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RESEARCH ARTICLE

MATERNAL RISK FACTORS FOR GROUP B STREPTOCOCCUS (GBS) VAGINAL COLONIZATION

Hanan H. Wahid[a], Ayesha Bahez[b], Mohammed I. A. Mustafa Mahmud[a], Farih N. Hashim[c], Norhidayah Kamarudin[d], Roesnita Baharuddin[e], Ahmad M. Ahmad Mustafa[f], Hamizah Ismail[c]

[a] Department of Basic Medical Sciences, Kulliyyah of Medicine, International Islamic University, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang Malaysia.
[b] Department of Microbiology and Parasitology, Kabul University of Medical Sciences (KUMS), Karte Sakhi, Kabul, Afghanistan.
[c] Department of Obstetrics & Gynaecology, Sultan Ahmad Shah Medical Centre @IIUM, Kulliyyah of Medicine, International Islamic University, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang Malaysia.
[d] Department of Pathology, Sultan Ahmad Shah Medical Centre @IIUM, Kulliyyah of Medicine, International Islamic University, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang Malaysia.
[e] Department of Pathology, Hospital Tengku Ampuan Afzan, Jalan Tanah Putih, 25100 Kuantan, Pahang Malaysia.
[f] Department of Obstetrics & Gynaecology, Hospital Tengku Ampuan Afzan, Jalan Tanah Putih, 25100 Kuantan, Pahang Malaysia.
****Corresponding author Email: hananwahid@iium.edu.my***

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ABSTRACT

Approximately 18% of pregnant women are colonized with Group B streptococcus (GBS), which are β-hemolytic, gram-positive bacteria. GBS conversion from the asymptomatic commensal in the vagina to an invasive pathogen predisposes the pregnant women to ascending intrauterine infection that tiggers preterm birth and initiate fetal and neonatal infections. Here, we review the prevalence of colonizing GBS serotypes and sequence types (STs) in different geographical regions. Maternal components including demographical and obstetric factors that increase the risk for GBS colonization during pregnancy are also further elucidated. The prevalence of colonizing GBS serotypes and sequence types (STs) are elucidated in this review in addition to the maternal components including demographical and obstetric factors that increase the risk for GBS colonization during pregnancy. Investigating the epidemiology is crucial for the development of new therapeutic and preventive measures to reduce the burden of invasive GBS disease worldwide including risk-factor based screening protocols.

KEYWORDS

Group B Streptococcus, vaginal colonization, ascending intrauterine infection, preterm delivery

1. INTRODUCTION

Preterm birth is known to cause the death of 1 million children under 5 years of age annually (Liu et al., 2016). In Malaysia, the rate of preterm birth is between 8.1% to 11.2% (Jeganathan and Karalasingam, 2011). One of the risk factors identified for the development of preterm birth is vaginal colonization Group B Streptococcus (GBS) during pregnancy (Bianchi-Jassir et al., 2017). GBS is known to asymptomatically colonize the gastrointestinal and urogenital tract of pregnant women (Kwatra et al., 2016).

GBS colonization, in some pregnant women allows the GBS ascension through the cervix to further breach the decidua, chorion, amniotic epithelium and amniotic fluid, to trigger preterm delivery and neonatal infections (Bastek et al., 2011; Whidbey et al., 2013). The transmission of GBS to the newborn may also occur through the aspiration of amniotic and vaginal fluids containing the bacterium during pregnancy and vaginal delivery respectively (Verani et al., 2010). The rate of GBS colonization, prevalence of serotypes and STs as well as maternal risk factors for GBS vaginal colonization will be discussed in this review. This knowledge is crucial to allow for the development of new therapeutic and preventive measures.

2. METHODS

Important and recent research related to GBS were identified using online databases including Google Scholar and PubMed. The terms used for the literature search include “Group B Streptococcus” or “Streptococcus agalactiae” in combination with “vaginal colonization,” “GBS serotypes,” “GBS sequence types,” “maternal risk factors,”. The literature search was restricted to articles published between 2016-2021. Nevertheless, articles published prior to 2016 that were identified using article reference list and considered to be crucial for this narrative review were also included.

3. GBS COLONIZATION RATE, PREVALENCE OF GBS SEROTYPES AND STS IN DIFFERENT GEOGRAPHICAL REGIONS

For epidemiological purposes, capsular serotyping, based on a sialic acid-rich capsular polysaccharide (CPS) is used traditionally to classify GBS. At present, 10 GBS serotypes (Ia, Ib, and II–IX) are identified and CPS is crucial especially for GBS evasion of immune responses (Carlin et al., 2009). However, this traditional picture of GBS epidemiology has changed due to the advances in nucleotide sequencing-based technologies. Molecular epidemiology of GBS colonization, which adopts a seven-gene multilocus sequence typing scheme (MLST) for GBS classification is introduced in 2003 (Jones et al., 2003). Based on the allelic variation of

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seven housekeeping genes, GBS strains with different STs are further grouped into clonal complexes (CC), with similar allelic profiles (Jones et al., 2003). Most importantly, the distinct capsular serotypes are discovered within the same ST. ST-1, ST-19 and ST-23 were frequently found in asymptomatic pregnant women (Jones et al., 2003). Meanwhile, ST-23 and ST-17 were associated with invasive disease cases and neonatal invasive infections respectively (Jones et al., 2003). The rate of GBS colonization, and the prevalence of GBS serotypes as well as STs among pregnant women in different geographical regions are summarized in Table 1.

It is clear that the prevalence of GBS serotypes and STs vary over time and according to different geographical regions. Therefore, the GBS vaccine candidates that target capsular polysaccharides may not benefit pregnant women in some parts of the world having different prevalent serotypes, rendering the development of vaccines that target other virulence factors to be crucial.

4. Risk Factors for Maternal GBS Vaginal Colonization

Pregnant women more than 40 years old are more likely to be colonized with GBS (Khan et al., 2015). Previously colonized pregnant women of more than 36 years of age have an increased chance to become persistantly colonized (Manning et al., 2008). GBS vaginal colonization is also associated with younger maternal age, of less than 20 years (Edwards et al., 2019; Kum-Nji et al., 2020). This might explain why a higher incidence of early onset GBS diseases was observed in neonates of young mothers (Schuchat et al., 1990; 1994). In Tanzania and Mexico, women with lower socio-economic status are more susceptible to GBS colonization (Ernest et al., 2015; Ocampo-Torres et al., 2000). This may be due to lower awareness of the importance of personal hygiene during pregnancy, which also explains why a higher rate of preterm birth is reported among mothers with lower education (Cantarutti et al., 2017; Ruiz et al., 2015) and living in low-income countries (Smid et al., 2016). In the United States of America and United Kingdom, black women have a higher frequency of GBS colonization as compared to other ethnicities, and this probably contributes to racial disparity in the incidence of neonatal infections (Capraro et al., 2020; Edwards et al., 2019; Gopal Rao et al., 2019).

Increasing number of studies have shown that maternal obesity is associated with GBS colonization (Alvareza et al., 2017; Gopal Rao et al., 2019; Manzanares et al., 2019; Venkatesh et al., 2019). Similar to pregnancy, obesity is linked to changes in the gut microbiome, particularly inducing a shift towards increased Firmicutes (the phylum to which GBS belongs) and decreased Bacteroidetes in both humans and mice (Koren et al., 2012; Ley et al., 2006; Turnbaugh et al., 2006; Koren et al., 2012; Ley et al., 2006; Turnbaugh et al., 2006). This shift can potentially elevate the capacity of the altered gut microbiome to obtain energy from the diet (Ley et al., 2006; Turnbaugh et al., 2006).

Although physiological gestational insulin resistance may be beneficial to direct glucose to the placenta and growing fetus, however high resistance is a cause for complications to both mother and fetus. Women with gestational diabetes especially when accompanied by obesity are also reported to have a higher GBS colonization rate as compared to non-diabetic pregnant women (Edwards et al., 2019; Ramos et al., 1997). It is known that hyperglycaemia especially via the elevated synthesis of advanced glycation end-products (AGEs) and inhibition of glucose-6-phosphate dehydrogenase (G6PD) causes dysregulation of the immune system that may consequently increase the susceptibility of the pregnant women with GDM to GBS colonization (Price et al., 2010; Xu et al., 2005).

Table 1: Geographical Distribution of GBS Colonization Rate, Prevalent Colonizing Serotypes and STs

Region	GBS Colonization Rate	Study Participants	Prevalent Colonizing Serotypes	Prevalent Colonizing STs	References
Indonesia	30%	Asymptomatic pregnant women (n=177)	II (30%), III (23%), Ia&IV (13%), VI (8%), Ib&V (6%)		(Safari et al., 2021)
India	15.1%	Pregnant women (n=345)	Ia (42.1%), VI (31.6%), II (15.8%), VII (10.5%)		(Gogoi et al., 2021)
China	6.5%	Pregnant women (n=863)	III (32.1%), Ia (17.9%), Ib (16.1%), V (14.3%)	ST19, ST23, ST12, ST1, ST485, ST17, ST10, ST625, ST8, ST24, ST27, ST28, ST163, ST653, ST652	(Wang et al., 2015)
Saudi Arabia	15%	Pregnant women (n=400)	Ia (30%), III&V (25%), II (11.7%), Ib (3.3%), VI (5%)		(Mohamed et al., 2020)
South Africa	16.6%	Pregnant women (n=301)	V (66.67%), III (21.05%), Ia, II, IV&IX (1.75%)		(Africa and Kaambo, 2018)
Argentina	9.09%	Pregnant women (n=3480)	Ia (33.5%), III (19%), Ib (15.5%), II (14%), V (7%), IX (5.5%)		(Bobadilla et al., 2021)
United States of America		Pregnant women	V (28.2%), III (25.6%), II (15.4%), Ia (12.8%), Ib (15.4%), IV (2.6%)	ST17	(Burcham et al., 2019)
Australia	24%	Pregnant women (n=814)	Ia (27.9%), III (20.9%), II (16.3%, V (15.8%), Ib (8.4%), VI (5.1%), IV (2.8%), VIII&IX (0.5%)		(Furfaro et al., 2019)
Canada		GBS colonized pregnant women (n=102)	III (25%), Ia (23%), V (19%), II (13%), Ib (9%), IV (6%), VI (5%)	ST1, ST23, ST8, ST12, ST22, ST28, ST 17, ST19, ST459, ST196	(Teatero et al., 2017)
Israel	26.1%	Asymptomatic pregnant women (n=1074)	VI (40.8%), III (17.5%), V (12.5%), IV (11.7%), Ia (7.1%), Ib (2.9%)	ST1, ST17, ST8, ST12, ST19, ST459	(Schindler et al., 2020)
Portugal	6.3%	Pregnant women (n=1310)	III (35%), V (33%), Ia (16%), II (10%)	ST23, ST8, ST19, ST27, ST44, ST106, ST369, ST17, ST10, ST1, ST2	(Florindo et al., 2010)

A few studies demonstrate that tobacco smoking during pregnancy is associated with GBS colonization (Edwards et al., 2019; Kum-Nji et al., 2020). Smoking is associated with altered vaginal microbiota, including reduced *Lactobacillus* species (Brotman et al., 2014). During pregnancy, human vaginal microbiome is dominated by *Lactobacillus* sp., which contribute to lowering the vaginal pH by metabolizing glycogen to produce lactic acid (Nuriel-Ohayon et al., 2016; Aagaard et al., 2012). Some strains of lactobacilli were shown to inhibit GBS adherence to vaginal epithelial cells in vitro thus protecting against GBS vaginal colonization during pregnancy (Ortiz et al., 2014; Zárate and Nader-Macias, 2006; de Gregorio et al., 2015; Priscilla Romina de Gregorio et al., 2016).

Previous studies revealed an elevated nicotine level in cervical mucus of smokers, as compared to non-smokers (McCann et al., 1992). Nicotine may affect the structure and functions of the cervical mucus plug (CMP) and this needs to be further investigated. CMP is a dense and viscous mucus that forms in the cervical canal to act as a physical barrier (Becher et al., 2009). CMP is demonstrated to harbor pro-inflammatory cytokines as well as antimicrobial compounds including lysozyme, lactoferrin, calprotectin, secretory leukoprotease inhibitor 1 (SLP1), and other antimicrobial

peptides (AMPs) (Arko et al., 2012; Becher et al., 2009; Hein et al., 2002). In whole blood killing assays, CMP proteins have been portrayed to diminish GBS viability, suggesting that these factors contribute in enhancing the complement-mediated killing and leukocyte activation to possibly restrain GBS ascending intrauterine infection (Vornhagen et al., 2018).

Meanwhile in other studies, maternal age, parity, socio-economic status, ethnicity and smoking are not found to be associated with GBS colonization (Kim et al., 2011; Clouse et al., 2019; Ali et al., 2020; Darabi et al., 2017; Chen et al., 2018). It is because these observable factors can be modified by other confounding factors including host genetics, environment and diet which may vary from one geographical location to another. The timing of specimen collection during pregnancy, specimen sampling site, GBS culture technique and sample size also may all contribute to this variation. It is also important to notice that the GBS colonization during pregnancy may be continuous, intermittent, or transient (Brzychczy-Wloch et al., 2014). Women who are found to be colonized in early or mid-pregnancy may turn non-colonized at delivery, indicating that the timing of GBS screening and specimen collection is crucial to determine the GBS colonization status at delivery (Verani et al., 2010).

5. Conclusion

Further studies are needed to determine the GBS serotypes and STs that are more likely to cause vaginal colonization among pregnant women in different geographical regions. More studies are also warranted in the future to explore the population characteristics, other than ethnic or race demography and age of pregnant women that increase their likelihood to be vaginally colonized with GBS, in order to better identify at-risk individuals. Thus, risk factor-based approach can possibly be considered in both, the screening protocols for maternal GBS colonization and the intervention by intrapartum antibiotic prophylaxis (IAP). Besides, this knowledge is crucial to elucidate the strategies to be proposed and implemented to prevent vaginal colonization and ultimately ascending intrauterine infection during pregnancy.

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