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ABSTRACT

Background: Group B streptococcus (GBS) is the most common isolate in mother-related infection in newborns.
Aims: To evaluate the epidemiology of GBS infection in the first 90 days after birth; to determine if prophylaxis for early-onset neonatal GBS infection can be based only on risk factors.
Design: National epidemiological surveillance.
Methods: Between April 2001 and March 2005 active, systematic, voluntary, national surveillance was performed through the Portuguese paediatric surveillance unit. Case definition: any infant <90 days of age with GBS-positive culture in any normally sterile site—blood, cerebrospinal fluid (CSF), joint aspirate. Early-onset infection defined as in the first six full days after birth.
Results: 242 cases were reported (estimated cumulated incidence 0.54/1000 live births (95% CI 0.47 to 0.61)). Infection occurred before day 7 in 194 babies (81%); 13% presented between days 7 and 28; 6% between days 28–90. The incidence of early-onset infection was 0.44/1000 live births; 196 were term infants (81%), 160 of whom became ill before day 7; only 35 (22%) of these had one or more risk factors for infection. Overall, there were 229 positive blood cultures; 46 newborns had meningitis and 48 pneumonia. Mortality was 6.6% (16/242); it was similar for early (6.7%) and late-onset infection (6.3%), but varied by gestation—4.6% for term infants, 15.2% for preterm and 18% for babies born <1500 g.
Conclusion: GBS infection is predominantly an early infection of the term infant. Mortality is higher in preterm and very low birthweight infants. GBS prophylaxis based on risk factors would leave untreated 78% of term babies who will present with early-onset disease.

In developed countries, the group B streptococcus (GBS) is the most frequent isolate in newborns with mother-related infection. Neonatal infection is associated with significant mortality and morbidity. Hence, the epidemiology of GBS disease has been the subject of studies in many countries in order to determine the optimum way to prevent the transmission of infection from mother to baby[1–5] while a GBS vaccine is not available.

In Portugal GBS is the most common isolate in early onset neonatal sepsis[6 7] and obstetric strategies to prevent early-onset neonatal bacterial infection were classically based on risk factors such as rupture of membranes (for more than 12 hours or 18 hours) or maternal fever, in which cases pregnant women were treated with ampicillin. Foul smelling amniotic fluid, pelvic pain, maternal fever and laboratory signs of infection were considered signs of possible chorioamnionitis and aggressively treated with two antibiotics. However, many infected newborns continue to be born to women with no risk factors. During the past five years, following the publication of international and Portuguese Neonatal Society guidelines,[8] recommending universal screening of pregnant women, many hospitals started screening for GBS at around 35 weeks of gestation independently of the governmental bodies that issue formal national guidance.

The objective of this study was to assess the prevalence of GBS infection in infants less than 3 months of age and to evaluate if prophylaxis of early-onset neonatal infection could be based on mother's risk factors or in a screening policy.

METHODS

The study was performed over four years between 1 April 2001 and 31 March 2005. Cases were identified through the monthly card reporting system of the Portuguese Paediatric Surveillance Unit (PPSU). Following a report of a case of invasive GBS disease, the clinician was asked to complete a data entry form. The investigator validated the data and entered them in an Excel (Microsoft Co) worksheet for data analysis. Three months after the primary reporting a copy of the inquiry was sent to the reporting physician to collect data about early follow-up (sequelae). Recapture of cases was achieved by direct contact with the units.

A case was defined as any infant of less than 90 days of age with positive culture for GBS in any supposed sterile fluid or site—blood, cerebrospinal fluid (CSF) or joint aspirate. Infants with clinical sepsis but negative blood/CSF culture, even if they had positive antigen in urine or blood or positive culture from gastric aspirate and even if they were born to a GBS positive mother, were excluded. Pneumonia was defined as new or progressive infiltrates or opacification on thorax radiography, respiratory distress (grunting, tachypnoea, apnoea), aggravation on gas exchanges, needing of ventilation or needing increased ventilator parameters, GBS isolation in the tracheal aspirate and laboratory signs of infection(C-reactive protein >2 mg/dl, leucocytosis, or leucopenia or neutrophilia). Early-onset infection was defined by presentation within the first 6 days of life.

Rates were derived from the number of live births between 2001 through 2004; for infants <1500 g (very low birthweight, VLBW) we used the population-based data from the National VLBW Registry; also, the calculation of incidence in the different geographic areas was population-based.

Mortality is defined as death on discharge from the neonatal intensive care unit (NICU) or from

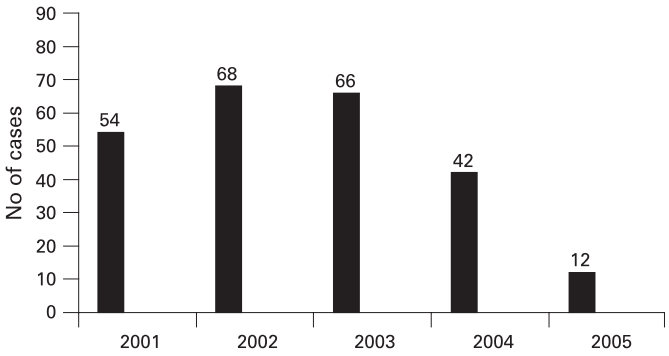

Figure 1 Number of cases per year of birth. The study started on 1 April 2001 and finished on 31 March 2005.

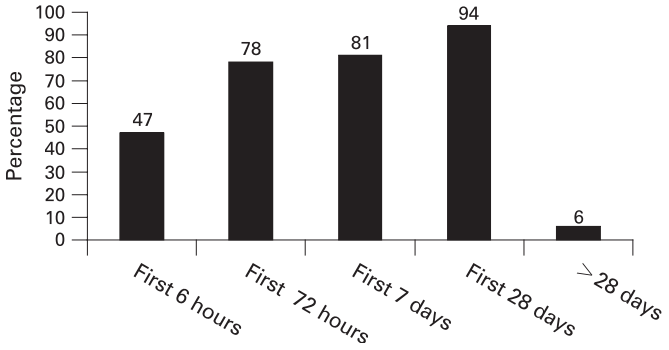

Figure 3 Age at the onset of disease. Cumulative data (%).

the hospital; sequelae were evaluated at discharge or 3 months of life and classified as moderate (mild psychomotor delay, axial hypertonia or hypotonia, one limb disability) or severe (severe psychomotor delay, hydrocephaly, hypertonia, cerebral palsy, severe hypotonia).

Confidence intervals for incidence rates were calculated using SISA, simple interactive statistical analysis.[9]

The study was approved by the ethics committee of the Hospital de Dona Estefânia; informed consent was not required.

RESULTS

In all, 374 reports were received: of these 43 were duplications, 76 were from patients with negative blood culture and 13 were born out of the study period; 242 reports fulfil the criteria for cases. During the data collection period there were 448 531 live births, 27 108 preterm and 4033 VLBW infants. Figure 1 shows the absolute number of cases in each year of the study.

The global incidence of the disease in live births and in term, preterm and VLBW infants is shown in table 1. There was a wide range in the incidence, according to geographic areas (0.9/1000 live births in the north, 0.4/1000 in the centre, 0.4/1000 in Lisbon and Tagus Valley and 0.1 and 0.2/1000 in Algarve and islands). It was possible to calculate the incidence on a population basis during the three full years of the study. In 2002, 2003 and 2004 the estimated incidence was, respectively, 0.60, 0.58 and 0.38/1000 live births (Pearson's r −0.90). There was a significant decrease in the incidence of the disease between 2002 and 2004 (p = 0.025); the odds ratio for GBS disease in 2004 was 0.4 (95% CI 0.18 to 0.90) compared with the first year of the study. Early-onset disease occurred in 0.44/1000 live births. The median maternal age of mothers with infants presenting with early-onset disease was 26 years (range 13–41) and 11% were under 20 years; nationwide, only 6% of mothers are <20 years (p = 0.003). Table 2 shows the characteristics of the population, the route of delivery, fetal and neonatal data. Among those infants born by caesarean section there were at least 13 with intact membranes, six of whom had early-onset infection with no known risk factor. Eighty-one per cent were born at term and 93% of reported cases were born after 33 completed weeks of gestation (fig 2). The majority of infants presented in the first few hours after birth—47% in the first 6 hours, 78% in the first 72 hours, 81% in the first six full days and 94% in the first 28 days of life. Only 6% became ill after the neonatal period (fig 3). Risk factors for infection were present in 71 of 194 mothers of newborns with early-onset infection (37%) (table 3). Excluding the 14 women known as GBS carriers (unknown if they had not been screened), only 57 (29%) were found to have other risk factors. This percentage is even lower for term newborns with early-onset infection for whom risk factors were present in 35/160 (22%). Twenty mothers of the 194 infants with early-onset disease (10%) had at least one dose of antibiotics before delivery, most commonly ampicillin, given not as prophylaxis but because of fever or suspected chorioamnionitis.

The sites of isolates are shown in table 4. It was known that lumbar puncture (LP) was performed in 111 infants; among

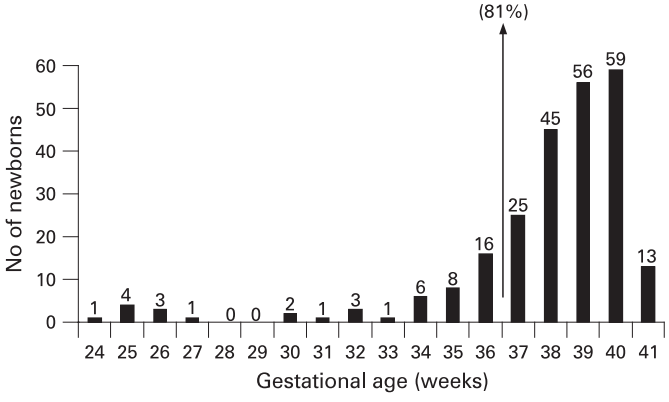

Figure 2 Number of newborns by gestational age—196/242 infants (81%) were born at term and 93% were more than 33 weeks of gestation.

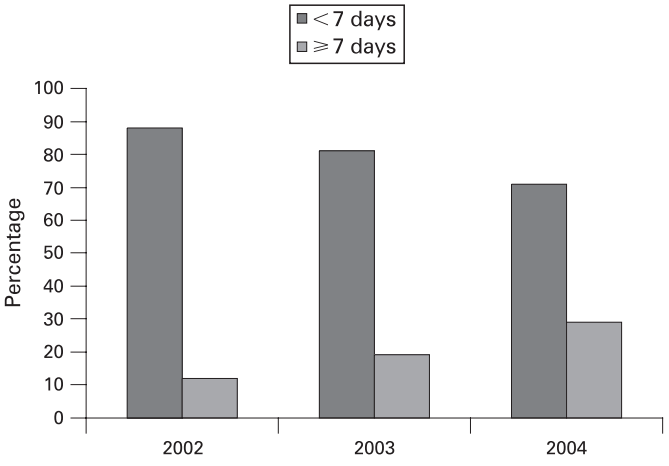

Figure 4 Evolution of early-onset and late-onset disease, full years.

Table 1 Incidence of GBS invasive disease by groups of gestational age (GA) and birth weight (BW)/1000 live births. The global incidence/1000 live births was 0.54 (95% CI 0.47 to 0.60)

⩾37 weeks GA	<37 weeks GA	<32 weeks GA
0.47 (95% CI 0.41 to 0.54)	1.5 (95% CI 0.64 to 2.9)	3.3 (95% CI 1 to 6.5)
⩾2500 g BW	**<2500 g BW**	**<1500 g BW**
0.5 (95% CI 0.43 to 0.57)	0.9 (95% CI 0.74 to 0.98)	2.7 (95% CI 0.60 to 6.1)

them CSF culture was positive in 25/72 (35%) with early-onset infection and in 21/39 (54%) of those with late-onset infection; six infants with meningitis had negative blood culture, three of them with early-onset infection. All cases of pneumonia occurred in infants with early-onset infection but one. Fifty per cent of infected infants (n = 122) needed intensive care and 20% (n = 48) mechanical ventilation. Mortality was 6.6% (16/242) and was similar for early-onset and late-onset infection (6.7% vs 6.3%) but higher for preterm (15.2%) and for VLBW (18%) compared to term infants (4.6%). Twenty-one survivors were reported to have sequelae, of whom eight were known to have had meningitis; for 10 infants these sequelae were moderate and for 11 it was graded as severe.

Over the three calendar years of the study, mortality declined from 8.7% in 2002 to 6.1% in 2003 and 2.3% in 2004 (Pearson's r −0.99; χ^2 p = 0,44); the prevalence of sequelae within the survivors was 9.5% in 2002, 3.2% in 2003 and 4.9% in 2004. Figure 4 shows the prevalence of early-onset and late-onset disease in the same period.

DISCUSSION

In industrialised countries over the past three decades, group B streptococcus (GBS) surpassed *Escherichia coli* as the most frequent isolate in neonatal early-onset infection and became the most severe cause of mother-related infection. This knowledge led many neonatologists, obstetricians and scientific societies to search for the source, the epidemiology and the possibility of prevention of neonatal disease.[10] Guidelines from many national bodies such as the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists and Centers for Disease Control and Prevention,[11–14] were published and successively updated, and have been adopted in many countries. Other countries started epidemiological studies,[5] some of them through the respective paediatric surveillance units[1–3] and, based on these data, have decided on a policy of screening and prophylaxis, or not.

In Portugal, during the 1990s, GBS was confirmed as the most common isolate in infants with maternally acquired infection[6 7] which stimulated us to carry out epidemiological surveillance to determine the extent of the disease and to provide data for a knowledge-based decision for prophylaxis policy.

There are some drawbacks in our study; one of them is the true number of cases during the surveillance period. The system is based on voluntary reporting that may miss some cases and it was impossible to access them through the hospital discharge code because of the lack of a precise diagnosis code for GBS infection in ICD11. Recapture through records of hospital departments of microbiology was not performed. The only strategy to increase reporting would be the direct contact with the units.

The other drawback is related to the use of such a restrictive case definition. We are aware that many cases of infection probably caused by GBS may have been lost—for example, infants with clinical and laboratory signs of infection born to GBS positive mothers or with GBS isolated in non-sterile places, but with negative blood culture. However, we wanted to compare our results with those of other epidemiological studies, which had used such a narrow definition. Despite the clear case definition we had to reject 76 cases of clinical sepsis with positive GBS findings but negative blood culture that were reported; overall, we accept that it would be better if these cases were included. We agree with others that infants with blood stream infection are probably the visible face of a deeper problem.[15]

The overall incidence of invasive GBS disease is between that found in other studies – 0.54 for Portugal, 0.72 for the United Kingdom and 0.47 for Germany.[2 3] This incidence varies widely from one geographic area to another, even in a small country like Portugal, probably reflecting the wide range of GBS carrier state during pregnancy; the rate of GBS positive pregnant women varied from 35% in the north to 13% in the south (data not shown).

In our study we would like to emphasise that the majority of infants were born at term (81%) and had early-onset disease (81%), and that 78% of term infants with early-onset disease had no risk factors to prompt treatment with antibiotics during delivery. This figure could potentially be reduced through screening and prophylaxis.

During the study, many scientific groups, including the neonatal branch of the Portuguese Society of Paediatrics, issued guidelines for the management of potential GBS disease. Many maternity units commenced screening and prophylaxis during the study period—despite the lack of national guidelines from the health authorities—a fact that might be responsible for the

Table 2 Characteristics of the population, perinatal period and delivery

Gestational age in weeks (median and range)	39 (24–41)
Preterm (gestational age <37 weeks)	19%
Birth weight in grams (median and range)	3170 (595–4300)
<1500 g	5%
<2500 g	13%
Male sex	58%
Caesarean section/instrumental delivery	47%
Fetal distress/low Apgar score	27%

Table 3 Early-onset infection and risk factors (71/194–37%)

Intrapartum fever	29/194 (15%)
Rupture of membranes ⩾18 hours	34/179* (19%) (4 with fever)
GBS known carriers	14/194 (7%) (2 with fever)
Clinical amnionitis/fetid amniotic fluid	5 (all with fever)
More than one risk factor	6

*Includes unknown rupture of membranes and those reported as being as <24 hours old.

Table 4 Clinical syndrome

Positive blood culture (40 with meningitis, 43 with pneumonia)	229
Pneumonia (5), meningitis (6), with negative blood culture	11
Other focus: endocarditis, osteomyelitis, cervical adenitis (2), arthritis (2)	6
Total No of infants with meningitis, 46	19%
Total No of infants with pneumonia, 48	20%

declining incidence of early-onset disease described in this report: a significant relative risk reduction of 40% between the first and the last full years of the study (from 0.60/1000 to 0.38/1000 live births) and decreasing of mortality from 8.7% to 2.3%.

These data also highlight three further facts: (1) infants with early-onset infection born by caesarean section with intact membranes remain at risk of invasive disease but, according to current guidelines, would not be offered prophylaxis even if the mother was known as a GBS carrier. Clearly the need for clinical surveillance should not decrease following the institution of a screening policy. (2) Some 20 babies with early-onset infection were born to mothers who had already received at least one dose of antibiotics. Screening and prophylaxis thus do not prevent all cases of early-onset infection[4 16]; also, blood culture should always be done even if antibiotics were given to the mother if the child is symptomatic. (3) Babies born to young mothers may be at increased risk as almost twice as many young mothers were found in the invasive disease group compared to the whole population of pregnant women. Mortality in our case series was similar to that found by others—6.6% in the Portuguese study, 9.7% for the British and 4.3% for the German study.[2 3] Probably the "low" mortality rate found in all these studies is the result of the high level of suspicion of infection, implying that early treatment may increase the survival of many infants who in the past would have died. In this study, intensive care was required for 50% of patients and 20% needed mechanical ventilation. The decreasing mortality rate over the three full years despite not statistically significant may have been influenced by the emergent screening and prophylaxis strategies. The same could be said about sequelae. However the short period of follow-up and the small number of files coming back at three months of age do not allow any comments.

There is much controversy concerning the adoption of universal screening and prophylaxis such as that recommended in the guidelines of the neonatal society. Our study provides circumstantial evidence that this policy may have benefit—namely, the high proportion of term infants with early-onset infection but no risk factors; the decreasing incidence over the course of the study; and, eventually, the improving prognosis for babies who developed infection.[17–19]

The cost/benefit ratio of a screening policy has to be based not only on the costs of inpatient hospital days of intensive care but also the rate of deaths, the effects of sequelae on survivors and the costs of caring for children with severe sequelae. However if a screening policy is adopted some rules have to be drawn up: women should be educated as to the meaning of a positive result, the need to present early in labour for prophylaxis on time and the establishment of good lines of communication so that at least two doses of antibiotics can be administered.[20] With universal screening GBS-positive mothers must receive prophylaxis on time.

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What is already known on this topic

- Group B streptococcus (GBS) is the most common isolate in early-onset mother-related infection.
- GBS invasive disease can be severe for neonates, with great morbidity and mortality.
- Screening the mothers and giving penicillin during labour may prevent early-onset neonatal infection.

What this study adds

- The rate of maternal carriage and invasive disease in neonates may show considerable geographical variation.
- Most affected babies are born at term without any risk factors, and present with GBS in the first 72 hours of life.

Competing interests: None.

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