A Survey of the Incidence of Neonatal Sepsis by Group B Streptococcus During a Decade in a Brazilian Maternity Hospital

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Group B Streptococcus (GBS) is the main etiological agent of neonatal sepsis in developed countries, however there is no detailed information on its incidence in Brazil. We registered the incidence and lethality of GBS infection in a Brazilian private maternity hospital from April 1991 to March 2000. Maternal risk factors contributing to neonatal infections were also scored. The rate of infection was determined by checking for GBS in the blood and liquor of symptomatic neonates within 72 hours of birth. Sepsis and/or early onset meningitis were diagnosed in 43 neonates (32 cases in blood, 1in liquor and 10 in blood and liquor). The overall incidence was 0.39 per thousand neonates and remained quite constant throughout the period, ranging from 0.25-0.63. Septic shock occurred in 33 neonates within 1 to 36 hours of birth (mean 15 hours). Among those patients, 26 (60%) died between the 5th and the 85th hour after birth. Maternal risk factors, according to CDC criteria, included: gestational age below 37 weeks in 26 cases (60%), amniorrhexis equal or superior to 18 hours in 7 cases (16%), and maternal temperature equal or superior to 38^{o}C in 4 cases (9%). None of the mothers had received prophylactic antibiotics during labor nor were urine, rectal or vaginal swabs screened for GBS. Although the incidence of GBS infection in the population in this study was lower than that found in developed countries, its rate of mortality was higher. The death rate could be reduced through recognition of the risk factors and prophylactic antibiotics during labor.
Key Words: Sepsis, newborn, Group B Streptococcus.

During the last three decades, group B *Streptococcus* (GBS) has been the most frequent etiological agent of neonatal sepsis in developed countries, being responsible for high morbidity-mortality rates. GBS is also an important agent of maternal infections, such as chorioamnionitis, endometritis, urinary and surgical-site infections [1,2]. The epidemiology of this disease, both in pregnant women and neonates, has been extensively studied in the United States and Europe but not so in Latin America. Group B streptococcus is synonymous with *Streptococcus agalactiae* in the obstetric as well as in the pediatric literature and in this paper we maintain this meaning, which is in common use [1].

There are two forms of neonatal sepsis: one early-onset or precocious, and the other late-onset. The former occurs during the first seven days of life, corresponding to 80% of all cases, and is due to vertical transmission during labor or birth. It includes bacteremia and/or sepsis, meningitis and pneumonia. Respiratory symptoms usually flare up during the first 24 hours after birth and are similar to those of hyaline membrane disease. Sepsis, which may evolve to septic shock, occurs in 25% to 40% of the neonates and meningitis in 5% to 15%.

Late-onset sepsis affects neonates from one to seven weeks of age. Its transmission can be vertical, horizontal or nosocomial. Its most common clinical manifestations

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are: meningitis (30% to 40%), bacteremia (40%), septic arthritis (5% to 10%) and, more rarely, omphalitis and osteomyelitis.

The worldwide incidence of early-onset sepsis is around 0.7 to 3.7 cases per thousand neonates, whereas the incidence of late-onset sepsis is about 0.5 to 1.8 per thousand neonates. Up to the 1970's, lethality in developed countries was around 15% to 55%, but during the last few years, it has dropped to 10% to 15% for the early-onset form and to 2% to 6% for late-onset sepsis [2-10]. There are no data about the lethality and mortality of neonatal sepsis in Brazil.

The determining factor diagnosis of neonatal sepsis is the presence of GBS in the mother's genital tract during birth. The distal third of the vaginal mucosa may be colonized by GBS from the anorectal canal. For that reason, diagnostic swabs are directed to these areas. The urinary tract is also an important site for infection, especially during pregnancy, when it manifests as asymptomatic bacteriuria [1,3,11].

The prevalence of maternal colonization by GBS depends on the swab source (vagina or rectum), time of pregnancy, race, origin, age, parity and social-economic level. These variables can explain the wide variation of positive swabs (from 5% to 41%) in studies conducted in different countries. Prospective studies indicate that vertical transmission varies from 29% to 85%, with an average of 51% [3,11-16].

The risk of neonates being infected by vertical transmission is directly related to the absolute number of microorganisms in the birth canal during delivery. The neonate born of a colonized mother is more prone to develop invasive disease; however, only 1% to 2% of babies born of women with a positive vaginal/rectal swab develop neonatal sepsis. This frequency increases if one or more maternal risk factors are present [3,12,13]. In a 1996 publication, the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACGO) and the Centers for Disease Control (CDC) informed that the most important factors included: previous history of fraternal infection by an invasive disease, bacteriuria caused by GBS during pregnancy, birth before the 37th week of gestation, membrane rupture after 18 hours or more of labor, mother's temperature equal or superior to 38°C, in addition to the presence of GBS in the vagina and/or rectum [15,17-19]. Other risk factors have also been reported, including low neonatal weight, multiparity and asphyxia at birth [1,3,20].

Adequate maternal diagnosis and treatment are necessary to reduce the neonatal morbidity and mortality associated with this disease. Many studies conducted in the U.S. confirm that prophylactic ampicillin and/or intravenous penicillin during labor in women with the above-mentioned risk factors would significantly reduce the vertical transmission of GBS and consequent neonatal sepsis [13,16-2 2].

Based on these considerations, our primary objective was to determine the incidence and lethality of neonatal sepsis and/or meningitis caused by GBS in the 1990's in a private Brazilian maternity hospital, and also to describe maternal risk factors associated with these infections.

Material and Methods

An analysis was made of the records of all neonates affected with sepsis and/or meningitis who presented symptoms within 72 hours of birth. These patients were treated at the Intensive Care Unit of the Hospital e Maternidade Santa Joana from April 1991 to March 2000.This is a private institution situated in São Paulo, Brazil, which cares for about 14,000 neonates /year with a hospital stay of, at least 72 hours. The Hospital Ethics Committee approved the study.

The subjects were neonates who had sepsis and/or meningitis and presented hyper or hypothermia, apnea, bradycardia and/or shock during the first 72 hours after birth, and had GBS in the blood and/or liquor [23].

Blood culture was performed manually: 0.5 ml to 1.0 ml of blood was inoculated into liquid broth (Soya Tryptone Broth), incubated at 35°C and then plated onto blood agar medium. Liquor was inoculated into chocolate agar medium, and in glucose and thioglycolate broth and incubated at 35°C in a 10%

carbon dioxide atmosphere. Isolated bacteria colonies were identified through the traditional methods of catalase, CAMP and the latex test. The antibiotic resistance test was done according to the Kirby-Bauer method [24].

Lethality and mortality by GBS were scored on a yearly basis. The following maternal and neonate data were recorded: prenatal follow up, parity, gestational age, use of antibiotics, type of delivery, weight at birth, the weight/gestational age relation [25], sex, Apgar score at the first and fifth minute of life, medication taken at delivery and the clinical evolution of sepsis.

Maternal risk factors were evaluated according to AAP, ACGO and CDC protocols (1996). These factors included: previous history of neonatal sepsis in a sibling, GBS bacteriuria during pregnancy, gestational age under 37 weeks, membrane rupture equal or superior to 18 hours, maternal temperature equal or superior to 38ºC and vaginal and/or anorectal presence of GBS during pregnancy and delivery.

A linear progression test was used to analyze the yearly incidence of neonatal sepsis.

Results

During the period of study, 43 out of 111,241 babies developed neonatal sepsis/meningitis within 72 hours of birth. Therefore, the incidence of invasive neonatal disease was 0.39 per thousand live births, with a minimum value of 0.25 and a maximum of 0.63. Statistical analysis showed that the rate of neonatal GBS infection did not change over the years (p=0.147). Among the 43 patients, 26 (60%) died (Table 1).

Maternal and demographic data on 43 neonates are shown in Table 2. In most cases (60%), the mother was primipara. All of them had had pre-maternal care; the average gestational age was 35.7 weeks and the median 36.4 (minimum value 23 and maximum 40 weeks). Thirteen neonates had a gestational age of less than 35 weeks, 17 patients were 35 to 37 weeks and 13 between 38 and 40 weeks. None of the mothers received antibiotic treatment during labor; 28 (65%) of the births were by cesarean section. The average weight at birth was 2,570g and the median 2,640g (minimum 550g and maximum 4,360g); 40 (93%) had an adequate weight and 19 (42%) were boys. In the first and fifth minutes after birth, respectively, 18 (42%) and 5 (12%) of the neonates had an Apgar score less than or equal to 7. Two patients received vasoactive drugs immediately after birth (Table 2).

Among the 43 neonates, 32 (72%) presented sepsis, with a positive blood culture for GBS, 10 (23%) had sepsis associated with meningitis and GBS in the blood and liquor, whereas one neonate had meningitis and GBS solely in the liquor. Considering all cases, 33 (77%) of the neonates eventually went into septic shock and had to undergo vasoactive therapy to maintain homeostasis. The symptoms of shock appeared an average of 15.5 hours after birth (1 to 36 hours) and death occurred a mean of 41 hours after birth (from 5 to 85hrs) in 26 patients (60%).

Maternal risk factors included: gestational age inferior to 37 weeks in 26 patients (60%), membrane rupture superior to 18 hours in 7 cases (16%) and maternal temperature superior to 38°C in 4 cases (9%). Among the 17 non-primipara patients, 9 indicated previous miscarriages, 2 had had stillborn infants and one a neonatal death of unknown cause.

No clinical risk factors were detected in 14 patients (33%). However, none of the patients had a record of bacteriuria by GBS during pregnancy. None of the mothers had a GBS vaginal and/or rectal swab test during pregnancy and/or labor. Risk factors are specified in Table 3.

Discussion

During the last 30 years, many published reports have confirmed that GBS is the most frequent cause of early neonatal infection in developed countries [2,4,11,13,22,23,26-28]. We determined the incidence of GBS infection in the 90's in a private maternity hospital where all patients undergo pre-natal follow up. We studied the clinical outcome and laboratory profile of neonatal GBS infection, as well as the associated maternal risk factors detected

Table 1. Incidence and lethality of meningitis/sepsis by Group B Streptococcus (GBS) in neonates at Hospital e Maternidade Santa Joana

	Number of neonates infected by GBS	Total number of liveborns	Incidence of GBS infection per 1,000 neonates	Lethality (%) due to GBS neonatal infection
1991(April-Dec)	2	7,380	0.27	2 (100%)
1992	4	8,433	0.47	4 (100%)
1993	4	10,128	0.39	2 (50%)
1994	3	11,873	0.25	2 (66%)
1995	5	12,606	0.40	5 (100%)
1996	6	13,952	0.43	6 (100%)
1997	6	14,597	0.41	0
1998	5	13,475	0.37	2 (40%)
1999	5	14,051	0.36	2 (40%)
2000(Jan-Mar)	3	4,746	0.63	1 (33%)
Total	**43**	**111,241**	**0.39**	**26 (60%)**

Table 2. Demographic data of the 43 cases of sepsis and/or neonatal meningitis by Group B Streptococcus

Maternal data	Number of cases (%)
Pre-natal care	43 (100%)
Primipara	26 (60%)
Gestational age	
23-34 weeks	13 (30%)
35-36 weeks	13 (30%)
37-40 weeks	17 (40%)
Antibiotics during labor	0
Caesarean Section	28 (65%)
Weight at birth	
< 1,500 g	3 (7%)
1,500-2,499 g	15 (35%)
> 2,500 g	25 (58%)
Weight/gestational age	
Adequate	40 (93%)
Small	1 (2%)
Males	19 (44%)
Apgar score	
< 7 at the 1st minute	18 (42%)
< 7 at the 5th minute	5 (12%)

Table 3. Maternal Risk factors present in the 43 cases of neonatal infection by Group B Streptococcus

	Patients (%)
Absent	14 (33%)
One risk factor	
GA < 37weeks	18
MR > 18 hours	1
Maternal Temperature > 38°C	2
Two risk factors	
GA < 37 weeks and MR > 18h	6
GA < 37 weeks and Temperature > 38°C	1
Three risk factors	
GA < 37 weeks, MR > 18h and Temp. > 38°C	1

GA = Gestational Age; MR = membrane rupture.

through maternal anamnesis and clinical exams used to register the development of this invasive neonatal disease.

The incidence we found of 0.39 cases of early GBS neonatal sepsis per 1000 neonates was constant over this last decade of the 20th century. This rate is lower than those observed in developed countries before antibiotic prophylaxis during birth was applied [1-3,6,7,9,12]. These countries reported an incidence of 0.7 to 3.7 per 1,000 neonates within the first seven days of life. We analyzed the occurrence of infections only during the first 72 hours after birth. The hospital's infection control staff routinely investigates any clinical suspicion of infection through cultures of all neonates, even those with good clinical indications, during their stay in the hospital. Although the disease may manifest itself between the 4th and 6th day after birth, a great majority of neonates return to the hospital if anything occurs after hospital discharge. In addition, there may be cases of sepsis and/or neonatal meningitis with negative GBS blood culture, depending on the phase of the inflammatory reaction during which the exam was performed. In 30% to 50% of the cases of neonatal sepsis, it is not possible to detect the etiological agent. This means that the actual frequency of this disease is probably higher.

The low invasive neonatal infection incidence of 0.39 per 1,000 neonates may be due to the low prevalence of maternal colonization by GBS. In this hospital, GBS was detected in the vaginal swab of 13% of 406 pregnant women in premature labor from 1995 to 1996, with no cases of infection of the babies born of these mothers [29].

Though we found a low incidence of invasive neonatal infection, lethality was high; from 1991 to 1996 it reached 100%, decreasing to 40% from 1997 to 2000. In developed countries, the mortality rate due to this disease declined from 55% in 1970 to 15% in the 80's and 5% during the last few years [30,31]. The drop in lethality was partially due to more intensive neonatal care, but also may be a result of the institution of antibiotic prophylaxis during labor in women colonized by GBS and/or women presenting one or more risk factors for neonatal GBS infection. Forty two percent of the neonate patients we studied required oxygen therapy at birth, whereas two of them required vasoactive drugs. This fact attests to the poor health of the neonates at birth. Also, all 43 neonates affected by the disease underwent intensive therapy and 77% of them eventually had septic shock during the first few hours after birth, and a great number died on the second day after birth. This unfavorable clinical evolution might be due to many factors, such as: GBS virulence,

maternal antibodies, inoculum size and bacterial serotype. Some reports recognize GBS serotype III as the most frequent, accounting for 61% of the cases in developed countries and associated with serious neonatal infection [3]. The conditions that might justify the elevated lethality of GBS neonatal infection have not yet been investigated in Brazil and constitute an open field for research in perinatology.

A large proportion (26%) of the 43 patients had meningitis. Thus, whenever a systemic infection is suspected, with an unclear meningitis diagnosis, the cerebrospinal liquor should be investigated. Meningitis requires prolonged antibiotic therapy and has a somber prognosis in terms of its neurological sequels [3,32].

As for the maternal risk factors detected through anamnesis and clinical examination, 60% of the patients were primipara, 60% of the neonates were premature and 42% weighed less than 2500g at birth. These data are similar to those reported in American and European studies [5,9,14].

Surprisingly, amniorrhexis longer than 18 hours and maternal temperature during labor higher than 38ºC were detected in only 16% and 9% of the cases, respectively. As for the relationships with previous pregnancies, only two patients reported stillborn babies whereas one reported neonatal death due to an unknown cause.

No risk factors could be assigned to 14% of the patients. However, although all patients received prenatal medical care, their records did not show any reference to a search for GBS in the urine, vagina and/or rectum during gestation and/or labor. If these exams had been carried out, they would have certainly detected asymptomatic bacteriuria and vaginal and/or rectal colonization by GBS, which would give the opportunity of starting antibiotic prophylaxis during labor.

We conclude that the incidence of early neonatal infection by GBS in Brazil is low when compared to the situation in developed countries, before antibiotic prophylaxis was applied during labor. Despite its low incidence, GBS has been the main agent identified in blood culture whenever the maternity hospital staff suspects neonatal sepsis [13]. Due to the elevated risk of death, it is necessary to prevent invasive disease by GBS. Many studies have shown that this practice significantly reduces GBS vertical transmission and neonatal sepsis. Based on these facts, in 1996, The American Academy of Pediatrics, the American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention created guidelines for the perinatal prevention of GBS infection. [11,17,18,30,34,35]. These institutions suggested the use of intravenous antibiotics during labor, using two strategies. The first one recommends a routine search for GBS with anogenital swabs in all women between the 35th and the 37th weeks of pregnancy but do not recommend anti-microbial therapy for the positive cases before the onset of labor. The second strategy, regardless of the results of the anogenital swab, considers several maternal risk factors (premature labor, membrane rupture equal to or longer than 18 hours or maternal temperature equal to or higher than 38°C) as an indication for labor antibiotic therapy. In cases when the patient has had a previous child with invasive GBS infection or bacteriuria by GBS during pregnancy, antibiotic prophylaxis is also indicated during labor [18,19,28,35,36].

Chemoprophylaxis during labor must consist of intravenous penicillin (5,000,000 U at the beginning and 2,5000,000 U each 4 hours until birth). G penicillin is most widely used because of its narrow spectrum and because of lessened microbial resistance. If the patient is allergic to penicillin, 900 mg of clindamycin may be injected intravenously every 8 hours or 500g of erythromycin every 6 hours until birth [17-19,21,22,31,35,36].

In the United States the reduction in neonatal sepsis by GBS in the last decade has been attributed to chemo prophylaxis during labor in women who present risk factors and/or are found to have GBS in the urine, vagina and/or rectum (11,13,16-19,21,22,28,31,36,37]. Prophylactic antibiotics during labor should have been recommended for 29 (67%) out of the 43 patients who presented some kind of risk factor, even if GBS cultures were not made from urine, vagina or rectal swabs.

The conclusion is that, in spite of its low incidence among this Brazilian population, efforts should be made to reduce morbidity and lethality associated with precocious invasive GBS neonatal disease. The determination of risk factors through the patient's anamnesis and clinical exams along with urine, vaginal and rectal cultures for GBS should be stimulated among health care professionals who are in charge of prenatal care. This will permit the identification of women colonized by GBS and the institution of intravenous antibiotic prophylaxis during labor, which would certainly reduce neonatal infection.

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