Colonization by *Streptococcus agalactiae* During Pregnancy: Maternal and Perinatal Prognosis

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We reviewed colonization by group B *Streptococcus β-haemolyticus* of Lancefield (SGB), or *Streptococcus agalactiae*, in pregnant women, and the consequences of infection for the mother and newborn infant, including factors that influence the risk for anogenital colonization by SGB. We also examined the methods for diagnosis and prophylaxis of SGB to prevent early-onset invasive neonatal bacterial disease. At present, it is justifiable to adopt anal and vaginal SGB culture as part of differentiated obstetrical care in order to reduce early neonatal infection. The rates, risk factors of maternal and neonatal SGB colonization, as well as the incidence of neonatal disease, may vary in different communities and need to be thoroughly evaluated in each country to allow the most appropriate preventive strategy to be selected.

**Key Words:** Pregnancy, prognosis, *Streptococcus agalactiae*.

*Streptococcus β-haemolyticus* of group B of Lancefield (SGB), or *Streptococcus agalactiae*, recognized in the 1920’s as the etiological agent of bovine mastitis [1], has been associated over the years with infections in parturients and newborn infants, provoking important morbidity and mortality among newborns and pregnant women [2-4]. SGB disease can occur in three clinical forms: 1) early-onset disease, defined by the development of disease in newborn infants up to the 7th day of life, accounting for about 85% of the neonatal infections caused by this agent; 2) late-onset disease, characterized by occurrence between the 8th day and the 3rd month of life; and 3) very late-onset disease, occurring after the 3rd month of life [5].

We made a review of the literature dealing with the influence of colonization by *Streptococcus agalactiae* during pregnancy from the maternal and newborn infant perspective, with an examination of factors that influence the risk for anogenital colonization by SGB, the maternal and perinatal prognosis and the methods for diagnosis and prophylaxis of SGB.

**Influence of Pregnancy Period on Colonization of Pregnant Women by *Streptococcus agalactiae***

The prevalence of SGB colonization among pregnant women ranges from 10 to 30% [6-8]. SGB colonization rates vary with ethnic groups, geographic localization and age; they are similar for pregnant and non-pregnant women [9].

The challenge of working with SGB is partly due to the transitory colonization observed in pregnant women, with approximately equal numbers of women being colonized in a transitory, intermittent or persistent manner. Thus, in order to minimize early-onset neonatal disease, the recommendation is to make a culture at...
between 35 and 37 weeks of pregnancy, due to the potentially stable profile of colonization during a period of five weeks before delivery [10-12].

Risk Factors for Colonization by *Streptococcus agalactiae*

Several maternal risk factors can significantly increase the probability of development of SGB disease in neonates. This is an important fact, since the presence of an isolated risk factor increases the probability that a pregnant woman will have a child with early neonatal SGB disease by 6.5 times [13]. The identification of a high-risk population to be screened for SGB colonization is a considerable challenge, since this colonization is also observed in mothers who do not have the classically known risk factors, and it represents 25% to 30% of neonates that develop early neonatal SGB [14].

The option for the identification of maternal risk factors, such as SGB bacteriuria during pregnancy, labor before 37 weeks of gestation, premature rupture of the fetal membranes lasting more than 18 hours, intrapartum fever, and a history of a newborn with early-onset neonatal SGB disease by 6.5 times [13]. The identification of a high-risk population to be screened for SGB colonization is a considerable challenge, since this colonization is also observed in mothers who do not have the classically known risk factors, and it represents 25% to 30% of neonates that develop early neonatal SGB [14].

The frequency of SGB colonization is highest among black women, followed by Hispanic women and white women [14]. However, in Brazil, in view of the high degree of racial miscegenation, it is difficult to establish a precise classification of a patient sample in terms of race or ethnic group. In an observational study of 101 pregnant women with HIV infection in Ribeirão Preto, SP, Brazil, a distinction was made between white and non-white women; there was a higher risk of colonization among non-white women and among women with associated diabetes mellitus (P. El Beitune & G. Duarte, unpublished data).

**Strategies to Prevent Early-Onset SGB Disease**

In 1996, the Centers for Disease Control and Prevention (CDC) recommended two strategies to identify mothers colonized with SGB, with the specific objective of preventing early-onset SGB disease in the neonate. The strategies consisted of the identification of important maternal risk factors or of the execution of routine cultures of anogenital swabs obtained from pregnant women at between 35 and 37 weeks of gestation [16].

After a recent review published in 2002 by the CDC, which was endorsed by the American College of Obstetrics and Gynecology and by the American Academy of Pediatrics, priority has been given to the systematic adoption of SGB culture for women at between 35 and 37 weeks of gestation [14].

**Methods for Diagnosis of Colonization by SGB**

Bacterial culture is considered to be the gold standard for SGB detection when it is applied to material obtained from both the vagina and the anus, using selective media for SGB; the result is later confirmed by specific diagnostic tests, such as latex agglutination or molecular biology techniques. This recommendation is based on the fact that 86% of cases of early-onset neonatal disease are prevented when anogenital culture is performed between 35 and 37 weeks of gestation, as opposed to a 68.8% rate of prevention when the conduct used is based on maternal risk factors. Screening tests during the prenatal period, followed by appropriate management of cases of colonization, present a clearly favorable cost-benefit ratio [13,14].

An important limitation of the detection of SGB in culture is the need for viable organisms and for an average culture period of 48-72 hours. Approximately 6 to 13% of the newborns colonized with SGB during the first 48 hours of life are born to women with negative SGB cultures, demonstrating the limitations of culture as a detection strategy. In some cases, this limitation may be due to the exponential fall in the number of
SGB colonies, as the swabs are kept out of the transport medium at eight hours after collection, and also due to the maternal use of antibiotics (such as penicillin G, ampicillin or erythromycin) and of personal hygiene products containing antifungal and antiseptic agents (douches and vaginal soap bars) [19].

Historically, SGB used to be detected by culture of a vaginal swab. However, the sensitivity of these cultures did not exceed 50 to 60% in the best series [6,8,10,19,20]. There is data from studies whose objective was to minimize false-negative results by recommending that the lower portion of the vagina be cultured instead of the cervix, and that the anorectal portion be submitted to simultaneous swabbing and cultured in selective and enriched media, such as Lim broth or Todd-Hewitt broth (THB). The media should be kept at 4°C and supplemented with antibiotics that suppress the growth of Gram-negative bacteria and of other saprophytic microorganisms of the vaginal flora, thus favoring the recovery of an adequate number microorganisms and facilitating their identification, even in samples with a reduced inoculum concentration [2,6,7,10].

Theoretically, an ideal test for the identification of maternal SGB colonization has still to be found. Such a test should be rapidly conclusive when used at the time of maternal admission during labor, should have a minimum sensitivity of 86% (the sensitivity of the gold standard), should be of low cost in order to be definitely included in the set of tests required during the intrapartum period, and should have low false-negative rates.

Among the rapid tests for the diagnosis of SGB colonization, molecular biology exams seem to be a promising reality. As an example, the fluorogenic polymerase chain reaction yielded conclusive results within 45 minutes, with 97% sensitivity and 100% specificity [21]. However, this test is not commercially available. Another test based on antigen detection, the latex agglutination test, has a period of incubation of 10 minutes and efficiently identifies β-hemolytic streptococci of the A, B, C, D, F and G groups of Lancefield. This test varies in sensitivity and specificity, depending on the time of culture of the bacteria in selective medium. It is an excellent confirmatory test after the gold standard culture test, with sensitivity and specificity close to 100% [20]. However, when the test is applied before culture on blood-agar medium, the sensitivity is 65%; it varies when this method is used without previous enrichment with THB medium, and it depends on the time of incubation on blood-agar plates, on the amount of inoculum present in the sample, and on the execution of the agglutination test immediately after dilution of the extraction fluid [20,22]. On the other hand, a group in Spain recently concluded that agglutination testing of selective broth is a sensitive method, which offers the advantage of saving 24 h in the turnaround time for detection of SGB in pregnant women, with 98% sensibility [23]. While these results were not confirmed by others, we still conclude that culture is ideal for screening during the prenatal period, but is not suitable for the rapid diagnosis required for patients in labor.

**Influence of Colonization by *Streptococcus agalactiae* during Pregnancy on Maternal Prognosis**

Complications due to SGB colonization during pregnancy are not limited to the neonatal period. According to some investigators, SGB colonization during pregnancy increases the risk of spontaneous abortion and influences the pathogenesis of premature rupture of the fetal membranes, of preterm labor and of low neonatal birth weight, though the consequences differ widely [24-26].

There is no consensus regarding the effect of SGB colonization on gestational prognosis. Studies evaluating this interaction in HIV-1-infected pregnant women are also lacking. Several studies evaluating pregnant women defined as clinically normal did not detect an association between SGB and an adverse gestational prognosis, such as preterm labor, premature rupture of the membranes, and low neonatal birth weight [27,28]. These results are similar to those observed in Ribeirão Preto, among HIV-infected pregnant women colonized by SGB (P. El
Beitune & G. Duarte, unpublished data). Although some investigators found that women with preterm delivery have a significantly higher frequency of SGB colonization at the time of delivery, they did not confirm the possible association between higher rates of preterm deliveries among women colonized by SGB in the 24th week of gestation [25]. On the other hand, a reduced latency period before delivery was observed in SGB-colonized women who developed preterm rupture of the membranes. However, a cause-effect relationship was not conclusively established [29]. In view of the above studies, the CDC published directives in 2002, advising obstetricians to follow a conservative conduct during the prenatal period, except in the case of urinary tract infection associated with SGB, which occurs in 2 to 4% of all pregnant women [14].

The complications due to SGB colonization during pregnancy are not limited to the gestational period. According to some investigators, this type of colonization also affects maternal prognosis. Several studies have reported that SGB is directly responsible for cases of chorioamnionitis and endometritis, being less frequently isolated in cases of abdominal wall infection, pelvic abscess, septic pelvic thrombophlebitis, osteomyelitis, and meningitis [14,24,30]. Additionally, in 2000 Schrag et al. [22] demonstrated a 21% reduction in the risk of chorioamnionitis and endometritis when antibiotic prophylaxis was applied [31]. Thus, if SGB colonization could be controlled, few adverse effects would be observed.

**Influence of Colonization by *Streptococcus agalactiae* during Pregnancy on Newborn Infant Prognosis**

Vertical transmission occurs in 30 to 70% of neonates whose mothers have an SGB-positive culture during pregnancy [2] and, in the absence of a prevention program, 1% to 2% of these neonates develop symptomatic SGB infection, with approximately 90% of cases occurring during the first 24 hours of life [13,32].

In absolute numbers, early-onset SGB disease affects 1 to 4/1000 liveborns; when only children born to mothers colonized with *Streptococcus agalactiae* during the prenatal period are considered, the neonatal rate of infection is 0.3% to 1.4%, with a 25-fold increase in early neonatal disease compared to children born to non-colonized mothers [13,14], mainly due to vertical transmission. This form of transmission can result from intrauterine infection, due to the ascending dissemination of SGB from the vagina, with secondary aspiration of contaminated amniotic fluid by the fetus, but it is undeniably facilitated by premature rupture of the fetal membranes, after the beginning of labor and during the passage of the fetus through the birth canal, resulting in higher than 50% neonatal mortality rates during the 1970s decade, compared to the current 4 to 20% rates. This notable reduction is due to a better understanding of the risk factors associated with neonatal infection and the considerable evolution of care at neonatal therapy centers [10,14,31,33].

Although the clinical manifestation of early-onset SGB disease more frequently involves pneumonia or septicemia, in the United States approximately 2,000 neonates develop SGB-induced meningitis each year, with a consequent permanent neurological deficit occurring in 30% to 50% of these cases [34].

**Effect of Prophylaxis Intrapartum on Perinatal Prognosis**

Antibiotic therapy during the prenatal, intrapartum and postnatal periods has been used in order to prevent early-onset neonatal SGB disease. Objectively, prenatal therapy has proven to be ineffective, due to the peculiar characteristics of the often persistent or intermittent colonization. It has currently been established that treatment of maternal SGB colonization during pregnancy does not eradicate the microorganisms in a definitive manner, regardless of the treatment used. Another equally frustrated strategy, i.e. the isolated administration of antibiotic prophylaxis during the postnatal period to all babies born to colonized mothers, resulted in half to 2/3 symptomatic and bacteremic...
infants at birth. Thus, the experience obtained with the use of these strategies indicates that the most efficient method available today is intrapartum chemoprophylaxis with parenteral antibiotic therapy, while maternal immunization, permitting effective and sustainable immunogenicity, is not yet a reality [13,14,35].

SGB is sensitive to many antimicrobial agents, especially β-lactam antibiotics. Among the antimicrobial agents extensively used against SGB are penicillin G and ampicillin [14]. Penicillin G continues to be the antibiotic of choice for intrapartum prophylaxis for SGB-colonized mothers because of the effective transplacental passage of this agent, its low cost, and broad spectrum of action directed at Gram-positive cocci, with a lower theoretical probability of the emergence of resistant microorganisms. Erythromycin and clindamycin are acceptable alternatives for mothers who are allergic to penicillin [14,16,36]. The prevalence of resistance among invasive SGB isolates ranged from 7 to 25 per cent for erythromycin and from 3 to 15 per cent for clindamycin [37,38] and might be associated with certain serotypes, especially type V [39,40]. In a study performed in Ribeirão Preto, there was no indication of uniform susceptibility to penicillin and to other beta-lactam antibiotics of SGB isolates from 101 HIV pregnant women and matched control pregnant women, so further surveillance is needed, particularly in the case of invasive SGB isolates (P. El Beitune & G. Duarte, unpublished data). Similar results were generally found in other studies [41-43]. In general, the studies demonstrate increased effectiveness four hours after the administration of antibiotic therapy to the mother, since adequate penicillin or ampicillin concentrations are achieved in amniotic fluid two to four hours after parenteral administration to the mother [5,14].

Among the nine currently-identified SGB serotypes, five (Ia, Ib, II, III, and V) are prevalent among pregnant women and neonates with early onset SGB disease in the United States and Western European countries [44, 45]. Types VI and VIII predominate in isolates from Japanese women [46]. Types IV and VII are encountered only rarely [44]. Serotype distribution may have implications for the development of a multivalent anti-SGB vaccine [44].

Conclusions

On the basis of our review, it is justifiable to adopt anal and vaginal SGB cultures as part of differentiated obstetrical care in order to reduce early neonatal infection. The rates and risk factors for maternal and neonatal SGB colonization may vary in different communities. These rates, as well as the incidence of neonatal disease, need to be thoroughly evaluated in each country, to allow the most appropriate preventive strategy to be selected.

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