

Changes in the incidence and epidemiology of neonatal group B Streptococcal disease over the last two decades in Crete, Greece

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Abstract

Group B streptococcus (GBS) remains a leading cause of neonatal disease. However, GBS rates and prevention strategies vary considerably worldwide. Herein, we investigated the burden and epidemiological trends of neonatal GBS infections in our area (Greece) over the last two decades. We conducted a multicenter retrospective study that includes all cases of culture-proven GBS disease in infants <90 days old in the last 22 years. Neonatal GBS incidence was 0.17/1000 live births (95%CI: 0.11-0.21). A significant increase was noted during the second decade (0.23 vs 0.10/1000, $P<0.05$). Late onset disease (LOD) significantly increased during the second decade (0.08 vs 0.02, $P<0.05$). Infants in the LOD group had a higher risk of meningitis (RR 1.8, 95%CI: 1.23-2.71). Long-term neurological sequelae were reported in 42.8% of meningitis cases. The mortality rate was 8%. The incidence of neonatal GBS disease in our area is among the lowest reported, but an increase was noted the last decade mainly due a rise in the LOD. The burden of LOD, the mortality and long-term disability are still substantial, thus effective prevention strategies – including maternal vaccination for neonatal GBS – are needed.

Introduction

Group B Streptococcus (GBS), or *Streptococcus agalactiae*, is a leading cause of sepsis and meningitis in neonates and young infants, with substantial mortality and morbidity including long term neurode-

velopmental sequelae.¹ Invasive neonatal GBS infection can be classified as early-onset disease (EOD) when it occurs within the first seven days of life, and late onset disease (LOD) when it develops after the first week of life until 90 days old.²

Neonates born from GBS-colonized mothers often become colonized during or before delivery and may develop invasive disease. Following the guidelines for prevention of perinatal GBS disease with universal antenatal screening and/or intrapartum antibiotic prophylaxis for culture-positive and high-risk pregnant women, the incidence of neonatal EOD has significantly declined.^{3,4} However, there is a substantial variability of GBS incidence rates worldwide; in several countries GBS disease affects a significant number of infants, while in others GBS burden remains low.⁵⁻⁸

Research has recently focused on additional strategies for GBS prevention, such as the development of a vaccine. Knowledge of local epidemiology is required to assess the role of prevention and the potential impact of GBS vaccination in pregnant women. Since information on the incidence of GBS neonatal disease is scarce in our country, we assessed GBS epidemiology in neonates and young infants less than 90 days of age in the island of Crete, the largest island of Greece, and we estimated the burden of GBS disease in terms of incidence, mortality and long-term morbidity over a 22-year period.

Materials and Methods

Study period, study participants, and definitions

A case was defined by the isolation of GBS from a normally sterile site on day 0-89 of life in an infant born in Crete. All culture-proven cases of GBS invasive disease were retrospectively included. These infants were managed in all the hospitals that have neonatal intensive care units and pediatric departments, in the study area during a 22-year period, from January 1995 to December 2016. The included hospitals do not only offer intrapartum services, but are also referral centers for pregnant or parturient women and neonates that have been followed either at public or private nursery centers. Microbiological records were reviewed to confirm the diagnosis.

Clinical variables included gender, age at presentation, birth weight, gestational age, delivery mode, time of membrane rupture, previous maternal hospitalization and number of deaths. Medical records of infants with GBS meningitis were addition-

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Key words: neonatal infections, Group B streptococcus, incidence, late onset, early onset, intrapartum prophylaxis.

Contributions: EV, AM, EC, EK and SM collected the case information, EG was involved in planning, drafted the manuscript and supervised the work, EV processed the experimental data, interpreted the results, performed the analysis, drafted the manuscript and designed the figures. All authors discussed the results and commented on the manuscript and contributed to the writing of the manuscript.

Conflict of interest: the authors declare no conflict of interest.

Funding: none.

Received for publication: 12 May 2018.

Revision received: 5 July 2018.

Accepted for publication: 28 June 2018.

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Infectious Disease Reports 2018; 10:7744
doi:10.4081/idr.2018.7744

ally reviewed to assess long-term outcomes. Furthermore, we performed consented parental interviews using a standardized questionnaire that assessed the developmental outcome of GBS subjects with meningitis, including the presence of seizures, movement disabilities, speech delay and learning disabilities, cognitive or behavioral problems and vision or hearing screening. This study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Statistical analysis

The information was used to calculate annual incidence rates (rate per 1000 live births) for EOD and LOD, using data on the total number of live births in Crete as provided by the national statistical authority.⁹ All data were evaluated for normality using Kolmogorov – Smirnov test (with Dallal – Wilkinson – Lilliefors P value). The samples that passed the normality test were analyzed with parametric tests and the rest with non-

parametric ones. The comparison of results between different groups was performed by t-test or one-way analysis of variance with Bonferroni's multiple comparison post test for normally distributed data and Mann Whitney U test or Kruskal-Wallis test with Dunn's multiple comparison post test for non-parametric data. Analysis of categorical data was performed with Fisher's exact test. P-value <0.05 was considered significant. Analysis was made using the GraphPad InStat software (GraphPad, San Diego, CA).

Results

During the 22-year period, there were 148,124 live births in Crete, and 25 neonates and young infants were affected by an invasive GBS infection. The overall incidence of GBS disease was 0.17/1000 live births (95%CI 0.11 to 0.21) and varied from 0.0 to 0.374 annually (Figure 1). The overall incidence of EOD and LOD was 0.11 (95%CI 0.06 to 0.21) and 0.06 (95%CI 0.025 to 0.10) respectively (Figure 1). There were no recurrent GBS cases during the study period.

In pre-term newborns, before 37 weeks of gestational age, GBS incidence was 0.37 per 1000 live births (95%CI 0.06 to 0.68) and was significantly higher compared to overall GBS incidence ($P=0.025$). In infants born at term, after 37 weeks of gestational age, GBS incidence was 0.12 (95%CI 0.07 - 0.17) per 1000 live births.

Interestingly, a significant increase in GBS incidence was noted during the last 11 years compared to the previous decade. In the period from 2006 to 2016, GBS rates raised to 0.23/1000 live births compared to 0.10/1000 live births during the period 1995-2005, $P<0.05$. Most cases were of EOD (incidence 0.10/1000) while LOD (incidence 0.06/1000) were significantly

increased during the last decade (0.08 vs 0.02, $P<0.05$, Figure 2).

The infants' clinical characteristics are depicted in Table 1. The median age of presentation of GBS infection was 2 days (range 0-77), median birth weight was 3,150 g (range 1100-4250) and median gestational age 38.8 weeks (range 24.5-40). Among infants with GBS infection, 7/25 were born with cesarean section, 8/25 presented with meningitis (median age 5 days, range 1-21) and the remaining 17/25 with septicemia. Most cases were of EOD (16/25, 64%) presenting at the ages of 0-3 (median 1) days and commonly within 24 hours of birth. The remaining nine cases were of LOD and presented between days 7 and 28 (6/25, 24%) and between days 28-90 (3/25, 12%).

Among the subjects with EOD, five (5/16, 31.25%) had risk factors for infection. Risk factors that were noted were prematurity (2/16), prolonged rupture of membranes above 18 hours (2/16), or both (1/16) (Table 1). Among the nine cases of LOD at the age of 7-77 (median 18) days, four (44.4%) had a history of previous hospitalization (Table 1). One death was reported in

the EOD group and one death in the LOD group. The overall case fatality rate was 8% (2/25).

In the LOD group, meningitis cases were more common compared to EOD group (44.4% vs 25%, $P=0.007$) (Figure 3). Infants with LOD had a higher risk of presenting with meningitis compared to infants with EOD (RR 1.8, 95%CI: 1.23-2.71).

Meningitis was diagnosed in 32% (8/25) of cases (males 6/8, 75%) in median age of 5 days (range 1-21) and half of them (4/8, 50%) presented with seizures. Infants with GBS meningitis were further assessed for long-term developmental sequelae. Outcome information was available in seven out of the eight meningitis cases. The median age at evaluation was 8.6 years (range 4.1-17.3 years). Four children were normal at evaluation, while three of them (42.8%) were found to have developmental impairments. Specifically, one infant developed cerebral palsy (quadriplegia) and mental retardation, one obstructive hydrocephalus with minor disability (hemiparesis) and another one speech delay without cognitive defects.

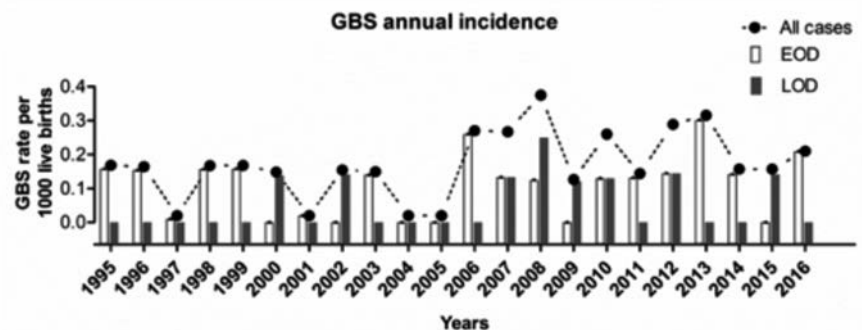


Figure 1. Annual incidence of Group B Streptococcus (GBS) infections in infants less than 90 days of age in Crete, Greece. The rate of all cases of GBS are depicted (circles, black line) as well as the incidence of early onset GBS disease (EOD, white bars) and late onset GBS disease (LOD, gray bars) per each year.

Table 1. Characteristics of infants less than 90 days old with Group B Streptococcus (GBS) invasive disease.

	Total	Early Onset	Late Onset	p values
GBS invasive disease		16/25 (64%)	9/25 (36%)	
Male sex	13/25 (52%)	8/16 (50%)	5/9 (55,5%)	ns
Gestational age (weeks, median)	38.8	38.1	38.8	ns
Prematurity (%)	5/25 (20%)	3/16 (18,7%)	2/9 (22,2%)	ns
Birth weight <1500gr	5/25 (20%)	3/16 (18,7%)	2/9 (22,2%)	ns
Cesarean section (%)	7/25 (28%)	3/16 (18,7%)	4/9 (44,4%)	<0.001
Age at diagnosis (days, median)	2 (0-77)	1 (0-3)	18 (7-77)	<0.001
Premature rupture of membranes	5/25 (20%)	3/16 (18,7%)	2/9 (22,2%)	ns
Meningitis	8/25 (32%)	4/16 (25%)	4/9 (44,4%)	0.007
Deaths	2/25 (8%)	1/16 (6,2%)	1/9 (11,1%)	ns

Discussion

In this study, we describe the incidence, long-term morbidity and mortality rates of GBS invasive disease in infants under 90 days of age in Crete. Over a 22-year period, a low overall incidence of GBS disease of 0.17 per 1000 live births was observed. Incidence was higher in premature infants, but still low compared to previous reports.^{10,11} However, over the last decade, a 4-fold rise in LOD was noted that resulted in a 2.3-fold increase in the total GBS incidence in this age group.

The GBS incidence presented in this study is among the lowest reported so far; the mean GBS incidence worldwide has been estimated at 0.53 per 1000 live births (95% CI 0.44-0.62),⁸ ranging approximately from 0.15 to 3.00.^{5-8,12-14} Information on GBS incidence in Greece is scarce up to now. Limited evidence based on physician records and short periods of observation has shown rates from 0.15 to 0.26 per 1000 live births,¹⁰ in accordance with our findings.

The variations in GBS incidence have been attributed to several factors, such as differences in maternal GBS carriage and GBS antibody levels, lifestyle, genetic susceptibility, GBS strain virulence or delivery outside hospitals that may lead to unrecognized causes.^{15,16} Studies on GBS carriage in Greek women have revealed rates between 4% and 12%,^{9,17-19} which are lower compared to the rates reported in other countries (18 to 37%) with a higher GBS incidence.²⁰⁻²³ Low rates of transmission from mothers to newborns (19-22%) have also been observed in Greece.¹⁰ However, given the retrospective design of our study, a few cases may have not been recorded.

Furthermore, we have no data for culture-negative cases or stillbirths due to GBS.

A substantial increase in perinatal GBS rates was observed during the last years of the study. Preventive measures and recommendations had a significant impact on the rates of GBS in many countries.^{15,16} Guidelines for GBS prevention have been issued by CDC in 1996, followed by national guidelines in many countries worldwide that led to up to a 70% decrease in the incidence of EOD.¹ However, in contrast with other countries where prevention strategies have been implemented, we did not observe a decrease of EOD in our area. In Greece, no national policy on GBS prevention measures has been issued, although the universal culture-based screening program and the intrapartum antibiotic prophylaxis are generally suggested. Failure of a risk-based approach of intrapartum chemoprophylaxis and a rise in rates of GBS invasive disease have been also recently reported in UK.²⁴

Importantly, we noticed a significant increase in GBS LOD invasive infections, that in generally are not affected by prenatal and intrapartum prevention strategies.²⁵ Several risk factors have been associated with LOD. Specifically, LOD due to GBS was found to be associated with hospitalization in infants and indeed almost half of the infants with LOD in our study (44.4%, 4 out of 9) had a history of previous hospitalization.²⁶ Additionally, several case reports have proposed that GBS-infected breast milk may also be a risk factor for LOD and may actually be a cause of LOD even if perinatal preventive measures have been applied.²⁶⁻²⁸ However, we have no information on the breastfeeding practices and on GBS cultures in the maternal milk in the study subjects. Thus, we cannot assess the

potential role of breastfeeding and milk contamination on the increase of LOD.

In infants with GBS meningitis, neurological sequelae were considerable, as neurological disability was observed in 42.5% of infants. This proportion is also comparable to that of recently published studies on long-term evaluation of infants who survived from GBS meningitis.^{1,29,30} The case-fatality rate for GBS neonatal disease is estimated at 1.4 to 18% in recent reports,^{5,7,8,12} and was 8% in our study.

Our results reveal a very low incidence of GBS EOD and LOD in neonates and infants less than 90 days old, lower than the rates reported by many other studies worldwide. However, even if the incidence of GBS neonatal disease remains low in our area, the burden of GBS LOD remains substantial and increases the risk of GBS meningitis. The burden of GBS disease is also reflected in considerably high long-term disability rates.

Conclusions

The above results raise important questions on the value of the existing preventing measures in countries with a low GBS incidence. Since LOD cannot be avoided by prenatal and intrapartum preventive measurements, in the areas with low incidence but substantial burden of LOD, the application of maternal GBS vaccination may be still necessary and important. Further research is needed in our region to determine the potential benefit of new preventive approaches, such as GBS maternal vaccination, on the effective elimination of not only EOD but also LOD burden.

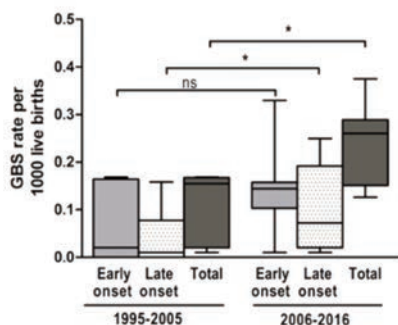


Figure 2. Group B Streptococcus (GBS) rates of early onset disease (EOD), late onset disease (LOD) and total rates of GBS invasive disease in infants less than 90 years old between the decades 1995-2005 and 2006-2016 in Crete, Greece. Boxes show 5–95 percentiles, horizontal line represents median, and whiskers represent minimum and maximum. * $P < 0.05$.

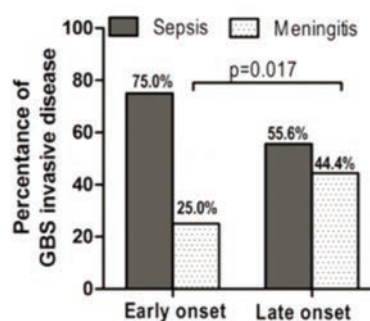


Figure 3. Percentage of Group B Streptococcus (GBS) invasive disease (sepsis and meningitis) in infants born to Crete the last 22 years. Data are categorized to early onset (0-6 days) or late onset (7-89 days) infections.

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