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Review Article

The importance of early diagnosis in the neonatal period for group B *Streptococcus*

A importância do diagnóstico precoce no período neonatal para Estreptococo do grupo B

Débora Lais Justo Jacomini[1], Heloísa Beraldi Murayama[2]

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ABSTRACT: Streptococcus agalactiae or Group B Streptococcus (GBS) correspond to Gram positive diplococcus, usually residing in the microbiota of the gastrointestinal and genitourinary tract of pregnant women. The transmission of GBS occurs mainly through vertical ascent, especially in the intrapartum period, being one of the main bacteria responsible for the development of sepsis in the neonatal period. Early diagnosis associated with adequate antibiotic prophylaxis predicts lower risks of neonatal infection, in addition to a lower rate of complications and infant mortality. To carry out the research, we used high-impact articles taken from MEDLINE, SciELO, Pubmed, CNPq and LILACS platforms (2015–2022) and compiled a recent theoretical reference, with the exception of the historical reference, under which there was no time limitation. In reference to the levels of preventive medicine it can be observed: The primary prevention shows that the possibility of developing vaccines is viable, but so far in phase II in international studies and with a lack of epidemiological studies regarding the specific capsular serotypes of each Brazilian regions, hindering the development of the measure. Regarding the microbiological screening of GBS indicated by the Ministry of Health in 2012, it should be performed between the 35th and 37th week of pregnancy, in contrast to more recent international literature. In secondary prevention, there are new ways of diagnosing GBS infection, for example, the Xpert GBS, a rapid test indicated to test women at risk of preterm birth or in labor who did not undergo the test during prenatal care. The secondary still involves the existing treatment, which would be through the use of first-choice antimicrobials, such as crystalline penicillin or ampicillin, however, in some cases they already have resistance, requiring microbiological evaluation with antibiogram. In conclusion, the topic is extremely important for maternal and child health. GBS infection is a preventable disease with a simple diagnosis, however, there is still a huge literature divergence and lack of Brazilian protocols emphasizing the relevance of screening for GBS, which should be performed extensively in pregnant women, with antibiotic prophylaxis only in specific cases and, if necessary, with a previous sensitivity analysis to antimicrobials, in order to obtain better results.

Keywords: Group B *Streptococcus; Streptococcus agalactiae;* Pregnancy infectious; Neonatal sepsis.

RESUMO: *Streptococcus agalactiae* ou Estreptococo do grupo B (EGB) correspondem às bactérias Gram positivas com formato de diplococo, geralmente residentes da microbiota do trato gastrointestinal e geniturinário de gestantes. A transmissão do EGB ocorre principalmente através da ascensão vertical, sobretudo no período intraparto, sendo uma das principais bactérias responsável pelo desenvolvimento da sepse no período neonatal. O diagnóstico precoce associado à adequada profilaxia

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1. Advisor. Prof. Dra. Claretiano University Center – CEUCLAR. https://orcid.org/0000-0002-7992- 5588. E-mail: deborajacomini@claretiano.edu.br
2. Student. Claretiano University Center – CEUCLAR Research Center and Scientific Initiation. Scientific Initiation Program linked to the Research Center of the Medicine Course. https://orcid.org/0000-0001-7315-1190. E-mail: heloisa.murayama@gmail.com
Address: Heloísa Beraldi Murayama. R. 6, 809 (apto 61) – Centro, Rio Claro – SP, 13500-040

antibiótica prevê menores riscos de infecção neonatal, além de menor taxa de complicações e mortalidade infantil. Para realização da pesquisa, utilizamos periódicos de alto impacto retirados de bases das plataformas MEDLINE, SciELO, Pubmed, CNPq e LILACS (2015-2022) compilou-se a utilização de um referencial teórico recente, com exceção do referencial histórico, sob o qual não houve limitação temporal. A partir dos resultados obtidos pode-se observar na medicina preventiva: A respeito da primária, a possibilidade de desenvolvimento de vacinas é viável, mas até o momento em fase II em estudos internacionais e com carência de estudos epidemiológicos a respeito dos sorotipos capsulares específicos das regiões brasileiras, dificultando o desenvolvimento da medida. Em relação ao rastreio microbiológico do EGB indicado pelo Ministério da Saúde em 2012 deve ser realizado entre a 35º e 37º semana de gestação, contrapondo literaturas internacionais mais recentes. Na prevenção secundária há novas formas de diagnóstico para a infecção por EGB, a exemplo, o Xpert GBS, teste rápido indicado para testar mulheres com risco de parto prematuro ou em trabalho de parto que não fizeram o exame durante o pré-natal. A secundária ainda envolve o tratamento existente, o qual seria através da utilização de antimicrobianos de primeira escolha, como a penicilina cristalina ou a ampicilina, entretanto, em alguns casos já apresentam resistência, necessitando de avaliação microbiológico com antibiograma. Entende-se, portanto, que o tema é de fundamental importância para a saúde materna e infantil. A infecção por EGB é uma doença prevenível e de simples diagnóstico, entretanto, ainda há uma grande divergência literária e falta de protocolos brasileiros enfatizando a relevância do rastreio para EGB, o qual deve ser realizado de forma ampla nas gestantes, com profilaxia antibiótica somente em casos específicos e se necessário com análise de sensibilidade aos antimicrobianos prévia, com intuito de melhores resultados.

Palavras-chave: Estreptococo do grupo B; *Streptococcus agalactiae;* Infecção gestacional; Sepse neonatal.

INTRODUCTION

Streptococcus agalactiae or group B *Streptococcus* (GBS) is a Gram-positive diplococcus with facultative anaerobic energy metabolism. It is a microorganism detected in the gastrointestinal and genitourinary tract in the microbiota of 10 to 30% of pregnant women. GBS transmission occurs through vertical ascent in 50% of newborns (NB) of colonized mothers, especially during the intrapartum period[1].

In 1970, was discovered that when the bacteria of Group B *Streptococcus* were present in pregnant women and also identified in neonates were considered the main cause of neonatal infection, largely associated with sepsis and meningitis in the GBS early-onset disease (EOD), beyond to causing severe neurological sequelae. The importance of GBS screening and prophylaxis is related not only to infant mortality, but also impacts on quality of life and development[2]. The maternal repercussions involve: urinary tract infection, abortion, chorioamnionitis, premature birth and endometritis[3].

There are several different capsular serotypes of this microorganism: Types Ia, Ib, II, III and IV being the most prevalent in colonized mothers, which vary according to geography and population. Serotype III, ST-17, is the most associated with meningitis and a worse prognosis[4].

Intrapartum prophylaxis reduces the number of neonatal infections, however, the inadvertent use of antimicrobials and lack of antimicrobial sensitivity tests has decreased the efficacy of protocols, which are replaced only in cases of drug allergies[5]. Another option, still little tested in Brazil and with no international results that exceeds phase II, are the vaccines for each capsular serotype, and also depending on prevalence studies in each region for better results[6,7,8].

According to Williams obstetrics when pregnant women are not treated, one in every two hundred NB presents some complication of GBS, whereas in case where mothers were properly treated one in every four thousand NB presented some complication of GBS infection[1]. The main concern with neonatal mortality is in relation to more than 1 million deaths per year of newborns related to infections[9].

OBJECTIVES

The general objectives aim to analyze the divergences between national and international protocols, in order to identify the best procedures and screenings to be recommended in Brazil in order to reduce maternal and neonatal GBS infections, in addition to exploring and investigating the development of new diagnostic and vaccines.

METODOLOGY

This study was carried through a deductive review of literature collected in scientific articles published on sites such as MEDLINE, SciELO, PUBMED and LILACS. Compiled an updated theoretical framework in the period between 2015-2022, with the exception of the historical framework, under which no temporal limitation was applied to the publication.

RESULTS

Group B *Streptococcus*: screening and profylaxis

The screening indicated by the American College of Gynecology and Obstetrics in 2020 was made through the culture of perianal and vaginal material collected between 36 and 37 weeks and 6 days and in Brazil the indication still prevails between 35 and 37 weeks. A positive result for GBS indicates intrapartum prophylaxis, except in cases

where cesarean section is performed before labor and with intact membranes[5].

A detailed prenatal care is the best way to track any symptoms that indicates a probability of the neonate contracting GBS. The following risk factors should be considered: delivery or rupture of membranes before 37 weeks[1], premature rupture of membranes 18 hours or more before delivery, chorioamnionitis, fever greater than or equal to 38°C during delivery, urinary tract infection as a result of a positive GBS during pregnancy (especially in cases of pyelonephritis during pregnancy)[10] and a previous delivery with complications from GBS[1].

Another alternative for diagnosing GBS infection would be to use Xpert GBS as a quick test for women at risk of preterm birth or in labor who did not undergo the test during prenatal care. With this exam it is possible to start appropriate antibiotic therapy if the result is positive[11].

Recent articles also mention that mothers of African origin[12,13], pregnant women under 20 years old[14] and pregnant women who live with more than one person are also more likely to have positive colonization[15]. These are valid factors that can be considered in the Brazilian population, since they fit into the country's socioeconomic scenario[16].

Antibiotic therapy is intended to reduce the GBS load in the maternal vaginal delivery, in addition to increasing the levels of the minimum concentration of the antibiotic in the fetal bloodstream to destroy GBS and, consequently, also protect the baby's mucosa and surface against possible colonization[3,17].

Chemoprophylaxis is mainly performed using crystalline penicillin, but intravenous ampicillin is a very common choice in Brazilian services and is an acceptable alternative. Women who are allergic or show low risk of anaphylaxis to penicillin can use first-generation cephalosporin but in cases of high severity for anaphylaxis, clindamycin should be used. Intrapartum intravenous prophylaxis has a prescription that antibiotics should be used 4 hours before delivery[1,5], however, 2 hours exposure with crystalline penicillin or ampicillin already demonstrates a decrease in the GBS count in the vaginal colonies, therefore, it reduces the frequency neonatal sepsis and should not be delayed any longer[18,19,20].

The lack of epidemiological studies regarding specific capsular serotypes in Brazilian regions makes it difficult to produce vaccines and create new protective measures. This fact, together with the already known misuse of antibiotics, not only during pregnancy, distances the reality of reduced bacterial resistance in nosocomial environments[5,7].

Group B *Streptococcus* and Brazilian protocols

Protocols are tools used with the objective of guaranteeing the best clinical care for the patient through the recommendation of conducts or therapeutic measures for a given disease, always based on studies that prove the best effectiveness of the measure. The use of this instrument benefits the quality of care, optimizes assistance and mainly adapts the scientific evidence to the local reality[21].

However, therapeutic guidelines must be based on constantly updated data that differ between locations. If it remains rigid and unalterable, it will not accompany more efficient measures and the emerge from new medications, as well as making it impossible to provide reliable data regarding the evolution of the disease[21].

In view of this, it is observed that several tests (with emphasis on blood count, blood typing, blood glucose, urinalysis and urine culture, rapid test for syphilis and VDRL, rapid HIV test, malaria test, hepatitis B tests and toxoplasmosis tests) are mentioned in the latest update of the Ministry of Health's Pregnancy Handbook, but at no time does it inform about the vaginal-rectal swab for GBS screening[22].

The booklet on primary care for low-risk prenatal care, updated in 2012, does not recommend the systematic performance of GBS collection in pregnant women and the use of intrapartum antibiotics[23].

The high-risk handbook recommends screening from the 34th week onwards and the search for GBS is characterized as auxiliary propaedeutics only mentioned in the chapter on premature rupture of the membrane, without clarifying information regarding the use of antimicrobials at the time of delivery[24]. The booklet should be a guide for propaedeutic decisions, however, due to outdated documentation, it ends up harming the choice of conducts based on more up-to-date and preventive studies[21].

Recent articles, not related to public policies, indicate that screening in Brazil should be done between 35 and 37 weeks[4,16], while in more developed countries, for example, the United States, schools of Gynecology and Obstetrics choose to perform between 36 and 37 weeks and 6 days. This difference is conflicting, since the validity window of the exam includes births that occur within 5 weeks, and term pregnancy, even if late, can occur up to 42 weeks[5,25].

In this way, information is outdated within the protocols found, not taking into account the statistics of the reduction of cases of neonatal infections in developed countries after the insertion of wide screening and prophylactic measures, data that has been confirmed since 2000. Screening is expensive, but it is known that admissions to neonatal ICUs imply greater economic reverberations[5,25].

Group B *Streptococcus* and neonatal infection

Neonatal infection can be defined as early or late. When the clinical picture appears within 7 days of life, it is determined as early, in which the fetus is infected by an

ascending route of bacteria that were in the vaginal tract or during the intrapartum period. It is closely related to septicemia and pneumonia in the first 12 to 48 hours after birth, and it's also unlikely to present with meningitis of onset[26].

Preterm infants born due to cervical insufficiency, premature rupture of membranes, chorioamnionitis, amniorrhexis, and non-reassuring fetal vitality status (tachycardia, tachypnea, particularly requiring ventilation support, and/or thermal instability) indicate greater likelihood of early GBS infection. In cases of GBS risk factors, blood tests and empiric antibiotic therapy should undoubtedly be performed; when not, but associated with an unstable condition of the newborn, the conduct should be maintained[25].

The septic condition caused by GBS has the same management of a common neonatal sepsis[27], with a diagnosis based mainly on the request for a blood count and lumbar puncture to analyze the cerebrospinal fluid. If meningitis is suspected, imaging tests are required to assess the presence of abscesses or ventriculitis, due to the risk of brain herniation. In both cases, antimicrobial susceptibility tests should be requested[25].

Unlike prophylaxis for GBS during pregnancy, for the treatment of GBS infection in newborns ampicillin is the first choice together with aminoglycosides in patients with up to 7 days of life, since β-lactams in neonates have a concentration level minimum, due to mutations in penicillin-binding proteins[25].

Late infection, however, occurs between 7 days of life and 2 to 3 months of age, transmitted mostly horizontally by the mother, but which can also occur in the community or hospital, characterized by meningitis, bacteremia or infection of soft tissues[25]. When the condition is much later, after 3 months, it occurs in premature babies or in babies with Human Immunodeficiency Syndrome. In addition, the rates of late infection remained practically the same even with intrapartum chemoprophylaxis[17].

Late GBS infection is characterized by unfocused bacteremia, thermal instability, irritability, vomiting, signs suggestive of central nervous system involvement with bulging fontanelle or seizures. When related to focal syndromes, it is related to pneumonia, bone infections usually without fever, cellulitis or adenitis, in addition to neurodevelopmental impairment. Other tests may be added for the diagnosis of late infection, such as urine culture, radiography, magnetic resonance imaging and culture of bone fluids as suspected[25].

Treatment for late infection varies according to the patient's condition, if it is a stable patient with no signs of meningitis, ampicillin associated with ceftazidime is chosen until the 28th day of life. When the same condition occurs between 29 and 90 days, the use of ceftraxone is indicated. If the patient is previously without signs of infection and then symptoms of meningitis, β-lactam-resistant pneumonia or critical illness appear, the addition of vancomycin to empirical therapy is recommended. β-lactams can be used when there is presence of Group B[25] Streptococcus in the culture[25].

DISCUSSION

Brazil is still a developing country in which prenatal care is concerned with the main diseases that affect most of the population and that can affect the development of the newborn during pregnancy, such as toxoplasmosis, syphilis, HIV, cytomegalovirus, rubella and malformations. The infection has its due importance in the protocols through the evolution of leukorrhea, however, when referring to the GBS screening, it does not have due notability[23,24], which, despite being an additional cost in public health, prevents complications from sepsis or meningitis that can reverberate in infant development and mortality[25,26,27].

Many of the high-risk diseases during pregnancy are linked to early age of the pregnant since 6 out of 100 pregnant women are aged between 15 and 19 years in Brazil[28]. Those facts combined with the low socioeconomic status are characteristics very present in national epidemiology[16], are directly related to GBS infection and prematurity, chorioamnionitis and/or premature rupture of membranes, which together can be lethal to the NB[2].

In addition, due to the lack of efficient screening for GBS in Brazil, there is little knowledge about the prevalence of serotypes in the population, a conflicting issue that preclude the development of vaccines, a therapeutic measure that would allow a reduction in the use of intrapartum antibiotics and consequently lower bacterial resistance[4,6,7]. However, while there is no elaboration of new measures, the use of intrapartum antimicrobials should remain in cases of positive screening for GBS infection, always opting, whenever possible, for penicillin or ampicillin, since some studies already show resistance to cefepime, erythromycin and clindamycin[1,5].

CONCLUSION

The GBS screening is fundamental for maternal and child health, due to the relevant frequency in which it occurs and the serious repercussions related to it. Screening and conduct are still topics of literature divergences. In developed countries more preventive measures have been adopted with mass screenings and with high sensitivity, unlike underdeveloped and developing countries, such as Brazil, in which there are screenings in specific situations, but with higher expenses directed to hospitalizations in neonatal ICUs.

In sum, screening should be carried out extensively in pregnant women, so that the main serotypes present in the population are discovered for later vaccine production and so that prophylaxis with antibacterial is reduced.

However, as it is the only therapeutic measure indicated at the moment, it should be used only in specific cases and, if possible, with prior microbial analysis.

Therefore, the importance of keeping up-to-date information about GBS infection in national protocols is resumed, through bibliographic reviews in addition to new studies to continue the development of vaccines and new faster screening methods.

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