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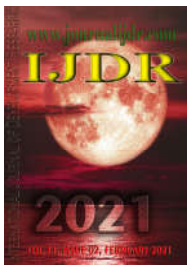

RESEARCH ARTICLE OPEN ACCESS

EARLY NEONATAL SEPSIS: RISK FACTORS, WITH EMPHASIS ON *STREPTOCOCCUS AGALACTIAE* INFECTIONS AMONG PREGNANT WOMEN

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ABSTRACT

Objective: Determine the prevalence of vaginal and rectal colonization by *Streptococcus agalactiae* (SGB) and determine risk factors for the development of early neonatal sepsis. **Methods**: The study considered pregnant women seeking obstetric services in a maternity school in Rio de Janeiro State, Brazil. The study was divided into two phases: i) material collection from the vaginal and anorectal regions using swabs, to be cultured on agar-blood plates, to determine the prevalence of SGB among 60 patients after the 28th week of pregnancy. Confirmation was performed using the Gram and Catalase test; ii) analysis of the risk factors for developing early neonatal sepsis using a case/control type study involving 15 cases and two controls for each case, resulting in a total sample size of 45 patients. The variables analyzed were: maternal age, gestational age, neonatal birth weight, and the occurrence of a urinary tract infection during gestation. **Results**: The risk factors for the development of early neonatal sepsis were found to be: prematurity (OR 2.61; $p < 0.001$), low birth weight (OR 2; $p < 0.001$), and the presence of a urinary infection during gestation (OR 2.66; $p < 0.001$). The prevalence of colonization by SGB was 40%. In 25% of the cases, the pregnant women reported symptoms of urinary tract infections: dysuria (55%), pollakiuria (50%), urinary urgency (45%), and vaginal discharge (40%). In 8% of the cases, the neonates evolved towards early sepsis, and of those, one progressed to death (4.16%). **Conclusions**: In light of the prevalence of SGB infections observed in our study, we confirm the necessity of routine culture exams for all pregnant women. Prematurity and low birth weight emerged as risk factors associated with early neonatal sepsis.

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INTRODUCTION

Early neonatal sepsis is a syndrome of a systemic inflammatory response that affects neonates in the first 72 hours of life after birth; it is characterized by diverse clinical and laboratorial alterations. (1) There are a number of documented risk factors associated with early neonatal sepsis, and they can be grouped as maternal, neonatal, or environmental. Among those factors are premature labor, membrane rupture more than 18 hours before the initiation of labor, maternal bacterial colonization, maternal fever (≥ 38º C) during or immediately after labor, male neonate sex, low birth weight (<2500 g), chorioamnionitis, and a previous birth with a neonatal infection (2-4).

Among the bacteria that can cause early neonatal sepsis is the gram-positive coccus *Streptococcus agalactiae* (SGB), which makes up part of the human microbiota and principally colonizes the gastrointestinal tract. It can also colonize the vagina chronically or intermittently in approximately one-third of all women. That pathogen is considered the main etiologic agent of early neonatal sepsis (most frequently followed by *Escherichia coli* in diverse multi-centric studies in Brazil) (5-7). Pregnant women colonized by SGB are generally asymptomatic, although that microorganism can cause infections responsible for from 2 to 4% of urinary tract infections experienced during pregnancy (8). Those infections can compromise the amniotic sac, the endometrium or abdominal wall, as well as become manifest

as sepsis during pregnancy – and can thus compromise the natural evolution of gestation and occasionally result in spontaneous abortion or premature labor (9). The transmission of SGB to the neonate can occur during intrauterine life through the mechanism of ascendant dissemination of the bacteria from a contaminated vagina, or through vaginal labor or cesarean birth, either by contact with maternal secretions or after the rupture of the amniotic membranes in the birth canal (9). In light of the possible consequences of SGB infections to the mother and the newborn, the World Health Organization (WHO) recommends that all pregnant women with gestational ages between 35 and 37 weeks be accompanied through the collection of culture material from the vaginal and rectal regions (8). Even though previous studies have demonstrated a high incidence of colonization by SGB in pregnant women in Brazil [20.4% in a study in Maranhão State (10), 14.9% in a study in Paraná State (11), and 21.6% in a study in Santa Catarina State (12)], accompanying SGB is not included as one of the standard prenatal exams undertaken through the Brazilian Health Service (SUS) (13). As such, the present study sought to analyze epidemiological aspects of SGB infections in pregnant women to establish the risk factors for the development of early neonatal sepsis and to determine the prevalence of vaginal and rectal colonization by that microorganism.

MATERIALS AND METHODS

This study was approved by the Ethics Commission (CAEE 13517919.4.0000.8044) and was undertaken in the Mariana Bulhões Maternity Ward in the municipality of Nova Iguaçu, Rio de Janeiro State, Brazil, between January and March/2020. The study was divided into two stages:

Stage 1: Analysis of the risk factors for early neonatal sepsis, January/2020.
Stage 2: A SGB infection prevalence study, February to March/2020.

Stage 1: Analysis of the risk factors of early neonatal sepsis.

This first stage consisted of a case/control study. The sample size was calculated by estimating the number of patients (cases and controls) necessary to establish a ratio of exposure occurrence (OR) to non-exposure events of at least 2.5 (OR = 2.5), with a confidence interval of 90% and power of 80%, for an expected exposure frequency of 50% among the controls. Our calculations indicated that 15 cases and two controls for each case would be necessary, resulting in a total sample size of 45 patients. In light of the difficulties involved in standardizing the diagnosis of neonatal sepsis, our evaluations were based on the recommendations of the *Society for Critical Care Medicine* adopted for children (14).

The inclusion criteria for cases were: neonates from vaginal or cesarean births with laboratory hemoculture test results, considering gestational ages after 28 weeks. We excluded from the study neonates diagnosed with early neonatal sepsis without laboratory hemoculture results. There were no inclusion or exclusion criteria for neonates considered as controls. To analyze risk factors for the development of early neonatal sepsis, we collected information from medical records in the health center among both cases and controls. The variables related to the diffusion of early neonatal sepsis included: maternal age, gestational age, birth weight, and the presence of Urinary Tract Infections (UTI) during gestation. In terms of the latter, any infection described in the medical record was necessarily confirmed by urinalysis. In terms of the statistical analyses: gestational age groups were established as from 28 to 34 weeks, from 35 to 37 weeks, and >37 weeks; neonate weights were grouped as ≤1000 grams, 1001 to 1499 grams, 1500 to 2499 grams, and ≥2500 grams; maternal ages were grouped as ≤15 years, 16 to 25 years, 26 to 34, years and ≥35 years; and UTI was classified as present or absent. The existence of associations between the independent variables of interest and the occurrence of sepsis was evaluated using the chi-square test, considering $p < 0.05$ as significant. When pertinent, we verified the existence of linear relationships between the different levels of a quantitative variable between two exposure categories using the chi-square test for linear tendencies. Data compilation was performed using EpiData program software and the Epi-Info 6.04 program.

Stage 2: SGB infection prevalence study

To determine the prevalence of SGB infections, 60 patients were evaluated after the 28th week of gestation. All of the pregnant women included in the study signed a free-consent and disclosure form. Material was collected from each pregnant woman in the selected study group using both vaginal and anorectal swabs. The samples were immediately stored for transport and subsequently inoculated in the laboratory into Todd-Hewitt selective medium. After culturing for 24 hours in an incubator, the material was cultivated on 5% blood agar plates for 24 hours. The plates were then evaluated, and those suggestive of SGB (1) were confirmed by the Gram and Catalase test. Excluded from the study were pregnant women who had used antibiotics in the previous seven days, those submitted to tocoginecological exams in the previous 24 hours, and those in advanced phases of labor (who were therefore unable to process information about the research).

RESULTS AND DISCUSSION

Analysis of the risk factors of early neonatal sepsis: This stage of the study included 45 pregnant women. Six hundred and thirty-eight births were recorded in the maternity hospital during the study period, so that the 45 pregnant women in the study represented 19.3% of the live births during that period. The cases studied, on the other hand, represented the total number of incidences of sepsis during that period. The frequency of early neonatal sepsis during that period was 50.3 cases per 1000 live births. Early neonatal sepsis was therefore observed in 2.35% of all live births during the study period.

The gestational age varied from 25 to 41 weeks, with a mean of 35.4 (±3.1). Data analysis demonstrated the greatest rate of early neonatal sepsis was among neonates born at between 28 and 34 weeks (61% of the entire sample), as can be seen in Figure 1.

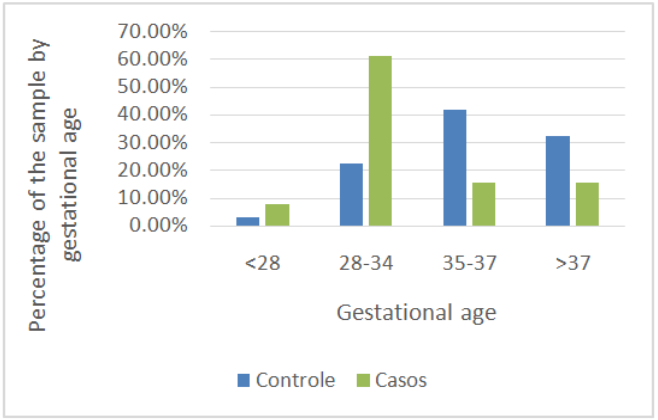

Figure 1. Presents the distribution (in percentages) of healthy controls and cases of neonatal sepsis as a function of gestational age. It is evident that the percentage of early neonatal sepsis in premature neonates (those with gestational ages less than 37 complete weeks) is greater than that observed in the control group (OR 2.61; p < 0.001)

Prematurity represents an important risk factor for early neonatal sepsis when compared to neonates born to term (with gestational ages of between 37 and 41 weeks and 6 days). Benitz et al (17) reported a 32.1 times greater probability of newborns less than 28 weeks-old developing sepsis in relation to newborns with gestational ages ≥37 weeks. Oddie and Embleton (18) determined an OR of 33.6 for the appearance of sepsis in newborns up to 34 weeks-old. The analysis of neonate weights demonstrated a range of between 610 and 4445 grams, with a mean of 2,411.7 (± 849.7). Our results revealed that neonates with extremely low (<1000 g) or low birth weights (1001 – 1499 g) demonstrated a greater risk of developing early neonatal sepsis (OR 2; $p < 0.001$). The percentages of early neonatal sepsis in

subsequent groups (1500-2499 g and >2500 g) diminished as birth weight increased, as can be seen in Figure 2.

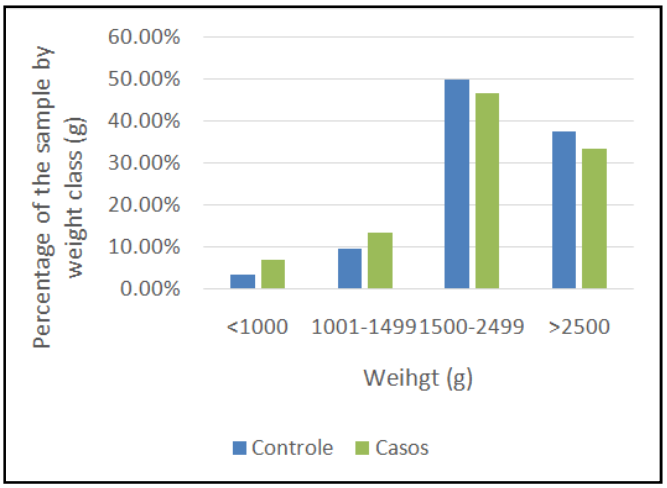

Figure 2. Distribution (in percentages) of healthy controls and cases of neonatal sepsis as a function of Weight. It is evident that the percentage of early neonatal sepsis in extremely low (<1000 g) or low birth weights (1001 – 1499 g) demonstrated a greater risk of developing early neonatal sepsis (OR 2; p < 0.001).

Pinheiro et al (19) reported that neonates having low birth weights were 20 times more likely to demonstrate sepsis, independent of their prematurity. The analysis of maternal age indicated the range as been from 15 to 40 years (mean of 24 ± 5.72). Sepsis was more prevalent among pregnant women younger than 25 (OR 1.96; p < 0.001). The data relevant to the maternal age groups ≤25 years and >25 years demonstrated that the former group had a 1.96 greater probability of neonatal sepsis than the latter. The analyses of the presence of infections in the urinary tracts of women during their pregnancy, indicated infection (together with prematurity) as the preponderant risk factor for the occurrence of early neonatal sepsis (OR 2.66; p < 0.001). Fifty percent of the pregnant women whose newborns developed early neonatal sepsis demonstrated UTI during their gestational period, with no relationship with the timing of its occurrence. The occurrence of maternal bacteriuria caused by SGB during gestation was therefore also a recognized factor of an increased risk of neonatal sepsis caused by that invasive pathogen (8,9).

SGB infection prevalence analysis: Based on our data, and considering the relationships between risk factors, we observed that gestational UTI and prematurity were the most statistically relevant factors related to the appearance of early neonatal sepsis. Knowing that infection by SGB represents one of the causes of UTI in pregnant women, with important clinical repercussions, we proceeded to determine the prevalence of SGB infection in the focal maternity population. Our results evidenced a SGB colonization rate of 40% in the pregnant women tested; colonization by that pathogen was identified in both the vagina and anorectal regions of 100% of those patients. Nogueira et al (10) reported that 10 to 30% of all pregnant women demonstrated SGB colonization in their vaginas or intestines, although the presence of those bacteria could be transitory, chronic, or intermittent. Those same authors noted that SGB has been isolated in cultures from the genital and/or lower gastrointestinal tracts of 10 to 40% of all pregnant women (with greater vaginal than rectal prevalence). Among the exams solicited during maternal gestation, testing for Streptococcus B is relatively new, although slowly increasing in Brazil and the world. That exam, however, is not yet routinely undertaken by the Brazilian public health service (4,21). In the present study, in 25% of the confirmed cases of infection by SGB, the pregnant women reported symptoms of urinary tract infection (and that diagnosis was confirmed during their pregnancy). The most-cited symptoms were: Dysuria (55%), pollakiuria (50%), urinary urgency (45%), and vaginal discharge (40%). Five of the neonates born to mothers colonized by SGB (8%) evolved towards early neonatal sepsis, and hospitalization in intensive care units was required during their treatments. Among those five, one neonate evolved towards death after less than seven days of life (4.16%). According to Amaral (12), and as demonstrated in studies published in this same journal, the rates of maternal SGB colonization, and the incidence of perinatal complications caused by that microorganism without prophylactic interventions, appear to be similar to those observed in the international literature. Zamudio et al (22) cited early neonatal sepsis as the principal cause of death among premature infants in a hospital in Mexico, as well as the second-highest cause of their hospitalization. Early neonatal sepsis occurred concomitantly with maternal infections by SGB in 49.1% of the cases in a third-level hospital in Paraná State in Brazil, with hospitalization being a complicating factor (as well as the necessary invasive procedures, especially orotracheal intubation) (23). Studies in Brazil have revealed the presence of SGB infections in up to 19% of all prenatal outpatients – a relatively high percentage – although less than observed in the present study (24,25). In light of the unquestionable efficiency of the strategy of prenatal SGB testing, if it is not immediately possible to track SGB infections through the public health service of Brazil, at least a diligent strategy of reducing risk factors must be implanted.

CONCLUSION

The present study indicates the fundamental importance of recognizing that prematurity, low birth weight, maternal age, and UTI during gestation are statistically significant risk factors for early neonatal sepsis. The SGB colonization rate in the population studied here was greater than that reported in other studies undertaken in Brazil (4,10,11,13). Additionally, the present study emphasizes that the principal etiological agent of early neonatal sepsis can be diagnosed through prenatal exams – even though they are not offered by the Brazilian Health Ministry. Future studies that demonstrate the effectiveness of such exams in preventing early neonatal sepsis in other countries will be important for promoting the adoption of adequate public policies that can help guarantee neonate health in Brazil.

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