Group B streptococcal perinatal infection: A Global, Latin American and Mexican Overview

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Abstract

Group B streptococci (Streptococcus agalactiae) cause a number of infections in women during pregnancy and postpartum, such as urinary tract infection, chorioamnionitis and endometritis, consequently may affect the newborn. Group B streptococci is the most common cause of severe infections in newborns in developed countries. Studies on the epidemiology of group B streptococci infections in Latin America are still limited. This information is also unknown in Mexico, but studies carried out in the center of the country have found high rates of vaginal colonization in pregnant women and there are case series and case reports of newborns. Microbiological and molecular epidemiology studies in Mexico have shown that populations of group B streptococci have a clonal distribution and that there are clones with genetic and phenotypic characteristics of high virulence that appear to be responsible for most of perinatal pathology. However, the actual role of group B streptococci in perinatal pathology in Mexico is unknown. Consequently, whether to perform or not the screening for determining the group B streptococci colonization status in pregnant women, and the indication or not for intrapartum antibiotic prophylaxis to prevent neonatal group B streptococci infection in Mexico, are still controversial.

KEY WORDS: *Streptococcus agalactiae. Group B streptococcus. Perinatal infection.*

Introduction

Streptococcus agalactiae or group B streptococcus (GBS) is a bacterium that can cause infections in women during pregnancy and puerperium, increase the risk of gestation product loss and complicate adequate management of the mother-child dyad. Since the GBS-colonized mother may transmit this microorganism to her newborn, there is risk of infection in the colonized neonate[1]. Most information on GBS infection corresponds to developed countries. Although there are studies on GBS perinatal infection published in Colombia, Argentina, Peru and Brazil, information on GBS infection epidemiology and behavior is still limited in Latin America[2-10]. In developed countries, in spite of different implemented prevention measures, including intrapartum antibiotic prophylaxis (IAP), GBS remains the most common etiological agent of serious infections in the newborn and the most common cause of neonatal sepsis and meningitis[11-14]. In Mexico, the real role of GBS in perinatal pathology is unknown, and most available information on the subject corresponds to the center of the country[15-20]. Owing to this, the performance or not of a deliberate search for GBS colonization in pregnant women and

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the indication or not of IAP to prevent the occurrence of GBS neonatal serious infection remain controversial in Mexico.

Causative agent

GBS is a Gram-positive bacterium that can be isolated from the genital and low gastrointestinal tract in 5%-40% of pregnant women, out of which 30% have asymptomatic infection[21,22]. Human GBS isolates express a capsular polysaccharide, which is an important virulence factor that allows for the microorganism to evade the host defense mechanisms, particularly opsonophagocytosis[23]. GBS isolates are classified in 10 serotypes according to the unique antigenic characteristics of their capsular polysaccharide (Ia, Ib, II, III, IV, V, VI, VII, VIII and IX)[24]. In 1974, in developed countries, it was demonstrated that although all GBS serotypes were able to cause neonatal infection, serotype III isolates had significantly increased in neonates with meningitis caused by this microorganism[25]. In the USA and Europe, the GBS serotypes that cause serious disease (known as "invasive") are predominantly Ia, Ib II, III and V[26-29], whereas a study in Gambia reported serotype V predominance[30]. A recent global review of invasive isolates demonstrated that serotype III is the most frequently identified one in all regions with data available (48.9%), followed by serotypes Ia (22.9%), V (9.1%), Ib (7%) and II (6.2%)[24].

In spite of the fact that colonized mothers' immune status appears to play a crucial role in providing protection to their children, different studies have suggested that differences in GBS isolates' virulence can also contribute to the development of neonatal infection[13,31,32]. Since serotype III causes more than two thirds of GBS-related neonatal disease, serotyping was proposed as a method to predict the risk of serious or "invasive" disease[2,11,20].

However, serotype III is also frequently isolated in asymptomatic colonized newborns, other serotypes different from III are often isolated in early-onset disease, and in up to 10%-15% of cases, the strains have been nontypeable[12,13,18,33]. Different molecular methods have been used to classify GBS isolates and associate particular genotypes with higher risk for disease[34-37]. In one study, a clone that appeared to be the cause of most cases of serious infections with GBS in the newborn was identified by multi-loci enzyme electrophoresis[34]. When 128 GBS isolates from different states of the USA were examined, serotype III strains were found to belong to two different evolutionary lineages, which were regarded as clonal types. One of these clonal types (phylogenetic division I) was the causative agent of the highest morbidity and mortality produced by serotype III isolates, and was then proposed to be a highly virulent clonal type. This clonal type was named "high virulence clone" (HVC). Subsequent studies demonstrated that this HVC possesses several characteristics that confer high virulence, such as elevated values of extracellular products, including type III antigen, hyaluronidase and protease[35-37]. A unique characteristic of isolates that belong to this HVC is its inability to grow at 40 °C in media with high contents of phosphate[20,38-40]. Several studies carried out in central Mexico have demonstrated the existence of this clone[38,41]. In a study with isolates from central Mexico, this virulent clone was identified in 15% of a sample of 286 isolates[20]. Subsequently, this HVC was shown to correspond to the high virulence clonal type RDP-III-3 identified by Takahashi et al.[42,43] in Japan. Summarizing current evidence, different studies have demonstrated that GBS populations have a clonal distribution, and that there are highly virulent subtypes that appear to be the cause of the higher morbidity and mortality produced by this microorganism.

GBS are well-adapted bacteria to asymptomatic colonization in human adults, but are also potentially invasive pathogens in certain susceptible neonates. Given that newborns are quantitatively and qualitatively deficient in their defense mechanisms, including phagocytes, complement system and antibody specificity, there is a microenvironment where a variety of virulence factors presented by GBS has been reported. The complex interactions of the bacterium and the newborn that lead to disease manifestation can be divided in several important categories (Table 1). The multi-functional nature of the GBS variety of virulence factors (summarized in table 1) represents a big challenge to the underdeveloped immune defense mechanisms of the newborn. Further knowledge on the molecular bases of this pathogenesis will help to have a clearer vision on efficacious innate immunity at first stages of human life and will provide new targets for GBS infection chemotherapy or immunoprophylaxis[44,45]. Several GBS virulence factors have been identified; in particular, the capsular polysaccharide and secreted hemolysin are highly important to virulence[46-49]. On the other hand, superoxide dismutase and D-alanylated lipoteichoic acid play important roles[50,51]. It should be added that many surface proteins can contribute to adherence and colonization in

Table 1. B-group streptococcus virulence factors and their role in the transition from colonization to invasive disease

Virulence factor	Colonization	Adhesion	Invasion	Immune system evasion	Neurotropism
Fibrinogen-binding protein A (FbsA)	+	+			
Fibrinogen-binding protein B (FbsB)			+		
Laminin-binding protein (Lmb)			+		+
Alpha C protein (ACP)	+	+	+	+	
Serine-rich repeat protein (Srr)	+	+	+		
Pili	+	+	+	+	+
Hypervirulent adhesin (HvgA)	+	+	+	+	+
Beta hemolysin-cytolysin (β-H/C)	+	+	+	+	+
Capsular polysaccharides (CPS)				+	
C5a peptidase (ScpB)				+	
H factor				+	
IgA-binding beta antigen				+	
D-alinination				+	
Superoxide dismutase				+	
Hyaluronate lyase				+	
CAMP factor				+	
Lipoteichoic acid		+		+	
Fibrinogen receptor		+		+	

Adapted from Landwehr-Kenzel et al.[45]

the host[52,53], as well as to immune system evasion (Table 1)[54].

Epidemiology

In 1935, Lancefield and Hare[55] identified GBS in vaginal smears and, in 1938, Fry[56] described three mortal cases in women after delivery; this event was highly important, since, previously, all serious streptococcal infections in that setting had been attributed to group A streptococcus[56]. Case reports of GBS-associated neonatal disease were occasional until the early 60's, when it was recognized as one of the main causes of neonatal sepsis in the USA[23,57], and in the early 80's it was identified as the most common cause of neonatal sepsis and meningitis in several developed countries[58-60]. GBS is able to cause serious ("invasive") disease, especially in newborns and pregnant and puerperal women[22]. In spite of the use of IAP in the USA and other countries, GBS remains the most common cause of neonatal sepsis and meningitis in those countries[11,12], with nearly 50,000 maternal infections per year and rates of vertical transmission to newborns of 29%-72%[21].

In Latin America, studies on GBS infection epidemiology and behavior are still limited. Nevertheless, GBS-related serious neonatal infection cases and fatal cases have been reported[3]. One study was carried out in Colombia describing epidemiological, clinical and microbiological characteristics of disease-causing (invasive) and non-disease-causing (non-invasive) GBS isolates from patients admitted to a tertiary care hospital over a 17-year period. From 1994 to 2001, 201 GBS strains were detected, out of which 46 were related to invasive infections, 11 (24%) in newborns and 35 (76%) in adults. Between 2004 and 2012, 671 strains were identified and 95 serious infections were reported: 12 (12.6%) in newborns, 5 (5.3%) in children and 78 (82.1%) in adults. Average prevalence of GBS invasive isolates was 17.4% over the 17-year period. Neonatal infections estimated incidence was 1.34 per 1000 live births (0.99 x 1000 live births for early-onset disease and 0.35 x 1000 for late-onset disease)[4]. In Argentina, a GBS maternal colonization percentage of

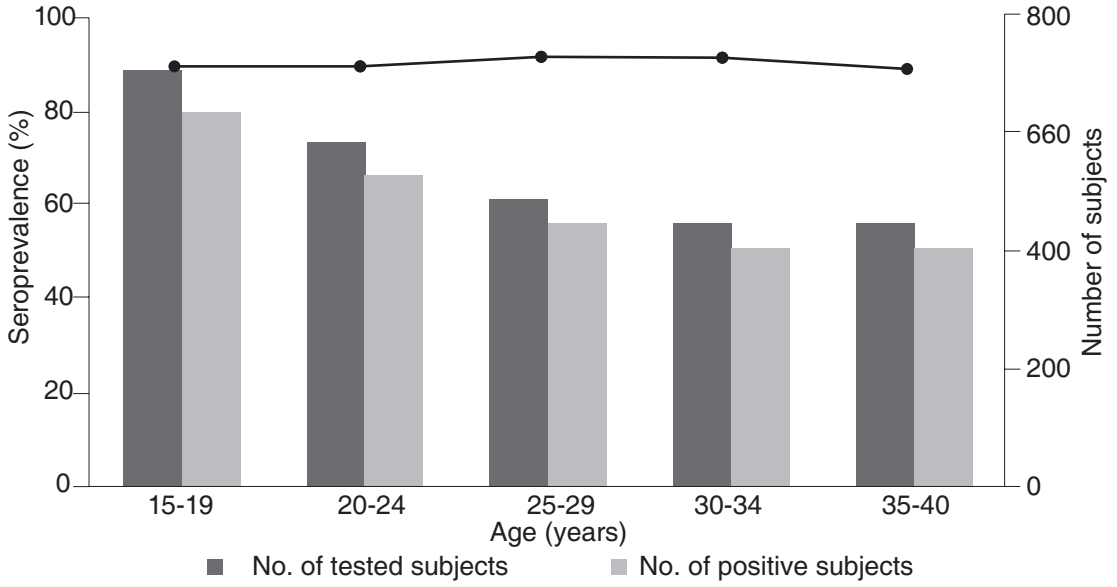

Figure 1. *Prevalence of anti-GBS group antigen antibodies in 2669 childbearing age Mexican women. The line indicates seroprevalence, dark bars are the number of tested women and clear bars are the number of seropositive women by age groups, Mexico, 1987-1988 (reproduced with permission of the editor)*[31].

1.4% (17 patients) was found, and one case of neonatal sepsis consistent with GBS (0.6%) was reported in a mother with negative culture[5]. In Peru, GBS could be isolated in 26 pregnant women (10.9%), out of which 9 (36.4%) referred having had previous abortions[6].

In general, the rates of genital colonization by GBS in Latin America range from 2 to 20.4%, as shown by studies conducted in Mexico, Argentina, Colombia and Brazil[7-10,19], with an incidence of neonatal serious ("invasive") infection of 0.3-1% of live births. In Mexico, GBS colonization deliberate search or IAP administration to prevent infection in newborns are generally not performed, since available information on the subject to this moment drives to consider GBS an uncommon cause of perinatal infections in this country[15-19,61,62]. However, several studies have found percentages of vaginal colonization un pregnant women of up to 20%, and a neonatal infection rate of 1/1500 live births, with a lethality of 38.5%[15-17,61]. On the other hand, a nation-wide seroepidemiological survey, where the presence of anti-GBS group antigen antibodies was assessed in women between 15 and 40 years of age, demonstrated an elevated frequency of exposure to GBS in the Mexican population, with a seroprevalence of 90% (Fig. 1)[31].

Studies conducted in Mexico in the decade of 1980 at the Instituto Nacional de Perinatología documented GBS cervicovaginal colonization in 10.3% of 340 pregnant women. The predominant type was serotype I (33%), with low participation of serotype III (3%) and high prevalence of nontypeable isolates (18.2%)[15,16]. Based on this, the low frequency of GBS-related neonatal disease in Mexico was attributed to the low prevalence of serotype III together with an elevated prevalence of nontypeable isolates[15,16]. Subsequent studies have confirmed that the predominant serotype in central and western Mexico is serotype I (58.8-61.3%), but higher participation of serotype III (5.9-12.8%) has been documented, with lower participation of nontypeable isolates (0-5.9%)[18,19,61]. In the year of 2007, Palacios et al.[20] documented the predominance of serotype I (48.6%) in pregnant women colonization, with serotype III growing participation (32.9%). In addition, they suggested serotype III higher participation in serious disease in neonates in Mexico. Although the information is still limited and most of it corresponds to studies carried out in central Mexico, previous studies show that the predominant serotype on Mexico is I; however, data suggest that serotype III participation is increasing, not only in Mexican women colonization, but also in newborn infection in Mexico[18-20,32].

Disease in newborns and infants

GBS is considered to be the most common etiological agent of neonatal sepsis in developed countries,

Table 2. Characteristics of B group streptococcus-caused disease in pediatric patients

	Early-onset disease	Late-onset disease	Late, late-onset disease
Serotypes	Ia (36%) III (32%) V (14%) II (10%)	III (70%) Ia (15%) V (7%) Ib (5%)	III (36%) Ia (36%) V (14%)
Age at onset	≤ 6 days	7-89 days	≥ 90 days
Affected patients	Premature Obstetric complications		Premature < 32 weeks Immunodeficiency
Clinical presentation	Bacteremia without focus (40-55%) Pneumonia (30-45%) Meningitis (6-15%)	Bacteremia without focus (55-67%) Meningitis (26-35%) Other* (1-6%)	As late-onset disease
Clinical findings	Acute respiratory distress, apnea, state of shock	Fever, irritability, unspecific signs	Fever, irritability, unspecific signs
Lethality	5-15%	2-6%	< 5%

*Osteoarthritis, cellulitis, adenitis, etc.
Modified from Pannaraj et al.[63]

and it is the cause of 40-50% of all cases of early-onset sepsis. Although GBS-related disease is not restricted to newborns, its highest impact, both in terms of seriousness and incidence, is in the neonatal period and up to the first 90 days of life[24]. GBS-related disease has been divided in two clearly distinguishable clinical syndromes: early-onset disease, which appears in the course of the first 7 days, and late-onset disease, which starts between the first week and the first 90 days of life. Recently, a third clinical syndrome has been added, which starts after 90 days of life. These syndromes differ in epidemiological characteristics, pathogenesis, clinical findings and prognosis (Table 2). Eighty-five percent of GBS neonatal infections are of early onset, and although clinical manifestations can appear until the seventh day of life, 90% of affected newborns get sick within the first 24 hours. Cases of late-onset disease manifest themselves from the seventh day on, and the infection can be acquired during the passage through the birth canal or horizontally, by contact with the colonized mother or other sources of horizontal transmission[10,63].

Early-onset disease

It is defined as infection that occurs within the first 6 days of life, and GBS serotypes Ia, II, III and V are the cause of most cases[64-66]. Maternal colonization by GBS in the gastrointestinal or genital tract is a requirement for early-onset disease occurrence, and transmission occurs more commonly during or just before delivery. In developed countries, 20-30% of pregnant women are estimated to be colonized with GBS[67,68], approximately 50% of their babies will be colonized, and 1% of these will progress to develop serious disease (Fig. 2). Early-onset disease is frequently associated with preterm birth (< 37 gestation weeks) and to the occurrence of obstetric complications, such as prolonged rupture of the fetal membranes (> 12 to 18 hours), intrapartum fever, chorioamnioitis and postpartum infectious complications. It can occur rapidly, with evident signs at birth or within the first 24 hours of life in 90% of cases (98% within the first 12 hours), and manifests itself typically as bacteremia with no evident infectious focus or pneumonia, and less commonly as meningitis (Table 2)[13-16,25,69]. Reported lethality in developed countries ranges between about 30% in newborns younger than 33-week gestational age and 2-3% in full-term newborns[11]. Early in the decade of 1970, the GBS-related early sepsis rate in the USA was estimated to be 1.7 cases for each 1000 live births, with a lethality close to 50%[12,26]. However, as knowledge on the pathophysiogenesis and clinical behavior of the disease has been developed, as well as on the role of previous colonization as the main risk factor known, together with the development of clinical guidelines for the prevention of this disease by the end of the 1990 decade, a decrease of said rate has currently been achieved to 0.37 cases for every 1000 live births (Fig. 3). Still, it remains the most common cause of neonatal sepsis and meningitis in the USA and other developed countries[11,12].

Factors associated with higher risk for neonatal colonization include maternal colonization, male gender,

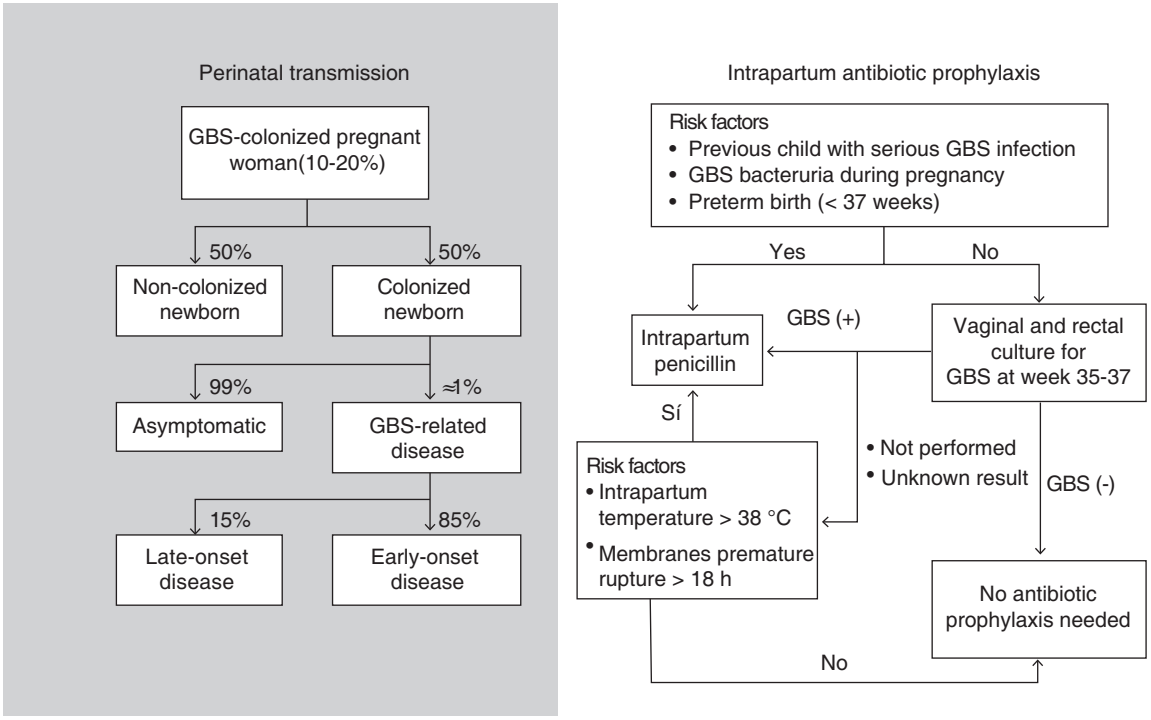

Figure 2. *Perinatal transmission and neonatal GBS-related disease development flow chart[61,64].*

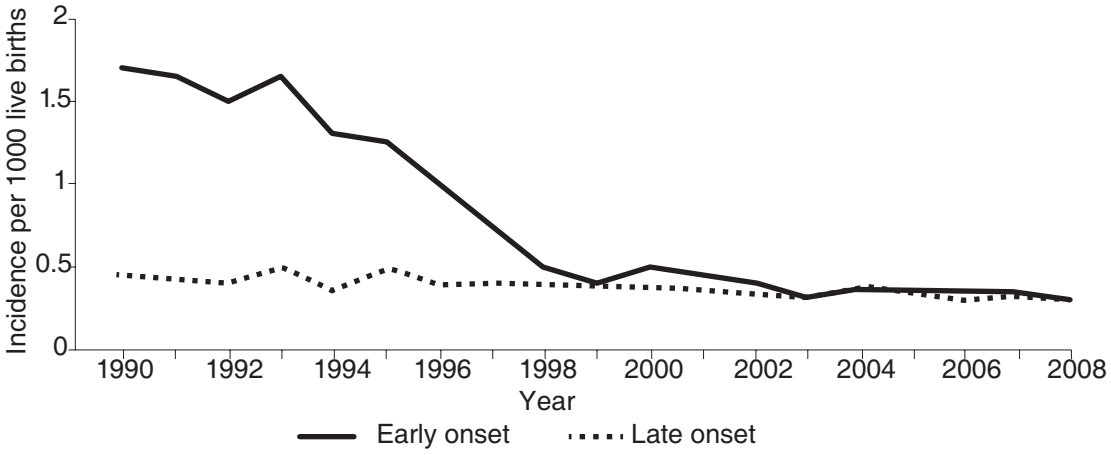

Figure 3. *Incidence of early-onset and late-onset GBS disease during the 1990-2008 period in the 10 areas of CDC active surveillance (modified from Verani et al.[12]).*

African-origin ethnicity, prolonged rupture of membranes, prematurity, maternal anti-GBS antibodies low titers and intrapartum fever[70]. In addition, newborns from mothers younger than 20 years or of African origin/Hispanic ethnicity[71], those with heavy GBS colonization, with low titers of anticapsular antibodies against GBS[26] or a history of previous newborn with early-onset disease[73], are at higher risk for early-onset disease.

Late-onset disease

It is mainly caused by serotype III, it is acquired by perinatal route, nosocomially or from community-based sources, and in up to 50% of cases it occurs with meningitis[64,69,74,75]. The cases occur within the first 90 days after the first week of life and, although infection occurs more commonly in patients with no relevant history of obstetric or neonatal problems it can

affect both full-term and preterm newborns or infants[12,12,63]. However, recent studies suggest that late-onset disease occurs more frequently in extremely premature newborns (< 34 gestation weeks)[76-79]. Risk factors for late-onset disease are less known. The male gender, African origin ethnicity, maternal colonization and having a twin with late-onset disease are associated with higher risk for late-onset GBS-related disease[71,74,79-81]. A higher incidence of late-onset disease has been observed in children born to mothers infected with the human immunodeficiency virus (HIV)[82]. The most common presentation forms of this type of disease are bacteremia without an identifiable focus and meningitis, which occurs in 26-40% of late-onset disease cases (Table 2).

Recent studies have also shown higher incidence of EGB-related disease cases in infants older than 3 months, and a third clinical syndrome has therefore been defined, known as late, late-onset disease. It occurs more often in infants who were extremely premature newborns (< 32 gestation weeks) and who have a corrected postnatal age older than 90 days, in infants with HIV infection and in children with other immunodeficiencies. Clinical presentation is similar to that of late-onset disease, with bacteremia without a detectable focus and meningitis as the most common clinical forms[63,83-85].

Late, late-onset disease

It occurs after the first 90 days of life and is mainly caused by serotypes III, Ia and V. Occurs especially in infants who were premature with < 32 gestation weeks, in those who had a prolonged hospital stay and in those with some immunodeficiency, such as children infected with HIV. Clinical presentation is similar to that of late-onset disease, and it can appear as bacteremia with no focus, meningitis, osteoarthritis, cellulitis, adenitis, etc. Its lethality is lower than 5%[63,83,86].

Disease in pregnant women

The incidence of EGB-related disease associated with pregnancy declined in the USA following the introduction of IAP, from 0.29 per 1000 live births in 1993 to 0.11-0.14 for every 1000 live births in 2005[28]. In a recent study, the incidence was 0.49/1000 in postpartum women[87]. This study emphasized that most cases of EGB-related disease associated with pregnancy occur in the postpartum period. Mean age of symptom onset was 28 years, and half the cases were associated with upper genital tract, placenta or amniotic sac infection[87,88]. Gastrointestinal tract is GBS main reservoir and the source of vaginal colonization. Inappropriate hygiene habits and certain sexual practices may increase the risk for vaginal colonization. Other factors associated with GBS maternal colonization include ethnicity (women of African-origin ethnicity), the use of tampons or intrauterine devices, obesity, absence of lactobacilli on intestinal flora and preterm delivery[89-91]. Bacteruria with GBS during pregnancy is associated with higher probability of intense colonization, which is an additional risk factor for perinatal transmission[92]. Furthermore, mothers with GBS-related bacteruria show higher incidence of obstetric adverse outcomes: usual abortion, intrauterine growth restriction, premature delivery, chorioamnionitis, endometritis and premature rupture of membranes[92,93].

Prevention

The recommendations for the prevention of GBS disease in newborns issued by the American Association of Obstetrics and Gynecology have suffered substantial changes since their first version in 1997. Currently, the Centers for Disease Control and Prevention (CDC) of the USA, together with different medical associations of that country, on their last 2010 revision recommend deliberate search for vaginal or rectal GBS colonization in every pregnant woman between 35 and 37 weeks of gestation in order to evaluate the use of IAP, which should be administered to every colonized pregnant woman. For IAP, penicillin G is intravenously (IV) administered, during at least 4 hours prior and until delivery, at an initial dose of 5 million international units (IU), followed by a maintenance dose of 2.5 million IU every 4 hours. Ampicillin (2 g IV initial dose followed by 1 g IV every 4 h) is an alternative. In case of penicillin allergy with no risk for anaphylaxis, cefazolin administration is recommended, but when there is such risk, clindamycin or vancomycin administration is recommended. Cefazolin is recommended for its capability to reach elevated concentrations in the amniotic fluid and to prevent early-onset disease; it is administered at an initial dose of 2 g followed by 1 g every 8 hours. Administration of 900 mg of clindamycin every 8 hours can only be used when the isolated GBS is sensitive. However, in the USA, 30% of GBS isolates are clindamycin-resistant and, if the sensitivity of the strain is not known, vancomycin should then be administered at 1 g every 12 hours. The capability of clindamycin or vancomycin to prevent early-onset disease has not been demonstrated.

Table 3. Intrapartum antibiotic prophylaxis indications and non-indications for the prevention of neonatal early-onset group B streptococcal disease

Intrapartum prophylaxis indicated	Intrapartum prophylaxis not indicated
Previous child with serious perinatal GBS disease	GBS colonization in previous pregnancy§
Bacteruria with GBS at any trimester of current pregnancy*	Bacteruria with GBS on previous pregnancy§
Recto-vaginal culture with GBS isolate within the 5 previous weeks†	Recto-vaginal culture negative for GBS on current pregnancy†, regardless of intrapartum risk factors
Unknown GBS colonization status, with any of the following: Preterm delivery (< 37 weeks) Premature rupture of membranes (≥ 18 h) Intrapartum fever (> 38 °C)‡	Cesarean section prior to labor with intact amniotic membranes, regardless of GBS colonization status and gestational age

*IAP is not indicated on this circumstance if c-section is carried out prior to labor initiation with intact amniotic membranes.
†The culture to assess for GBS colonization is performed between gestation weeks 35 and 37.
‡If chorioamnionitis is suspected, change IAP for antibiotic treatment that includes an agent with antimicrobial activity against GBS.
§Unless there is indication for IAP in current pregnancy.
Modified from Verani et al.[12]

Administering this prophylaxis is recommended in all pregnant women with demonstrated urinary infection or bacteruria with this microorganism, in those with a previous child with serious GBS infection and in those with unknown colonization status and preterm delivery or with rupture of fetal membranes ≥ 18 hours or with fever[10-12,63]. In general, these recommendations are similar in other developed countries (Table 3)[12,63,86,94-97].

In spite of the above, the previously described recommendations for prevention have not been officially adopted in Mexico, since there are no established criteria for GBS deliberate search in pregnant women in this country. This is partly due to the low percentages of GBS isolation in pregnant women and newborns, and to the predominance of less virulent serotypes identified in different studies[13,15-18,31-33,61]. Consequently, sample taking for cultures between gestation weeks 35 and 37 with the purpose to deliberately seek for GBS, is an almost inexistent procedure. The collection of these samples for culture is rather directed to isolation of other microorganisms that cause disease in pregnant women, such as Candida albicans and bacterial vaginosis-associated agents[23], than to GBS isolation, which in these samples constitutes an incidental finding. For all the above, although prevention strategies have not yet been officially established in Mexico, research works are needed to allow for Mexican population-specific risk factors for GBS colonization and infection to be evaluated, as well as studies directed to assess the validity in Mexico of applying the prevention criteria implemented in other countries. However, as long as such information is not available, it seems reasonable adopting the criteria proposed by the CDC, or at least adopting and adapting some recommendations, such as treatment of pregnant women with GBS urinary infection or bacteruria in current gestation, and IAP administration in these women, in those with a previous history of a child with serious GBS infection and in those with an available culture with GBS isolated without subsequent follow-up[3].

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