Original Article

Early-Onset Group B Streptococcal Disease Following Culture-based Screening in Japan: A Single Center Study

Akane Miyata, Hironori Takahashi, Takahiko Kubo, Noriyoshi Watanabe, Keiko Tsukamoto, Yushi Ito, Haruhiko Sago

Department of Maternal-Fetal and Neonatal Medicine, National Center for Child Health and Development

Corresponding author: Hironori Takahashi

Department of Maternal-Fetal and Neonatal Medicine, National Center for Child Health and Development, National Center for Child Health and Development

2-10-1 Okura, Setagaya-ku, Tokyo, 157-8535, JAPAN

Tel: +81-3-3416-0181

Fax: +81-3-3416-2222

E-mail: hironori@alto.ocn.ne.jp

Short title: EOD trend in Japan

Key words: Bacterial infection, group B streptococcus, neonate, screening

Abstract

Aim: We investigated trends in early-onset group B streptococcal disease (EOD) after the introduction of culture-based screening in Japan.

Method: A retrospective cohort study examined EOD trends in 9506 pregnancies and 10715 neonates at our center from 2002 to 2009.

Result: EOD occurred in 4 neonates (4/7332: 0.55/1000 live births). The EOD incidence among infants born to women positive for GBS by screening was 0.90 cases per 1000 live births (1/1107). In contrast, the EOD incidence among infants negative by GBS screening was 0.48 cases per 1000 live births (3/6225). Thus, of the 4 affected neonates, 3 had mothers who tested negative on antepartum GBS screening. Two neonates had symptoms of infection during labor and intrapartum antibiotic agents were administered. The other 2 neonates received no antibiotics because deliveries were uneventful and they were negative on GBS screening.

Conclusion: The incidence of EOD is 0.90 cases per 1000 live births among GBS-positive women and 0.48 cases per 1000 live births among GBS-negative women. The results of our study implied that EOD can develop regardless of GBS screening and intrapartum clinical course, although the method of sample collection, indications for antibiotic prophylaxis, and the antibiotics regimen should be considered.

Introduction

Group B streptococcus (GBS) infection is a significant cause of neonatal morbidity and mortality. GBS neonatal disease is divided into 2 types: early-onset GBS neonatal disease (EOD) and late-onset GBS disease (LOD). EOD occurs during the first seven days of life and presents with respiratory distress, sepsis and meningitis. A randomized controlled trial have shown that intrapartum antibiotic administration decreased EOD [1]. Subsequently, the Centers for Disease Control and Prevention (CDC) published universal screening-based guidelines in 2002 [2]. These guidelines involve intrapartum antibacterial prophylaxis for pregnant women who tested positive on GBS screening at 35 to 37 gestational weeks. This prophylaxis has contributed to a modest reduction in EOD. Moreover, there are racial differences associated with maternal GBS colonization and the incidence of EOD. In fact, persons of African descent are considered to be a high risk for EOD [3, 4]. Trends in perinatal GBS-related epidemiology are most frequently investigated in the United States. EOD rates in Asian populations are apparently low and little is known about EOD trends since the introduction of intrapartum antibiotic prophylaxis in Asian racial groups and/or countries. Our facility is a tertiary health care center in Tokyo. We have managed approximately 10,000 cases employing culture-based screening for GBS since 2002 and

reported EOD trends, including maternal GBS colonization, in Japan.

Materials and Methods

We reviewed the medical records of 9506 pregnancies and 10715 neonates (including multiple fetus pregnancies) that were managed at our center between March 2002 and March 2009. Among these, preterm deliveries, stillbirths and elective cesarean deliveries were excluded. Patients who did not undergo GBS screening were also excluded. The mothers consented to the use of their medical records in advance. GBS screening for all pregnant women was performed at 35 to 37 gestational weeks. Swabs for culture were taken from the vaginal introitus and perianal lesions. No swabs were obtained from the rectum. When the swab revealed evidence of a streptococcal colony, we used latex agglutination to identify GBS colonization. Furthermore, the BD Phoenix system (Beckton Dickinson, NJ, USA) was used for antimicrobial susceptibility testing of GBS. Intrapartum GBS prophylactic treatment was administered to the pregnant women who tested positive on screening (culture-based approach). In addition, we used a risk-based approach for intrapartum treatment. Antibiotics were administered to mothers who had given birth to an infant with EOD and to those with a previous incidence of GBS bacteriuria. Furthermore,

intrapartum antibiotics were given to women for whom more than 18 h had passed since membrane rupture or whose body temperature was ≥38.0°C, regardless of whether they had GBS colonization. As for the antibiotic regimen, ampicillin 1g was given intravenously every 6 hours. Prophylaxis was begun at the time of hospitalization for labor or membrane rupture and continued until delivery. Nasal and auricularis swabs were taken after delivery from neonates who had tested positive on GBS screening. Obstetricians in our center managed all pregnancies and deliveries. Furthermore, neonatologists in our center took care of all neonates from birth. Nasal and auricularis swabs were also taken from neonates whose mothers had tested positive on GBS screening. Complete blood counts (CBC) and blood biochemistry of the umbilical vein were obtained in all neonates. For neonates who had tested positive on GBS screening, neonatal CBC and blood biochemistry values were measured on days 1 and 2 to detect infection and inflammation. EOD was diagnosed by multiple neonatologists in accordance with clinical and laboratory findings. LOD was not evaluated in this study.

Results

The GBS screening results and EOD incidence are summarized in Figure 1. We performed

GBS screening for 6582 pregnant women (7332 fetuses). In these 6582 pregnancies (7332 neonates), the GBS positive rate was 14.9% (979/6582). All GBS strains detected were sensitive to ampicillin. Of 7332 fetuses, EOD was seen in 4 neonates (4/7332; 0.55/1000 live births). The clinical characteristics of these 4 EOD neonates are presented in Table 1. Of the 4 affected neonates, one (Case 1) was born to a woman who had tested positive on GBS screening (1/1107: 0.90/1000 live births), whereas the other 3 (Case 2-4) were born to women who had tested negative (3/6224: 0.48/1000 live births). Furthermore, of the 4 cases, 2 (Cases 1 and 2) were delivered by emergency cesarean section due to non-reassuring fetal status and maternal fever. These 2 cases manifested chorioamnionitis on placental histology. The other 2 (Cases 3 and 4) were normal vaginal deliveries. However, symptoms related to EOD occurred on days 1 and 5, respectively. Consequently, longer hospitalizations were required as compared to the two infants delivered by emergency cesarean section. The 4 affected neonates recovered fully with antibiotic administration and intensive therapies.

Discussion

The incidence of EOD was 0.55 per 1000 live births in this study. In the United States,

EOD incidence has decreased from 1.7, in the early 1990s, to 0.34 to 0.37 cases per 1000 live births in the recent years, due to intrapartum chemoprophylaxis for pregnant women who tested positive on universal GBS screening[5]. However, mortality and morbidity did not change significantly after the introduction of universal antenatal screening for GBS [5]. To further decrease EOD, the CDC recommended that racial and/or regional differences be taken into account [5]. EOD incidence among term black neonates is high, at 0.49 cases per 1000 live births in 2008. [5] This is not attributable to lack of screening or intrapartum chemoprophylaxis. Meanwhile, little is unknown about EOD trends in Asian countries or Asian racial/ethnic groups. To our knowledge, there is only one previous report on the incidence of EOD in Japan [6]. According to that study [6] , the EOD incidence was very low, at 0.10 cases per 1000 live births in hospitals with and 0.11 cases per 1000 live births in hospitals without preventive practices. Although the survey was actually a multicenter study, the data relied on self-reports. Thus, there is a possibility of underestimation of the results. In contrast, our study was performed in a single hospital. Perinatal management was based on uniform clinical practices. In addition, in terms of EOD detection, the active surveillance protocol included frequent blood tests (days 1 and 2 for GBS screening-positive subjects). Thus, not only reliability but also the detection rate can be

regarded as high in this study. In terms of maternal colonization, 14.9% of pregnant women were GBS-screening positive in our study. In Korea, a small study showed that the GBS carrier rate was 10.0% (121/1,205), which was considered to be high in Korea [7]. On the other hand, the rate is 18.6% in the United States [8]. Furthermore, the rate ranged from 6.5% to 36%, with one-third of studies reporting rates of 20% or greater in European countries [9]. Taken together, these observations may suggest that the maternal GBS colonization rate in East-Asian countries is relatively low.

Four infants developed EOD in this study. Three of these neonates were born to GBS screening-negative mothers. Previous reports have suggested that more neonates with EOD had mothers who tested negative, rather than positive, for GBS [10, 11]. A retrospective review showed that 116 of 189 term neonates with EOD (116/189; 61.2%) were born to women who had tested negative on screening [11]. Another review demonstrated that 16 of 25 neonates (16/25; 64%) were born to mothers who were negative on GBS screening [10]. Also, two of our cases had symptoms of infection during labor and chorioamnionitis on histological examination. Fortunately, these 2 infants could be discharged earlier than the other 2 cases. Intrapartum antibiotics might have ameliorated their clinical conditions. Risk factor-based intrapartum chemoprophylaxis for EOD is very important. However, the other

2 infants developed EOD after uneventful deliveries and were born to mothers who were negative on GBS screening. In these cases, EOD prevention might not have been possible under current the protocol.

There are a few limitations that need to be addressed in the present study. First, we adopted a combination of screening-based and risk-based approach of antibiotic treatment as CDC recommended[2]. However, our "risk-based approach" is slightly different from that of the CDC [2]. Risk-based approach of CDC involves administration of prophylactic drugs to women with unknown GBS status at the onset of labor, for whom the duration of membrane rupture is ≥18 h, or whose body temperature is ≥38.0°C [2]. However, we administered antibiotics to women with the duration of membrane rupture as ≥18 h or temperature as ≥38.0°C, even if their GBS screening results were negative. Second, our antibiotics regimen for EOD prophylaxis is different from that of CDC. For CDC, intravenous ampicillin 2 g is administered as the initial dose, and then, 1 g is administered every 4 h until delivery [5]. However, in this study, we administered intravenous ampicillin 1 g as the initial dose, and then, 1 g was administered every 6 h because of a unique national insurance issue in our country. Third, we swabbed the vaginal introitus and perianal lesions and did not swab the rectum for GBS screening in this study. Because swabbing vagina

plus rectum increases the culture yield compared with only vagina[12], CDC recommends that the sample to be taken from the vaginal introitus and rectum [5]. However, the detection rate of vaginal-perianal culture is equivalent to that of vaginal-rectal culture, though the former produces a small number of colonies[13, 14]. In any case, the method of sample collection needs to be standardized to allow comparison of the rate of GBS colonization. Considering these limitations, we cannot compare the incidence of EOD with that mentioned in previous reports.

In conclusion, the incidence of EOD is 0.90 cases per 1000 live births among GBS-positive women and 0.48 cases per 1000 live births among GBS-negative women in our management method. Physicians need to understand that EOD can develop in infants who are born to mothers with negative GBS-screening results, even after an uneventful delivery.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

[1] Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. *N Engl J Med.* 1986; **314**(26): 1665-9.

[2] Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. *MMWR Recomm Rep.* 2002; **51**: 1-22.

[3] Trends in perinatal group B streptococcal disease - United States, 2000-2006. *MMWR Morb Mortal Wkly Rep.* 2009; **58**: 109-12.

[4] Stapleton RD, Kahn JM, Evans LE, Critchlow CW, Gardella CM. Risk factors for group B streptococcal genitourinary tract colonization in pregnant women. *Obstet Gynecol.* 2005; **106**: 1246-52.

[5] Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. *MMWR Recomm Rep.* 2010; **59**: 1-36.

[6] Matsubara K, Kawai M, Nakahata T, *et al.* Procedure for prevention of perinatal group B streptococcal diseases: a multicenter questionnaire survey of hospitals in the Kyoto Neonatal Disease Study Group, Japan. *J Infect Chemother*. 2007; **13**: 59-62.

[7] Hong JS, Choi CW, Park KU, *et al.* Genital group B Streptococcus carrier rate and serotype distribution in Korean pregnant women: implications for group B streptococcal disease in Korean neonates. *J Perinat Med*. 2010; **38**: 373-7.

[8] Regan JA, Klebanoff MA, Nugent RP. The epidemiology of group B streptococcal colonization in pregnancy. Vaginal Infections and Prematurity Study Group. *Obstet Gynecol*. 1991; **77**: 604-10.

[9] Barcaite E, Bartusevicius A, Tameliene R, Kliucinskas M, Maleckiene L, Nadisauskiene R. Prevalence of maternal group B streptococcal colonisation in European countries. *Acta Obstet Gynecol Scand*. 2008; **87**: 260-71.

[10] Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. *Pediatrics*. 2005; **115**: 1240-6.

[11] Van Dyke MK, Phares CR, Lynfield R, *et al.* Evaluation of universal antenatal screening for group B streptococcus. *N Engl J Med.* 2009; **360**: 2626-36.

[12] Philipson EH, Palermino DA, Robinson A. Enhanced antenatal detection of group B streptococcus colonization. *Obstet Gynecol.* 1995; **85**(3): 437-9.

[13] Orafu C, Gill P, Nelson K, Hecht B, Hopkins M. Perianal versus anorectal specimens: Is there a difference in group B streptococcal detection? . *Obstet Gynecol.* 2002; **99**: 1036-9.

[14] Jamie WE, Edwards RK, Duff P. Vaginal-perianal compared with vaginal-rectal cultures for identification of group B streptococci. *Obstet Gynecol.* 2004; **104**: 1058-61.

Figure legend

Figure 1 Maternal GBS colonization and EOD occurrence

Table 1 Characteristics of 4 neonates with early-onset GBS disease

Case	GBS screening	Gestational age	Mode of delivery	Delivery information	Birth weight (g)	Apgar scores 1min/5min	UmA pH	Placental pathology	Intrapartum chemoprophylaxis	EOD	Onset	Symptom	Duration of hospitalization	Prognosis
1	Positive	39w5d	CS	Maternal fever, NRFS	3956	6/7	7.104	Severe chorioamnionitis	Yes	Pneumonia	day 0	RD	11 days	Good
2	Negative	40w2d	CS	Maternal fever, NRFS	3804	3/9	7.269	Mild chorioamnionitis	Yes	Pneumonia	day 0	RD	10 days	Good
3	Negative	38w5d	VD	Unremarkable	3105	8/9	7.34	NA	No	Sepsis	day 5	Doing poorly	18 days	Good
4	Negative	38w1d	VD	Unremarkable	2875	8/9	7.209	NA	No	Pneumonia, sepsis	day 1	RD	18 days	Good

CS; cesarean section, EOD; early-onset disease, NA; information not available, NRFS; non-reassuring fetal status, RD; respiratory distress, UmA; umbilical artery, VD: vaginal delivery

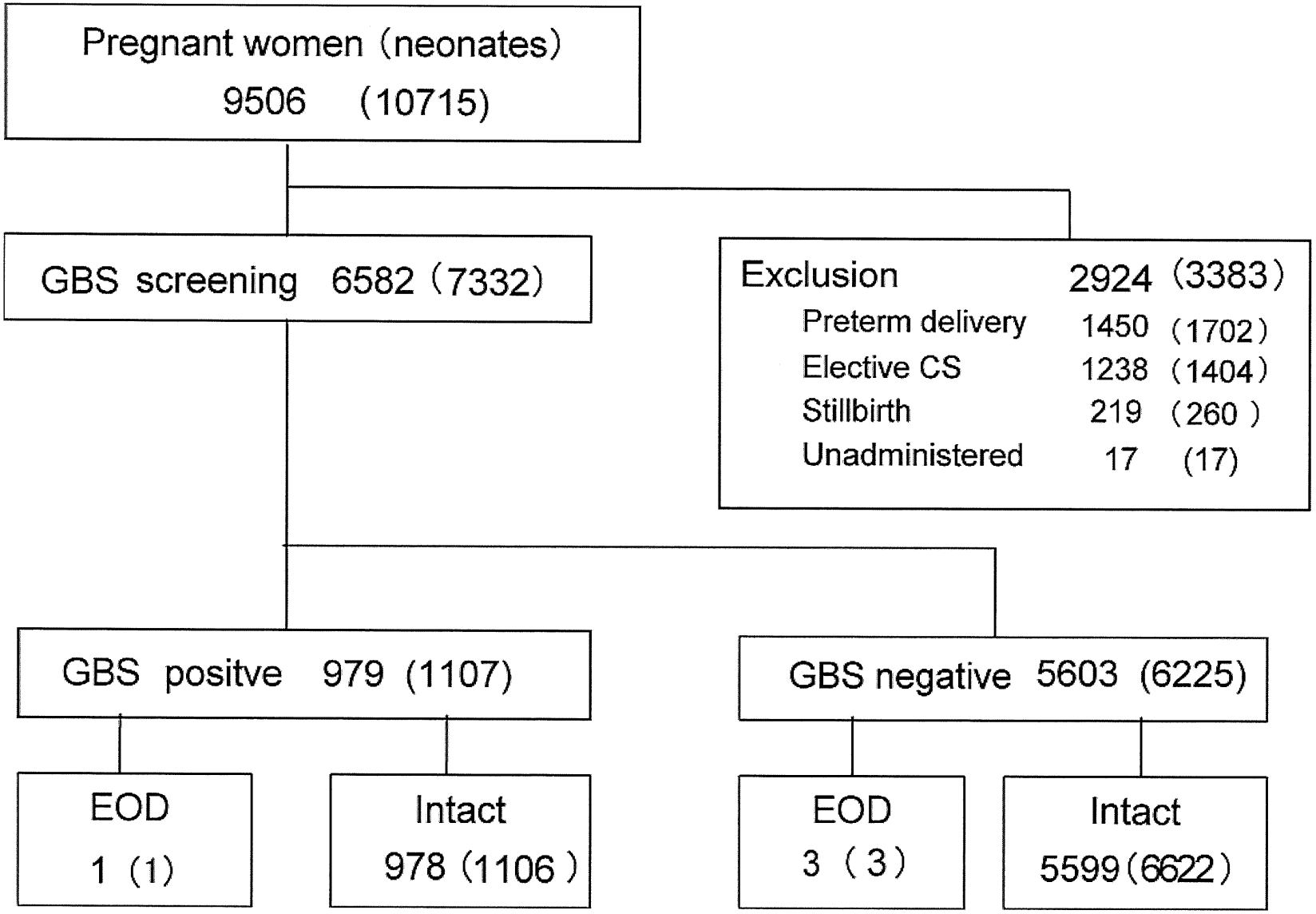

Figure 1 Miyata, et al