ORIGINAL ARTICLE

Different Prevention Strategies for Early-Onset Neonatal Group B Streptococcal Disease in a Level III Maternity

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Abstract

Introduction: Early-onset neonatal group B *Streptococcus* disease remains the most frequent cause of perinatal bacterial infections in developed countries, despite maternal antimicrobial prophylaxis programs. The present study was conducted to evaluate the effectiveness of different prevention strategies on the incidence rate of early-onset neonatal group B *Streptococcus* disease over the past few years in our institution. Therefore, we aimed to compare the incidence rates associated with early-onset group B *Streptococcus* disease in three periods characterized by different prevention strategies, including no screening and no risk-based approach (January 1996 to December 2003), antibiotic prophylaxis only when there are risk factors (January 2004 to December 2011), and universal screening for group B *Streptococcus* disease in pregnant women (January 2012 to December 2019). In addition, maternal risk factors, clinical features, and outcomes were analyzed.

Methods: We performed a cross-sectional study with nested historical cohort study with a review of records of the neonates with early-onset group B *Streptococcus* disease over a 24-year period, with 27 cases registered.

Results: When a strategy of risk factors alone was applied, the incidence rate was 0.41 per 1,000 live births (95% confidence interval 0-0.84). During the universal screening period, the incidence rate was 0.30 per 1,000 live births (95% confidence interval 0-0.72). However, this reduction was not a statistically significant difference (p = 0.55). Maternal risk factors were registered in 41% of the neonates. The onset of symptoms occurred in the first six hours of life by 67% of the neonates. One death occurred.

Discussion: Although without statistical significance, this study showed a global reduction in the registered cases of early-onset neonatal group B *Streptococcus* disease over the three different prevention strategies.

Keywords: Infant, Newborn; Infectious Disease Transmission, Vertical/prevention & control; Portugal; Pregnancy Complications, Infectious; Streptococcus agalactiae; Streptococcal Infections/prevention & control

Introduction

Streptococcus agalactiae, also known as group B *Streptococcus* (GBS), is a facultative Gram-positive coccus. It was first known as a cause of bovine mastitis, and later in the 1930s, as a distinct entity by Rebecca Lancefield, who used serological tests to distinguish the carbohydrate antigens of GBS.[1,2]

The capsular polysaccharide that encapsulates GBS has long been recognized as its major virulence factor and a total of 10 distinct serotypes have been identified (Ia, Ib and II-IX).[2,3] In accordance with previous studies, serotypes III and Ia were dominant, together accounting for 81% of all isolates.[3-5]

Group B *Streptococcus* remains the most frequent etiologic agent of perinatal bacterial infection in developed countries, despite the administration of intrapartum antibiotic prophylaxis.[6]

The primary risk factor for early-onset neonatal GBS disease is the maternal colonization of the genitourinary and gastrointestinal tracts.[7] Several Portuguese studies assessed the maternal colonization rates and concluded that they ranged between 13.9% and 34.9%.[8,9]

Around 50% of women who are colonized with GBS will transmit the bacteria to their newborns, either through ascending infection or during the process of vaginal delivery.[10] In the absence of intrapartum antibiotic prophylaxis, 1%-2% of these will develop early-onset GBS disease.[11]

Group B *Streptococcus* disease in newborns can be classified based on the time of onset. Early-onset disease occurs in the first six postnatal days, whereas

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disease after seven days and up to three months of life is classified as late-onset.[6,7,11]

Early-onset neonatal GBS disease can present in two forms based on the time of onset and its clinical manifestations.[12] Some newborns may be clinically ill soon after birth, usually presenting with respiratory distress, and others will present in the first 24-48 hours of life, typically with signs and symptoms suggestive of sepsis.[12]

Since 1992, the American Academy of Pediatrics guidelines have advised the screening for the prevention of GBS vertical transmission, with the aim to decrease early-onset infection. The Centers for Disease Control and Prevention published, in 1996, the first consensus guidelines that recommended either an antenatal culture-based or a risk factor-based approach for the administration of intrapartum antibiotic prophylaxis to prevent invasive early-onset neonatal GBS disease.[6] The guidelines were updated and systematic universal screening for GBS was recommended for all pregnant women at 35- 37 weeks.[6,7]

According to the recent committee opinion of the American College of Obstetricians and Gynecologists, published in 2019, intrapartum antibiotic prophylaxis at the time of presentation for delivery is indicated for all women with identified GBS colonization by antenatal vaginal-rectal culture, for women with GBS bacteriuria identified at any point during pregnancy, for women with a history of a previous infant with GBS disease, and for women who present in preterm labor and/or with preterm pre-labor rupture of membranes under 37 0/7 weeks of gestation.[11] This guidance updates the 2010 guidelines published by the Centers for Disease Control and Prevention.[11]

With the implementation of universal maternal antenatal screening, the incidence of early-onset GBS disease has declined from 1.8 cases per 1,000 live births (LB) in 1990 to 0.23 cases per 1,000 live births in 2015.[13]

Even though Portuguese national health authorities only formally implemented the universal GBS screening of pregnant women in September 2011, the neonatology branch of the Sociedade Portuguesa de Pediatria published these recommendations in 2004.[14,15]

The aims of this study were:

- To evaluate the effectiveness of different prevention strategies (no strategy *versus* risk-based strategy *versus* universal screening) for early-onset neonatal GBS disease, implemented during a period of 24 years in a level III maternity;
- To describe a case-series of neonates with early-onset GBS disease, including reported maternal risk factors, neonatal characteristics, and short- and long-term outcomes.

Methods

Study

We performed a cross-sectional study with a nested historical cohort study, based on the clinical and laboratory records of all newborns with the diagnosis of early-onset GBS disease, over a period of 24 years.

Maternidade Bissaya Barreto is a level III maternity integrated in Centro Hospitalar e Universitário de Coimbra, with an average of 3,000 births and 270 neonatal intensive care unit (NICU) admissions per year.

Inclusion criteria

All neonates born between 1 January 1996 and 31 December 2019 in Maternidade Bissaya Barreto with early-onset GBS disease were included in this study. In our hospital, all neonates with disease or suspected disease are admitted to the NICU for surveillance, monitoring and treatment.

Exclusion criteria

All neonates transferred from other care units with early-onset GBS disease were excluded. Cases of late-onset GBS infection have not been analyzed in this study.

Definitions

Early-onset GBS disease was defined by a positive blood culture for GSB associated with a clinical of sepsis and/or meningitis and/or pneumonia in the first 6 days of life.

Group B *Streptococcus* sepsis was defined as a positive blood culture for GBS accompanied by two or more of the following criteria: hypothermia or hyperthermia, apnea, bradycardia, or tachycardia, capillary refill time > 2 seconds, metabolic acidosis not explained by another clinical context, hyperglycemia, hypotonia, lethargy, need of ventilation or worsening of gas exchanges.[16]

Meningitis was defined as newborns who developed two or more signs of central nervous system infection: cerebrospinal fluid white blood cell count > 20/mL, glucose cerebrospinal fluid level < 70%-80% of plasma glucose or proteins > 150 mg/dL and a positive cerebrospinal fluid culture for GBS.[16]

Diagnosis of pneumonia was defined as new or progressive infiltrates or opacification on the chest X-ray, worsening of gas exchanges, and four or more of the following criteria: bradycardia or tachycardia, tachypnea or apnea, hypothermia or hyperthermia, respiratory distress, in neonates with a positive blood culture or with a positive culture from a tracheal aspirate.[16]

Short-term complications were related to the use of

vasopressor/inotropic agents, the need of mechanical ventilatory support, or death occurring during the NICU stay.

After the discharge, all neonates had a follow-up until 2 years of life. Long-term severe neurological or functional impairment was defined as blindness, bilateral sensorineural hearing loss, cerebral palsy, and/or significantly delayed development and learning (defined by a global development quotient < 70 points using the Griffiths mental development scale or significant delays in two or more developmental domains using growing skills scale).[17]

Protocols

In our institution, different GBS prevention strategies were used over time to identify women at risk of having a newborn with early-onset GBS disease. For analysis, three different periods were considered:

Period 1: No screening and no risk-based approach (1996-2003) and

Period 2: Risk-based approach (2004-2011). In 2003, antibiotic prophylaxis based on the presence of intrapartum risk factors for early-onset GBS disease was introduced (risk-based strategy). Women who presented risk factors were started on intrapartum antibiotic prophylaxis in labor. Risk factors for GBS disease were defined as: maternal GBS colonization, GBS bacteriuria/urinary tract infection identified at any point during pregnancy, a previous sibling with invasive GBS disease, preterm labor and/or preterm pre-labor rupture of membranes, under 37 0/7 weeks gestation, maternal intrapartum fever (≥ 38ºC), prolonged rupture of amniotic membrane ≥ 18 hours, and clinical signs of maternal chorioamnionitis or an intraamniotic infection.

Period 3: Universal screening (2012-2019). In 2012, the universal antenatal screening for GBS carrier in all pregnant women was introduced in our maternity unit (screening strategy). This includes, in all pregnant women, the culture of GBS by rectal and vaginal swabs at 35-37 weeks gestational age and starting intrapartum antibiotic prophylaxis in those with positive results.

Data collection

All data were obtained from the clinical and laboratory records of each patient.

Initially, the authors assessed the progress in the incidence rate of early-onset neonatal GBS disease in the neonatal intensive care unit over a period of 24 years, determining the cumulative rates of disease for each year and for each of the three defined periods.

The analyzed variables included demographic variables, including gestational age, type of delivery, Apgar score, need for resuscitation in the delivery room, sex, birth weight, and maternal risk factors for neonatal GBS disease were obtained. The clinical signs, type, and duration of antibiotic therapy as well as the length of stay and outcome were also analyzed.

Statistics

The early-onset GBS disease incidence rate (i) was expressed as the number of cases per 1,000 live births:

$$\text{i} = \frac{\text{number of cases of early} - \text{onset GBS disease}}{\text{total number of live births}} \; x \; 1{,}000$$

The case fatality rate (CFR) refers to the proportion of fatal cases among those who have the disease. The case fatality rate was expressed by the following formula:

$$\text{CFR} = \frac{\text{number of deaths due to early} - \text{onset GBS disease}}{\text{total number of cases with early} - \text{onset GBS disease}} \; x \; 100$$

Severe impairment rate (SIR) refers to the proportion of these cases among those who have the disease. The severe impairment rate was expressed by the following formula:

$$\text{SIR} = \frac{\text{number of cases of severe impairment due to early} - \text{onset GBS disease}}{\text{total number of cases with early} - \text{onset GBS disease}} \; x \; 100$$

For statistical analysis, SPSS® Statistics version 25 was used and was assessed at a significance level of 0.05. A descriptive analysis was carried out, with the parameters median and standard deviation (SD) in numerical continuous variables and frequencies and percentages for discrete variables. We calculated the incidence rates and their 95% confidence intervals (95% CI).

Results

Infection rates

From a total of 69,080 LB (average of 2,878 per year) during the study period, 27 met the inclusion criteria. Therefore, in our institution, the global incidence rate of early-onset GBS disease was 0.38 cases per 1,000 LB (95% CI 0.23-0.54).

When analyzing cases according to the different protocols in place, the incidence rate before the risk-based protocol for intrapartum antibiotic prophylaxis (period 1: 1996-2003) was 0.44 cases per 1,000 LB (95% CI 0.28-0.60), during the implementation of the risk-based strategy (period 2: 2004-2011) was 0.41 cases per 1,000 LB (95% CI 0-0.84) and after the universal screening (period 3: 2012-2019) was 0.30 per 1,000 LB (95% CI: 0-0.72) (Table 1). These findings were not statistically significant (p = 0.55, Kruskal-Wallis test) (Table 1).

Case series analysis

Reported risk factors for early-onset GBS disease

Eleven of 27 (41%) mothers of newborns with early-onset GBS infection presented with risk factors for infection (Table 2).

Infants characteristics and perinatal period

Most newborns (20/27, 74%) were born at term, 4/27 (15%) were low birth weight for gestational age, and 5/27 (19%) needed active resuscitation in the delivery room. Table 3 shows the characteristics of the cases, the route of delivery, the and fetal and neonatal data.

Table 1. Crude incidence and incidence rates of early-onset neonatal group *B Streptococcus* disease per year and during the different periods of the study in the neonatal intensive care unit between 1996 and 2019.

Study period	Year	Cases (n)	LB (n)	Incidence (/1000 LB)	95% IC	*p* value
No screening and no risk-based approach	1996	1	2807	0.36	0-2	
	1997	1	2953	0.34	0-1.9	
	1998	1	3040	0.33	0-1.8	
	1999	1	3210	0.31	0-1.7	
	2000	1	3312	0.30	0-1.7	
	2001	3	3100	0.97	0-2.6	
	2002	1	3110	0.32	0-1.7	
	2003	2	3225	0.62	0.1-2.2	
	Total	11	24 757	0.44	0.28-0.60	0.752◊
Risk-based factors strategy	2004	0	3121	0.00	0-1.2	
	2005	0	3101	0.00	0-1.2	
	2006	1	3086	0.32	0-1.8	
	2007	0	3189	0.00	0-1.2	
	2008	2	3282	0.61	0.1-2.2	
	2009	1	2977	0.34	0-1.9	
	2010	3	3036	0.99	0.2-2.9	
	2011	3	2857	1.05	0.1-3.1	
	Total	10	24 649	0.41	0-0.84	0.55†
Universal screening	2012	3	2618	1.15	0.2-3.3	
	2013	2	2441	0.82	0.1-3	
	2014	0	2361	0.00	0-1.6	
	2015	0	2510	0.00	0-1.5	
	2016	0	2490	0.00	0-1.5	
	2017	0	2426	0.00	0-1.5	
	2018	0	2411	0.00	0-1.5	
	2019	1	2417	0.41	0-2.3	
	Total	6	19674	0.30	0-0.72	
Total		27	69 080	0.38	0.23-0.54	0.537*

95% CI - 95% confidence interval; LB - Live births.
*Mann-Whitney test.
†Kruskal-Wallis test.

Table 2. Prevalence of the reported risk factors among the early-onset group *B Streptococcus* infection cases in the neonatal intensive care unit between 1996 and 2019.

Preterm labor and/or with preterm pre-labor rupture of membranes	7 (26%)
Prolonged rupture of amniotic membrane ≥ 18 hours	3 (11%)
Maternal intrapartum fever (≥ 38ºC)	2 (7%)
Clinical signs of maternal chorioamnionitis or intraamniotic infection	2 (7%)
Maternal group B *Streptococcus* colonization*	1 (4%)
Group B *Streptococcus* bacteriuria/urinary tract infection identified at any point during pregnancy	0
Previous sibling with invasive group B *Streptococcus* disease	0
More than one risk factor	4 (15%)

*In this case, the mother did not receive intrapartum antibiotic prophylaxis.

Among the 27 neonates, all had sepsis (100%), five (19%) had sepsis associated with meningitis, and one (4%) had sepsis associated with pneumonia.

Most of the infants presented with symptoms in the first few hours after birth: 67% in the first six hours, with 96% of all cases occurring in the first 72 hours. One case presented at the 4th day of life.

Antimicrobial therapy

The median length of stay was 10 days (SD 18 days, range 4-100 days). Most newborns admitted to the NICU were treated with ampicillin in association with an aminoglycoside (18/27, 67%). The median duration of antimicrobial treatment was 10 days (SD 4.5 days, range 7-23 days).

Outcomes

Short-term outcomes are reported in Table 4.

The case fatality rate was 4% (1/27) (95% CI 0-13). In this fatal case, maternal GBS colonization was unknown and no other maternal risk factor was identified. This full-term neonate was born by spontaneous vaginal delivery and had a good adaptation to extrauterine life. At 7 hours of life, she was found to be unresponsive and apneic in the newborn nursery at the maternity hospital. Cardiopulmonary resuscitation was initiated immediately and later she showed signs of severe neonatal encephalopathy. A positive blood culture for GSB was registered. She died at NICU after 31 days of hospitalization. The fatal case occurred in 2012 during the universal screening period.

All the neonates were followed during the first two years after discharge from the NICU, with the case from 2019, currently 19 months old, still under follow-up. Four infants were reported to have long-term impairment, of which two were diagnosed with meningitis (Table 5).

Table 3. Characteristics of the delivery and perinatal period of the newborns with early-onset group *B Streptococcus* disease in the neonatal intensive care unit between 1996 and 2019.

Gestational age (weeks), median (range)	38 (26-41)
Birth weight (g), median (range)	2,995 (800-3,850)
Males, n (%)	17 (63%)
Vaginal/instrumental delivery	13 (48%)
Active resuscitation at birth	5 (19%)
Five-minute Apgar score < 7	2 (7%)

Table 4. Short-term outcomes of infants with early-onset group *B Streptococcus* disease in the neonatal intensive care unit between 1996 and 2019 (n = 14).

Ventilatory support	9 (33%)
Vasopressor/inotropic drugs	4 (15%)
Death	1 (4%)

Discussion

This study characterizes the cases of early-onset neonatal GBS disease admitted to the NICU of the neonatology service of Maternidade Bissaya Barreto, from 1996 to 2019.

In the last 24 years, 27 cases were registered, with annual variations. During the study period, the estimated cumulated incidence was 0.38 per 1,000 LB (95% CI 0.23-0.54). There was a reduction in the incidence rate along the three studied periods, although this finding was not statistically significant.

During the period between 1996 and 2003, when no organized approach was used for GBS prophylaxis (period 1), the incidence of early-onset neonatal GBS disease was 0.44 cases per 1,000 LB (95% CI 0.28-0.60). When risk-based strategy started being applied in Portugal, and despite the lack of national guidelines from the health authorities, a drop on the incidence of neonatal GBS disease between 2002 and 2004 was noticed (from 0.60 per 1,000 LB to 0.38 per 1,000 LB), particularly in early-onset disease cases, suggesting that the implementation of intrapartum antibiotic prophylaxis adopted by many maternity units was having a beneficial effect.[15] In the national surveillance performed through the Portuguese Pediatric Surveillance Unit implemented between 1 April 2001 and 31 March 2005, the overall national incidence of early-onset GBS disease was 0.44 per 1,000 LB (95% CI 0.25-0.64).[17]

Overall, the number of cases and the incidence of early-onset GBS disease was consistently low comparing to national data. 2002-2004: 0.31 per 1,000 LB (95% CI 0-0.66) in this maternity *versus* 0.44 per 1,000 LB (95% CI 0.18-0.9) in national surveillance.[18]

This evidence led us to delay the implementation of the risk-based intrapartum antibiotic prophylaxis approach, unlike other hospitals in the country.

By late 2003, and due to a sudden increase in the cases of early-onset GBS disease in recent years, antibiotic prophylaxis based on the presence of intrapartum risk factors was introduced (period 2: risk-based strategy) in this maternity hospital. During the following years (2004-2009), we registered only four cases of early-

Table 5. Long-term outcomes of infants with early-onset group *B Streptococcus* disease in the neonatal intensive care unit between 1996 and 2019

Follow-up	
▪ Normal psychomotor development	23 (85%)
▪ Cerebral palsy	2 (7%)
▪ Bilateral sensorineural hearing loss	1 (4%)
▪ Learning disability and developmental delay	1 (4%)

onset GBS disease. During the period when the risk-based approach was followed, the overall incidence was 0.41 cases per 1,000 LB (95% CI -0.02-0.84).

Comparing the aforementioned periods (period 1: no screening and no risk-based approach *versus* period 2: risk-based strategy) there was a marginal reduction in the incidence rate, but this was not a statistically significant finding. Later, between 2010-2013, an increase in the number of cases per year was noticed (11/27, 41% of the total number of cases), which led to a change in strategy in 2012 (universal screening).

In agreement with our findings, a study led by the Portuguese group for the study of streptococcal infections analyzed all of the documented neonatal invasive GBS infections in Portugal between 2005 and 2015 and showed an increase in these infections taking place after 2011.[5]

In England and in Wales, in spite of the implementation of obstetric risk-based recommendations for the prevention of GBS disease, the rates of early-onset disease also fell slightly between 2003 and 2005, from 0.35 to 0.31 per 1,000 LB, but subsequently increased back to the same rate by 2006.[19] Although it is tempting to look at these data to assess the impact of the applied guidelines, this has to be done with caution.

Universal screening for the prevention of early-onset GBS disease was introduced in our maternity in May 2012. However, in 2012 and 2013, the cases were still high, which is likely to be related to the time required for the implementation of universal screening. However, since 2014, only one case of early-onset neonatal GBS disease was identified. In this case, maternal GBS colonization was positive and the mother did not receive intrapartum antibiotic prophylaxis (GBS result was only known after delivery).

Although the incidence of neonatal early-onset GBS disease differs by gestational age, with more cases in earlier gestational ages, we would like to emphasise that most infants were born at term (74%). This could be explained by the fact that the total number of preterm newborns is much lower and all of them receive prophylaxis, even if we do not know the condition of colonization.

In our study, in more than half (59%) of the mothers no risk factors for early-onset GBS infection (59%) were registered. Other authors also found that only 60% of newborn infants with early-onset neonatal GBS disease had risk factors apparent at labor.[20] Several studies indicate that additional conditions (maternal, obstetric, and neonatal), although less consistently, can be associated to early-onset disease and increase the risk of this illness, such as young maternal age, African Americans, multiple gestations, frequency of intrapartum vaginal examinations, and newborns with low birth weight.[7,13,21]

Despite several studies, multiple gaps remain in neonatal GBS disease prevention. Nevertheless, the authors advocate that risk assessment for early-onset GBS disease should follow the general principles established in the American Academy of Pediatrics clinical reports on the management of neonates with suspected or proven early-onset bacterial sepsis.[8]

A five-minute Apgar score of 0-3 correlates with neonatal mortality in large populations.[22,23] Furthermore, a five-minute Apgar score < 7 has a consistent association with the prevalence of neurologic disability and with low cognitive function in early adulthood.[24] In our study, a five-minute Apgar score < 7 was registered in two newborns (Apgar score 6 at five minutes) and both have shown normal psychomotor development.

In agreement with the results of other studies, in the vast majority of cases, early-onset GBS disease manifests as sepsis, without a specific focus (77%).[2,13,23,25] In our study, one fifth of newborns had sepsis associated with meningitis or pneumonia.

Most infants presented with symptoms in the first 72 hours after birth (96%), almost in line with other studies.[18,26] Commonly, infants may appear ill at the time of delivery, and most infants become ill within 24 hours after birth, as was also the case in our unit.[26]

Considerable morbidity can be associated with GBS infection, and GBS meningitis is an important risk factor for neurodevelopment impairment.[27] Long-term follow-up demonstrated that around 20% of neonates with GBS meningitis have moderate to severe neurodevelopment impairment.[28] In our study, the overall morbidity was 15% (n = 4) and the severe impairment rate was 11% (n = 3).

The overall case fatality rate (4%, 95% CI 0-13) for early-onset neonatal GBS disease was in line with other publications.[18,25]

There are some limitations to our study, such as the reduced sample size and the use of data from clinical records. Furthermore, in our unit, serotyping assays are not routinely performed. The molecular characterization is recommended in order to define GBS virulence potential and its antibiotic resistance phenotype.[4]

This study allowed us to better understand the epidemiology of early-onset GBS disease in our maternity hospital. This long study period showed a global reduction in the incidence rate of early-onset neonatal GBS disease over the three different prevention strategies. However, this was not statistically significant

in supporting the effectiveness of universal intrapartum GBS screening. The results do not exclude a clinically significant effect, and more studies are required to be conducted to increase power and narrow the confidence interval. Moreover, neonatal invasive GBS infections still exist. Better screening and intrapartum antibiotic prophylaxis and avoidance of missed opportunities to prevent neonatal infection are desirable and should be strictly enforced.

WHAT THIS STUDY ADDS

- This single center study on the effectiveness of the different prevention strategies over time for early-onset neonatal group B *Streptococcus* disease was not able to demonstrate a statistically significant effect. However, it is important not to dismiss the clinical value of the reduction in reported cases after the implementation of the universal screening.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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References

1. Lancefield RC. A serological differentiation of human and other groups of hemolytic streptococci. J Exp Med 1933;57:571-95. doi: 10.1084/jem.57.4.571.
2. Randis TM, Baker JA, Ratner AJ. Group B streptococcal infections. Pediatr Rev 2017;38:254-62. doi: 10.1542/pir.2016-0127.
3. Pinto AM, Pereira TA, Alves V, Araújo A, Lage OM. Incidence and serotype characterisation of Streptococcus agalactiae in a Portuguese hospital. J Clin Pathol 2018;71:508-13. doi: 10.1136/jclinpath-2017-204646.
4. Florindo C, Damião V, Silvestre I, Farinha C, Rodrigues F, Nogueira F, et al. Epidemiological surveillance of colonising group B Streptococcus epidemiology in the Lisbon and Tagus Valley regions, Portugal (2005 to 2012): Emergence of a new epidemic type IV/clonal complex 17 clone. Euro Surveill 2014;19:20825. doi: 10.2807/1560-7917.es2014.19.23.20825.
5. Martins ER, Pedroso-Roussado C, Melo-Cristino J, Ramirez M. Streptococcus agalactiae causing neonatal infections in Portugal (2005-2015): Diversification and emergence of a CC17/PI-2b multidrug resistant sublineage. Front Microbiol 2017;8:499. doi: 10.3389/fmicb.2017.00499.
6. 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.
7. Puopolo KM, Lynfield R, Cummings JJ. Management of infants at risk for Group B streptococcal disease. Pediatrics 2019;144:e20191881. doi: 10.1542/peds.2019-1881.
8. Lito D, Francisco T, Salva I, Tavares MN, Oliveira R, Neto MT. Análise das serologias para infeções do grupo TORCH e do rastreio para Streptococcus do grupo B na população de grávidas de uma maternidade. Acta Med Port 2013;26:549-54.
9. Areal A, Moreira M, Nunes S, Faustino MA, Cardoso L, Sá C. Determinantes da colonização materna e da infecção neonatal por Streptococcus do grupo B. Acta Obstet Ginecol Port 2008;2:72-9.
10. Furfaro LL, Chang BJ, Payne MS. Perinatal Streptococcus agalactiae epidemiology and surveillance targets. Clin Microbiol Rev 2018;31:e00049-18. doi: 10.1128/CMR.00049-18.
11. Prevention of group B streptococcal early-onset disease in newborns: ACOG committee opinion, number 797. Obstet Gynecol 2020;135:e51-72. doi: 10.1097/AOG.0000000000003668.
12. Oh W. Early onset neonatal group B streptococcal sepsis. Am J Perinatol 2013;30:143-7. doi: 10.1055/s-0032-1332804.
13. Nanduri SA, Petit S, Smelser C, Apostol M, Alden NB, Harrison LH, et al. Epidemiology of invasive early-onset and late-onset group B streptococcal disease in the United States, 2006 to 2015: Multistate laboratory and population-based surveillance. JAMA Pediatr 2019;173:224-33. doi: 10.1001/jamapediatrics.2018.4826.
14. Direção Geral da Saúde. Exames laboratoriais na gravidez de baixo risco. Norma da Direção-Geral da Saúde. Norma nº. 37/2011 (30/09/2011). Lisboa: DGS; 2911.
15. Almeida A, Agro J, Lourdes F. Protocolo de rastreio e prevenção de doença perinatal: Estreptococo β hemolítico do grupo B [accessed 30 December 2020]. Available at: https://www.spneonatologia.pt/wp-content/uploads/2016/11/201107201730-consensos_neonatologia__2004.pdf
16. Direção-Geral da Saúde. Vigilância epidemiológica das infeções nosocomias nas unidades de cuidados intensivos neonatais. Lisboa: DGS; 2007.

17.World Health Organization. International classification of functioning, disability and health (ICF). Geneva: WHO; 2001.
18. Neto MT. Group B streptococcal disease in Portuguese infants younger than 90 days. Arch Dis Child Fetal Neonatal Ed 2008;93:F90-3. doi: 10.1136/adc.2007.127464.
19. Lamagni TL, Keshishian C, Efstratiou A, Guy R, Henderson KL, Broughton K, et al. Emerging trends in the epidemiology of invasive group B streptococcal disease in England and Wales, 1991-2010. Clin Infect Dis 2013;57:682-8. doi: 10.1093/cid/cit337.
20. Steer PJ, Plumb J. Myth: Group B streptococcal infection in pregnancy: Comprehended and conquered. Semin Fetal Neonatal Med 2011;16:254-8. doi: 10.1016/j.siny.2011.03.005.
21. Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'Sullivan MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: A multicenter case-control study. Pediatrics 2000;105:21-6. doi: 10.1542/peds.105.1.21.
22. Casey BM, McIntire DD, Leveno KJ. The continuing value of the Apgar score for the assessment of newborn infants. N Engl J Med 2001;344:467-71. doi: 10.1056/NEJM200102153440701.
23. Thavarajah H, Flatley C, Kumar S. The relationship between the five minute Apgar score, mode of birth and neonatal outcomes. J Matern Fetal Neonatal Med 2018;31:1335-41. doi: 10.1080/14767058.2017.1315666.
24. Ehrenstein V, Pedersen L, Grijota M, Nielsen GL, Rothman KJ, Sørensen HT. Association of Apgar score at five minutes with long-term neurologic disability and cognitive function in a prevalence study of Danish conscripts. BMC Pregnancy Childbirth 2009;9:14. doi: 10.1186/1471-2393-9-14.
25. Heath PT, Balfour G, Weisner AM, Efstratiou A, Lamagni TL, Tighe H, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days. Lancet 2004;363:292-4. doi: 10.1016/S0140-6736(03)15389-5.
26. Madrid L, Seale AC, Kohli-Lynch M, Edmond KM, Lawn JE, Heath PT, et al. Infant group B streptococcal disease incidence and serotypes worldwide: Systematic review and meta-analyses. Clin Infect Dis 2017;65:S160-72. doi: 10.1093/cid/cix656.
27. Zaleznik DF, Rench MA, Hillier S, Krohn MA, Platt R, Lee ML, et al. Invasive disease due to group B Streptococcus in pregnant women and neonates from diverse population groups. Clin Infect Dis 2000;30:276-81. doi: 10.1086/313665.
28. Kohli-Lynch M, Russell NJ, Seale AC, Dangor Z, Tann CJ, Baker CJ, et al. Neurodevelopmental impairment in children after group B streptococcal disease worldwide: Systematic review and meta-analyses. Clin Infect Dis 2017;65:S190-9. doi: 10.1093/cid/cix663.

Diferentes Estratégias de Prevenção da Sépsis Neonatal Precoce por *Streptococcus* do Grupo B Numa Maternidade de Nível III

Resumo:

Introdução: A sépsis neonatal precoce por *Streptococcus* do grupo B é a causa mais frequente de infeção bacteriana perinatal nos países desenvolvidos, apesar dos programas de profilaxia antimicrobiana materna. O objetivo deste estudo foi avaliar a efetividade das diferentes estratégias de prevenção na incidência da doença neonatal precoce por *Streptococcus* do grupo B durante os últimos anos na nossa instituição. Comparámos a incidência associada à doença neonatal precoce por *Streptococcus* do grupo B em três períodos caracterizados por diferentes estratégias de prevenção: ausência de rastreio (janeiro 1996 a dezembro 2003), profilaxia antibiótica baseada em fatores de risco (janeiro 2004 a dezembro 2011) e rastreio universal do estado portador de *Streptococcus* do grupo B nas grávidas (janeiro 2012 a dezembro 2019). Adicionalmente, foram avaliados e caracterizados os fatores de risco maternos, a clínica e a evolução dos casos.

Métodos: Realizámos um estudo documental transversal, com estudo prospetivo aninhado, com análise dos processos clínicos dos recém-nascidos com doença precoce por *Streptococcus* do grupo B durante 24 anos e foram incluídos 27 casos.

Resultados: No período da estratégia baseada em fatores de risco, a taxa de incidência foi de 0,41 por 1000 nados-vivos (intervalo de confiança 95% 0-0,84). Durante o rastreio universal a incidência foi de 0,30 por 1000 (intervalo de confiança 95% 0-0,72). No entanto, esta redução não foi estatisticamente significativa (p = 0,55). Foram identificados fatores de risco em 41% dos recém-nascidos. O início dos sintomas ocorreu nas primeiras seis horas de vida em 67%. Verificou-se um óbito.

Discussão: Embora sem significância estatística, este estudo mostrou uma redução nos casos de doença precoce por *Streptococcus* do grupo B ao longo das três diferentes estratégias de prevenção.

Palavras-Chave: Complicações Infeciosas na Gravidez; Infeções Estreptocócicas/prevenção & controle; Portugal; Recém-Nascido; Streptococcus agalactiae; Transmissão Vertical de Doença Infeciosa/prevenção & controle