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Editorial

The urgent need to recognize and properly address prenatal-onset group B *Streptococcus* disease

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October is the "Prenatal-onset GBS Disease Recognition Month", which brings into focus the importance of preventing neonatal infections. Neonatal infections are a remarkable cause of infant morbidity and mortality worldwide and have become the dominant component of all child mortality as overall infant mortality rates decline. Among bacteria associated with neonatal infections, *Streptococcus agalactiae* or group B *Streptococcus* (GBS) stands out as a leading agent of neonatal meningitis, pneumonia, and sepsis since the 1960s. A high global burden is associated with GBS, accounting for 518,000 preterm births, 392,000 neonatal infections and 91,000 neonatal deaths every year (WHO, 2021).

GBS neonatal infections can be classified according to the timing of symptoms' onset and mode of microorganism acquisition into early- and late-onset disease (Figure 1). Early-onset GBS disease (EOGBS) occurs up to 7 days after birth and is usually associated with vertical intrapartum acquisition. Late-onset disease (LOGBS) occurs between 7 and 90 days after birth and is due to horizontal postpartum acquisition from a variety of sources, including the hospital environment, the mother or other caregivers, or by breastfeeding (Steer et al., 2020). A much less well-known form of GBS infection is the prenatal-onset GBS disease (POGBS), which occurs any time before delivery due to *in utero* acquisition (Figure 1). Bacteria can reach the fetus due to an ascending infection from the vagina, even in the presence of intact membranes. GBS colonizes asymptomatically the vaginal tract of 18% of pregnant women worldwide, varying from 10% to 40% according to the geographic region (Seale et al., 2017). POGBS can lead to miscarriage, stillbirth, early rupture of membranes and preterm labor.

The term "prenatal-onset GBS disease (POGBS)" was first coined in 2007, and in 2010 recommended guidelines on its prevention were published by the US Centers for Disease Prevention and Control (CDC) (CDC, 2010). Nonetheless, POGBS is still not widely recognized as a distinct entity and cases of GBS infection in unborn babies are usually classified as EOGBS. This has been justified by the apparent rare occurrence of miscarriage and stillbirth associated with GBS worldwide. However, a recent report of the World Health Organization (WHO) estimates that GBS is responsible for 46,000 cases of stillbirth every year (WHO, 2021), a number high enough to raise questions around the alleged rarity of POGBS.

Recent studies show that the burden of POGBS has been far underestimated (Gonçalves et al., 2022). Annually, 518,100 preterm births, representing 3.5% of all preterm births worldwide, are associated with GBS maternal colonization. Likewise, 46,200 stillbirths result from a GBS infection *in utero*. Sub-Saharan Africa and Central and South Asia bear the highest burden related to GBS, with 68,500 preterm births and 20,300 stillbirths; followed by East and Southeast Asia, North Africa and West Asia, Europe and North America, Latin America and the Caribbean, and Oceania (Gonçalves et al., 2022). Furthermore, among the total number of deaths related to GBS perinatal infections, stillbirths account for

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	Prenatal-Onset GBS Disease	Early-Onset GBS Disease	Late-Onset GBS Disease
Timing	Before birth	Up to 7 days after birth	7 to 90 days after birth
Transmission	*In utero* acquisition	Vertical intrapartum acquisition	Horizontal postpartum acquisition
Main Clinical manifestations	Stillbirths, Preterm birth and Miscarriage	Pneumonia	Meningitis
Prevention	No prevention guidelines	Intrapartum Antibiotic Prophyaxis	No prevention guidelines

Figure 1. Major characteristics of the 3 types of perinatal/neonatal infections related to group B *Streptococcus* (GBS)

25-50% depending on the geographic region, overcoming EOGBS and LOGBS associated deaths in many countries. In Europe and North America, for example, stillbirths account for more than half of the total deaths associated with GBS (Gonçalves et al., 2022). These are estimated numbers and the true burden could be higher, mainly in under-resourced areas where there is limited screening and testing.

The prevention of neonatal GBS infections has been centered on maternal screening practices and intrapartum antibiotic prophylaxis (ACOG, 2020). Whereas these policies have efficiently decreased the incidence of EOGBS in many countries, such strategies do not seem to have impacted the occurrence of LOD or POGBS. On the other hand, maternal vaccination could be an effective way to prevent all types of GBS diseases. In this regard, one of the goals in WHO's roadmap is to obtain at least one licensed vaccine for immunization during pregnancy by 2026 (WHO, 2017). Despite all the obstacles faced during the 40 years since the first studies on GBS vaccine started (Baker and Kasper, 1976), we have now reached advanced stages in this process, which makes possible for a licensed GBS vaccine to be available within a few years (Absalon et al., 2022).

Even though no universal protocol to prevent POGBS has been established or recommended, some knowledge-based strategies can help prevent GBS infections before birth, by allowing immediate medical intervention with effective outcomes. Performing periodic urine cultures during pregnancy is one of them, since the presence of GBS in urine indicates anovaginal colonization and potential ascending infection. Also, some clinical signs and symptoms can suggest the occurrence or a higher risk of fetal infection, such as maternal fever, frantic or reduced fetal movement, vaginal bleeding, nausea, vomits, diarrhea, increased pressure in vagina or pelvis, cramping in lower abdomen, severe lower backache, and regular or frequent contractions. Vaginal colonization by GBS may cause yellow or green vaginal discharge, besides vaginal burning and irritation, which could be mistaken for yeast infection or bacterial vaginosis and thus treated incorrectly (GBSI, 2018). Moreover, it is essential to avoid unneeded invasive procedures in pregnant women since they may facilitate GBS crossing the intact membranes.

In view of the emerging importance of POGBS, the "Prenatal-onset GBS Disease Recognition Month" aims to increase awareness among healthcare professionals and pregnant women, by providing information on strategies that may help protect unborn babies, and to strengthen the implementation of robust surveillance systems that can ultimately contribute to improved preventive measures against POGBS. To better prevent POGBS, there's the need of research that focuses on GBS maternal colonization, which seems to be the greater risk factor for POGBS. Although the rates of GBS maternal colonization in different places of the world are widely known, research on how and why GBS can lead to miscarriage, stillbirth, or preterm birth is still incipient. The licensing of a GBS vaccine soon will open a promising avenue to prevent POGBS, the effectiveness of which requires research in real world setting. Meanwhile, the importance of routine detection of

GBS maternal colonization should be emphasized among healthcare workers worldwide, and adequate support for this purpose should be available in low- and middle-income countries, where the burden is high but the access to required infrastructure is still low.

Author declarations

All authors declare no conflicts of interest.

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