = late-onset disease; ND = infants without GBS disease, OR = odds ratio (95% confidence interval); IAP = intrapartum antibiotic prophylaxis, PROM = premature rupture of membrane (≥18 h); PPROM = preterm premature rupture of membrane, S/S = symptoms and signs; NA = not applicable.

births, with a mortality rate of 13—14%.[27,29] We identified 20 cases with EOD among 9845 newborn babies delivered at our hospital during the study period, for an incidence rate of 2.03 per 1000 live births. However, when focusing on invasive EOD, the incidence rate was 0.4 per 1000 live births, which is similar to studies in Western countries.[24] In the current study, four babies were delivered out of the delivery room, either at home or in an ambulance. The infants with EOD generally manifested with respiratory distress, apnea, poor muscle tone, poor response to stimuli, or other signs of sepsis. Two babies had positive GBS cultures from both blood and ear swabs, two from blood, the other 29 from ear swabs. These results are compatible with our policy that ear swabs were only performed for neonates who have just been born with suspected perinatal infections. In addition, the EOD group had an increased risk of the need for ventilatory support compared to the LOD group; which is compatible with their relatively high rates of intensive care unit admission and initial presentation with respiratory distress. Urosepsis and meningitis occurred exclusively in the LOD group. Central nervous system involvement such as meningitis, ventriculitis, intraventricular or intracranial hemorrhage, ventricle dilatation, involuntary movement, and neurologic sequelae including seizure, and developmental delay that required long-term rehabilitation all occurred in the LOD group.

Thirty percent of GBS-infected babies were premature, with a higher rate in the EOD group. Compared to the infants without GBS disease, prematurity significantly increased the risk of EOD. Four of the 13 mothers who gave birth to premature babies were unable to receive screening examinations, and none of the mothers colonized with GBS received adequate antibiotic treatment due to unexpected preterm labor. In addition to unknown GBS status and inadequate antibiotic treatment, relatively weak immunity, and a lack of adequate protection from maternal transplacental immunoglobulin may all have resulted in vulnerability to infection. Except for a younger gestational age, the babies delivered vaginally had a greater risk of developing EOD than LOD. EOD is thought to be acquired vertically through exposure to GBS from the vagina when GBS ascends to the amniotic fluid after the onset of labor or rupture of the membrane, even potentially invading through an intact membrane. Skin-to-skin exposure had no significant effect in developing disease in this study.

Maternal (obstetric factors)

With regards to obstetric factors, previous studies have reported that infants with LOD often have no predisposing factors, while those with EOD are associated with maternal obstetric complications.[30,34—37] A study published in 1980s reported that pregnant women with GBS colonization were more than 25 times more likely to deliver infants with EOD than pregnant women with the negative prenatal cultures, mainly due to vertical transmission from endogenous bacteria in the maternal reproductive tract.[38,39]

In the present study, no adequate IAP, PROM or PPROM, positive GBS screening results, fetal distress, and the presence of symptoms or signs of maternal infection outweighed other related factors for GBS transmission to neonates. Among these factors, no adequate IAP revealed the highest OR in infant with EOD, not LOD, in comparison to infants of no GBS disease. Furthermore, the presence of positive GBS screening results had significant impact on the occurrence of both EOD and LOD group. These results provide the evidence that maternal GBS carrying status do relate to both EOD and LOD of their babies, and no adequate IAP definitely increase the risk of EOD. The results are compatible with the previous studies. Therefore, pediatricians should pay more attention to neonates of mothers having the above risk factors. Obstetricians should provide IAP in mothers with positive or unknown GBS screening results to protect their neonates from GBS, especially EOD.

Our study noted that PROM or PPROM associated with high risk of both EOD and LOD. The relationship between PROM/PPROM and EOD is reasonable to be explained by ruptured membrane and increased neonates' bacteria exposure rate during perinatal period. However, the mode of infection route in LOD is more likely to be by direct respiratory (droplets) or gastrointestinal contact of people with close contact to the infant. If there is any possibility that the newborn infants get colonized GBS from ruptured membrane that onset of disease is delayed until the subjects are weak requires further investigations in the future.

There are several limitations to this study. First, it was retrospective research conducted at a single tertiary medical center, and the protocols of maternal colonization and perinatal infection management may be different from other clinics or hospitals. The results may not totally represent the general situation in Taiwan. Second, selection bias should be considered since the pregnant women admitted to our hospital may have had a higher prevalence of risk factors, a higher socioeconomic status, and higher education level. Finally, the study period was relatively short and may be insufficient to show an adequate number of cases and related sequelae. Further investigations with nationwide case number and a longer study period are warranted.

In conclusion, the maternal GBS colonization rate in Taiwan was 22.6% between 2011 and 2016. The universal GBS screening program with adequate IAP launched in 2012 successfully reduced the occurrence rate in neonatal EOD of GBS infections to be lower than 1‰. The infants with EOD had a stronger association with obstetric risk factors. Pediatricians should pay attention to infants with LOD, since almost one-third of the GBS-infected infants in our study had LOD and its incidence rate remained unchanged.

References

1. Wong SS, Tsui K, Liu QD, Lin LC, Tsai CR, Chen LC, et al. Serotypes, surface proteins, and clinical syndromes of invasive Group B Streptococcal infections in northern Taiwan, 1998—2009. *J Microbiol Immunol Infect* 2011;**44**:8—14.
2. Tien N, Ho CM, Lin HJ, Shih MC, Ho MW, Lin HC, et al. Multilocus sequence typing of invasive Group B Streptococcus in central area of Taiwan. *J Microbiol Immunol Infect* 2011;**44**:430—4.
3. Regan JA, Klebanoff MA, Nugent RP. The epidemiology of Group B Streptococcal colonization in pregnancy. *Int J Gynecol Obstetrics* 2004;**38**:71.

4. Davies HD, Miller MA, Faro S, Gregson D, Kehl SC, Jordan JA. Multicenter study of a rapid molecular-based assay for the diagnosis of Group B Streptococcus colonization in pregnant women. *Clin Infect Dis* 2004;**39**:1129—35.
5. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrision LH, Petit S, et al. Epidemiology of invasive Group B Streptococcal disease in the United States, 1999-2005. *JAMA* 2008;**299**:2056—65.
6. Lin MC, Chi H, Chiu NC, Huang FY, Ho CS. Factors for poor prognosis of neonatal bacterial meningitis in a medical center in Northern Taiwan. *J Microbiol Immunol Infect* 2012;**45**:442—7.
7. Chen IL, Chiu NC, Chi H, Hsu CH, Chang JH, Huang TN, et al. Changing of bloodstream infections in a medical center neonatal intensive care unit. *J Microbiol Immunol Infect* October 2015:1—7.
8. Lin MC, Chiu NC, Chi H, Ho CS, Huang F-Y. Evolving trends of neonatal and childhood bacterial meningitis in northern Taiwan. *J Microbiol Immunol Infect* 2015;**48**:296—301.
9. Yancey MK, Duff P, Clark P, Kurtzer T, Horn FB, Kubilis P. Peripartum infection associated with vaginal Group B Streptococcal colonization. *Int J Gynecol Obstetrics* 2004;**50**:115.
10. Agnoli FL. Group B streptococcus: perinatal considerations. *J Fam Pract* 1994;**39**:171—7.
11. McKenna DS, Matson S, Northern I. Maternal Group B Streptococcal (GBS) genital tract colonization at term in women who have asymptomatic GBS bacteriuria. *nfect Dis Obstet Gynecol* 2003;**11**:203—7.
12. Wu CS, Wang SM, Ko WC, Wu JJ, Yang YJ, Liu CC. Group B Streptococcal infections in children in a tertiary care hospital in southern Taiwan. *J Microbiol Immunol Infect* 2004;**37**:169—75.
13. Verani JR, McGee L, Schrag SJ. Division of bacterial diseases, national center for immunization and respiratory diseases, centers for disease control and prevention (CDC). Prevention of perinatal Group B Streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep* 2010;**59**(RR-10):1—36.
14. Ancona RJ, Ferrieri P, Williams PP. Maternal factors that enhance the acquisition of Group -B streptococci by newborn infants. *J Med Microbiol* 1980;**13**:273—80.
15. Pass MA, Gray BM, Khare S, Dillon HC. Prospective studies of Group B Streptococcal infections in infants. *J Pediatr* 1979;**95**:437—43.
16. Gibbs RS. Group B Streptococcal infections. In: *Management of high-risk pregnancy*. Oxford, UK: Blackwell Publishing Ltd; 2007. p. 234—7.
17. Polin RA. Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. *Pediatrics* 2012;**129**:1006—15.
18. Schuchat A, Deaver-Robinson K, Plikaytis BD, Zangwill KM, Mohle-Boetani J, Wenger JD. Multistate case-control study of maternal risk factors for neonatal Group B Streptococcal disease. The Active Surveillance Study group. *Pediatr Infect Dis J* 1994;**13**:623—9.
19. Zangwill KM, Schuchat A, Wenger JD. Group B Streptococcal disease in the United States, 1990: report from a multistate active surveillance system. *MMWR CDC Surveill Summ* 1992;**41**:25—32.
20. Schuchat A, Oxtoby M, Cochi S, et al. Population-based risk factors for neonatal Group B Streptococcal disease: results of a cohort study in metropolitan Atlanta. *J Infect Dis* 1990;**162**:672—7.
21. Centers for Disease Control and Prevention (CDC). Decreasing incidence of perinatal Group B Streptococcal disease—United States, 1993-1995. *MMWR Morb Mortal Wkly Rep* 1997;**46**:473—7.
22. ÓConnor KA. Group B Streptococcal disease in the era of intrapartum antibiotic prophylaxis. *Clin Pediatr* 2001;**40**:361.
23. Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, et al. A population-based comparison of strategies to prevent early-onset Group B Streptococcal disease in neonates. *NEJM* 2009;**347**(4):233—9.
24. Lin FYC, Brenner RA, Johnson YR, Azimi PH, Philips III JB, Regan JA, et al. The effectiveness of risk-based intrapartum chemoprophylaxis for the prevention of early-onset neonatal Group B Streptococcal disease. *Am J Obstetrics Gynecol* 2001;**184**:1204—10.
25. Yang MJ, Sun PL, Wen KC, Chao KC, Chang WH, Chen CY, et al. Prevalence of maternal Group B streptococcus colonization and vertical transmission in low-risk women in a single institute. *J Chin Med Assoc* 2012;**75**:25—8.
26. Liao CH, Huang LM, Lu CY, Lee CY, Hsueh PR, Tsao PN, et al. Group B streptococcus infection in infancy: 21-year experience. *Acta Paediatr Taiwan* 2002;**43**:326—9.
27. Ho MY, Wu CT, Ku YT, Huang FY, Peng CC. Group B Streptococcal infection in neonates: an 11-year review. *Acta Paediatr Taiwan* 1999;**40**:83—6.
28. Yang YJ, Liu CC, Wang SM. Group B streptococcal infections in children: the changing spectrum of infections in infants. *J Microbiol Immunol Infect* 1998;**31**:107—12.
29. Chung MY, Ko DJ, Chen CC, Huang CB, Chung CH, Chen FS, et al. Neonatal Group B Streptococcal infection: a 7-year experience. *Chang Gung Med J* 2004;**27**:501—8.
30. Huang FY. Neonatal Group B streptococcus infection in Taiwan: an increasing trend. *Acta Paediatr Taiwan* 2002;**43**:312.
31. Yu HW, Lin HC, Yang PH, Hsu CH, Hsieh WS, Tsao LY, et al. Group B Streptococcal infection in Taiwan: maternal colonization and neonatal infection. *Pediatr Neonatol* 2011;**52**:190—5.
32. Baker CJ. Early onset Group B Streptococcal disease. *J Pediatr* 1978;**93**:124—5.
33. Al-Kadri H, Bamuhair S, Al-Johani S, Buriki Al N, Tamim H. Maternal and neonatal risk factors for early-onset Group B Streptococcal disease: a case control study. *IJWH* 2013:729—37.
34. Baker CJ, Barrett FF, Gordon RC, Yow MD. Suppurative meningitis due to streptococci of Lancefield Group B: a study of 33 infants. *J Pediatr* 1973;**82**:724—9.
35. Hussain SM, Luedtke GS, Baker CJ, Schlievert PM, Leggiadro RJ. Invasive Group B Streptococcal disease in children beyond early infancy. *Pediatr Infect Dis J* 1995;**14**:27881.
36. Farley MM, Harvey RC, Stull T, Smith JD, Schuchat A, Wenger JD, et al. A population-based assessment of invasive disease due to Group B Streptococcus in nonpregnant adults. *NEJM* 2008;**25**:1807—11.
37. Bonadio WA, Jeruc W, Anderson Y, Smith D. Systemic infection due to Group B beta-hemolytic streptococcus in children. A review of 75 outpatient-evaluated cases during 13 years. *Clin Pediatr* 1992;**31**:230—3.
38. Boyer KM, Gotoff SP. Strategies for chemoprophylaxis of GBS early-onset infections. *Antibiot Chemother* 1971;**1985**(35):267—80.
39. Chan GJ, Lee AC, Baqui AH, Tan J, Black RE. Risk of early-onset neonatal infection with maternal infection or colonization: a global systematic review and meta-analysis. Santosham M *PLoS Med* 2013;**10**(8):e1001502—20.