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REVIEWS

Review

Perinatal Group B Streptococcal Infections: Virulence Factors, Immunity, and Prevention Strategies

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Group B streptococcus (GBS) or *Streptococcus agalactiae* is a β-hemolytic, Gram-positive bacterium that is a leading cause of neonatal infections. GBS commonly colonizes the lower gastrointestinal and genital tracts and, during pregnancy, neonates are at risk of infection. Although intrapartum antibiotic prophylaxis during labor and delivery has decreased the incidence of early-onset neonatal infection, these measures do not prevent ascending infection that can occur earlier in pregnancy leading to preterm births, stillbirths, or late-onset neonatal infections. Prevention of GBS infection in pregnancy is complex and is likely influenced by multiple factors, including pathogenicity, host factors, vaginal microbiome, false-negative screening, and/or changes in antibiotic resistance. A deeper understanding of the mechanisms of GBS infections during pregnancy will facilitate the development of novel therapeutics and vaccines. Here, we summarize and discuss important advancements in our understanding of GBS vaginal colonization, ascending infection, and preterm birth.

Infections by GBS during Pregnancy

GBS is a leading cause of infection during pregnancy, preterm birth, and neonatal infection [1–3]. GBS was first identified in 1887 as a cause of bovine mastitis [4], and later was isolated from the human vagina [5] and associated with cases of human disease [6]. Subsequently, GBS vaginal colonization was identified as a risk factor for the development of neonatal GBS disease [7,8] and preterm birth [2,3]. Women who are vaginally colonized during pregnancy are at risk for ascending infection or transmission of GBS to the newborn during delivery. Ascending infection is a widely accepted route by which vaginal bacteria move from the vagina, through the cervix, and into the uterus and penetrate gestational tissues (Figure 1). Once GBS has invaded the amniotic cavity, or come into contact with the placenta, there is the potential for chorioamnionitis or inflammation of the placental membranes that is frequently associated with preterm births and stillbirths [9]. Globally, preterm birth is a significant contributor to neonatal death. Every year, approximately 6 000 000 births are preterm, and more than 500 000 neonates die due to prematurity, accounting for 44% of all deaths under the age of 5 years [10,11]. The majority of early preterm births are due to microbial infection [9], and approximately 10% are attributable to GBS [12–14]. The bacterial and host determinants that promote GBS vaginal colonization, ascending infection, and adverse perinatal outcomes are poorly understood.

Trends

Group B streptococcus (GBS) has to evade genitourinary immune responses for successful colonization and infection.

A number of virulence factors promote GBS vaginal colonization and subsequent ascension into the pregnant uterus.

The GBS hemolytic pigment and hyaluronidase enable the pathogen to resist immune responses; however, dysregulation of the hemolytic pigment can also lead to bacterial clearance from the vagina.

GBS invasion of the amniotic fluid is not absolutely necessary for induction of inflammatory responses and preterm birth.

Development of a GBS vaccine is critical to reduce or prevent the risk of infection during pregnancy, thereby reducing GBS disease burden.

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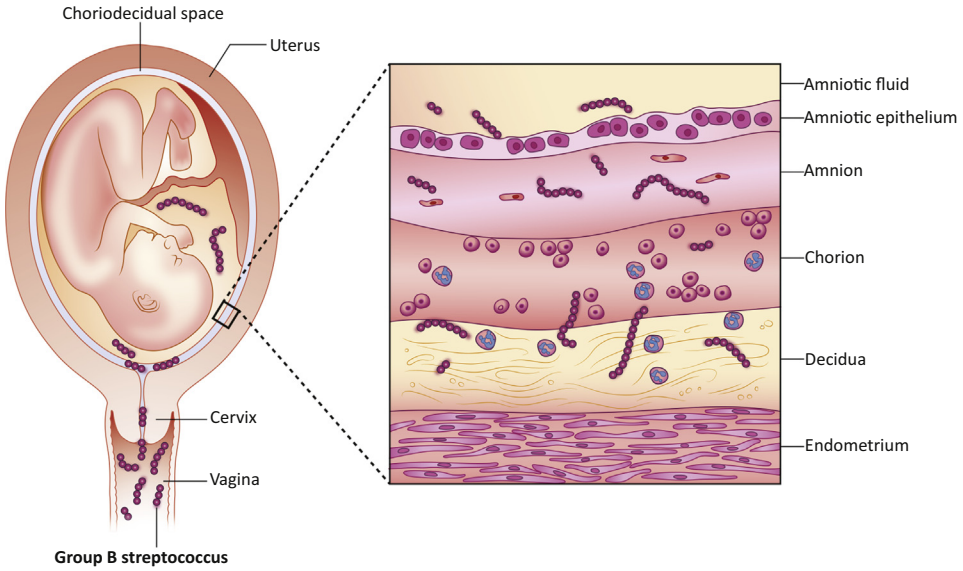

Figure 1. Ascending Group B Streptococcus (GBS) Infection. GBS vaginal colonization increases the risk of ascending infection during pregnancy. Ascending GBS infection during pregnancy involves bacterial trafficking from the vagina, ultimately leading to bacterial invasion of placental membranes (chorion and amnion), the amniotic cavity, and the fetus. GBS expresses a number of virulence factors that promote vaginal colonization, adhesion and invasion of host cells, and for either activation or suppression of inflammatory responses (Table 1 and Figure 2). These factors increase the risk of ascending infection, fetal injury, or preterm birth.

Recently, significant effort has been dedicated to measuring the global rates of GBS colonization (Box 1) [15,16], invasive disease [8,17,18], and related risk factors [19,20]. These studies show that increased GBS colonization in many low-income countries correlates with increased neonatal infection and preterm birth [11]. Additionally, women of African descent have a higher incidence of GBS vaginal colonization [15,21,22] and neonatal disease [23–25]. In the USA and many other countries, women are routinely screened in the late third trimester (between 35 and 37 weeks' gestation) for GBS colonization by rectovaginal swab and subsequent culture [26]. If the rectovaginal swab is culture-positive, or if the patient has GBS in the urine, or has a prior history of GBS perinatal infection, intrapartum prophylactic antibiotics are administered to prevent vertical transmission of GBS to the neonate during labor and delivery. Unlike the USA, some countries have not adopted the GBS screening program but instead administer antibiotics upon the development of a risk factor for GBS neonatal disease (e.g., prolonged rupture of membranes) [26]. However, these approaches have not fully eliminated neonatal GBS infections. This is because these prevention strategies do not address the risk of ascending infection, which can potentially occur anytime during pregnancy, leading to preterm birth or stillbirth. Also, these approaches do not prevent late-onset GBS infections (observed in neonates who are older than 1 week of age) where vertical transmission is not the only mode of acquisition [27]. Overall, prevention of GBS infection in pregnancy is still a complex question, with risk likely imparted by several factors, including: pathogenicity of the GBS strain, host factors, influence of the vaginal/rectal microbiome, false-negative screening results, and/or changes in GBS antibiotic resistance. As current interventions targeting GBS infections are limited to antibiotic therapy, and given that antibiotic resistance is on the rise [28], a deeper understanding of how GBS is able to colonize the vagina and cause neonatal disease is critical for the development of new therapeutics. Recently, a number of studies have described host and bacterial factors important for GBS infections during pregnancy. In this review, we discuss recent advancements in GBS pregnancy-associated infections and therapeutic strategies.