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RESEARCH ARTICLE

A REVIEW OF GROUP B STREPTOCOCCUS (GBS) VAGINAL COLONIZATION AND ASCENDING INTRAUTERINE INFECTION: INTERACTION BETWEEN HOST IMMUNE RESPONSES AND GBS VIRULENCE FACTORS

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ABSTRACT

Vaginal colonization with Group B streptococcus (GBS) or *Streptococcus agalactiae* can potentially cause ascending intrauterine infection among pregnant women, and hence it is known as one of the risk factors for preterm delivery. Ascending intrauterine infection may also cause the transmission of GBS to the fetus in utero and the newborn during delivery, leading to the development of early onset of neonatal infection. GBS are β-hemolytic, gram-positive bacteria that are opportunistic commensal of the gastrointestinal and urogenital tract of approximately 18% of pregnant women globally. Intrapartum antibiotic prophylaxis (IAP) only reduces the rate of early onset neonatal infection, but not the late onset neonatal infection. Thus, the development of GBS vaccine is thought to be important to decrease the rate of preterm delivery and neonatal infections particularly in low-and-middle income countries where IAP program is not feasible. Vaccination can also be cost-effective for the healthcare system when executed together with IAP program. The aim of the current review is to summarize the mechanisms on how the GBS virulence factors interact with host immune components in the gestational tissues, leading to cervicovaginal colonization and ascending intrauterine infection. The elucidation of these mechanisms is essential for expediting the development of vaccines and novel therapeutic measures targeting these GBS virulence factors that will hamper the vaginal colonization, ascending intrauterine infection and conceptus tissue invasion by GBS. These strategies are crucial to potentially reduce the rate of preterm delivery and subsequent serious complications in the newborn.

KEYWORDS

Group B Streptococcus, Vaginal Colonization, Ascending Intrauterine Infection, Preterm Delivery

1. INTRODUCTION

Preterm delivery is defined as the delivery that occurs before 37 weeks of gestation. The rate of preterm delivery ranges between 8.1% to 11.2% in Malaysia (Jeganathan and Karalasingam, 2020). Preterm delivery is estimated to affect 11% of births worldwide, causing 1 million children under 5 years of age to die annually (Vogel et al., 2018). GBS vaginal colonization during pregnancy is one of the risk factors identified for development of preterm delivery (Bianchi-Jassir et al., 2017). GBS are β-hemolytic gram-positive bacteria, that colonize the gastrointestinal and urogenital tract of almost 18% of pregnant women worldwide (Seale et al., 2017).

GBS colonization predisposes the pregnant woman to ascending intrauterine infection (Agrawal and Hirsch, 2012; Vornhagen et al., 2017). GBS gets access to the uterus and eventually cause bacterial invasion of the chorioamnionitic membranes of the placenta, amniotic cavity and fetus triggering an inflammatory reaction that leads to preterm delivery and neonatal GBS infections (Agrawal and Hirsch, 2012; Vornhagen et al., 2017). Neonatal infections by GBS are classified into early onset disease (that occurs <7 days after birth) and late onset disease (that occurs 7-90 days postnatally). In early onset neonatal infection, the principle route of GBS acquisition is ascending intrauterine infection that may cause the transmission of GBS to the fetus in utero and the newborn during delivery via aspiration of contaminated amniotic fluid and vaginal fluids respectively (Verani et al., 2010).

Meanwhile in late onset disease, the route for GBS transmission is less clear. In this review, the host innate and adaptive immune responses that are stimulated following vaginal colonization to either facilitate GBS clearance or invasion are discussed. Later, GBS virulence factors that are crucial for cervicovaginal colonization, invasion of the cervix, amniotic membranes and fluid are further elaborated. Emphasis is given to the advances recently made in understanding of the interaction between the host immune responses and GBS vaginal colonization and invasive factors. The preventive strategies to reduce the global burden of GBS diseases

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among pregnant women and their neonates are finally highlighted. This knowledge needs to be further explored in order to facilitate and expedite the development of vaccines and novel therapeutic measures targeting these GBS virulence factors to reduce global GBS burden among pregnant women and their neonates.

2. Methods

Online databases including Google Scholar and PubMed were used to identify current and pivotal research relating to GBS. The terms used for the literature search include "Group B Streptococcus" or "Streptococcus agalactiae" in combination with "pregnancy," "preterm delivery," "vaginal colonization," "uterus," "ascending infection," "virulence factors," "cervix," "placenta," "chorioamnion," "amniotic fluid," "immune responses," "vaccine". The literature search was restricted to articles published between 2016-2021. Nevertheless, articles published prior to 2016 that were identified using snowball searches of article reference list and considered to be crucial for this narrative review were also included.

3. Host Immune Responses to Gbs Vaginal Colonization and Ascending Intrauterine Infection

In vivo mouse model of GBS vaginal colonization portrayed the recruitment of neutrophils, macrophages and mast cells to contribute to the synthesis of pro-inflammatory mediators including cytokines and histamine and thus enhancing GBS clearance from vaginal tract (Carey et al., 2014; Gendrin et al., 2015; K. A. Patras et al., 2015; Kathryn A Patras et al., 2013). Lymphocytes, specifically T helper 17 (Th17) cell production of pro-inflammatory cytokines together with specific antibody responses also appear to be crucial in reducing GBS colonization (Baker et al., 2017; Carey et al., 2014; K. A. Patras et al., 2015).

There are also limited studies to explore the host immune response for the GBS clearance in the cervix. In mice, it seems that interleukin-17 (IL-17)-producing neutrophils and Th17 cells mediated cervical immunity against GBS infection (Patras et al., 2015). Intravaginal inoculation of mice with GBS also caused GBS invasion of uterus, decidua, placenta and fetal membrane (Kothary et al., 2017; Rogers et al., 2018). In these mice, infiltration of macrophages into placenta and fetal membrane, recruitment of neutrophils into placenta and decidua, as well as elevation of prostaglandin in the amniotic fluid were also documented following inoculation of GBS intravaginally (Kothary et al., 2017; Rogers et al., 2018). Microflora is known to regulate the host immune response and it is important to note that the microflora of the mouse vagina are different to human vagina, as one of the limitations to be considered for this mouse model of vaginal colonization (Zheng et al., 2020). The host immune responses induced by GBS in the gestational tissues are illustrated in Figure 1.

4. Gbs Virulence Factors

4.1 GBS Virulence Factors That Enhance Cervicovaginal Colonization

The microbial virulence factors that are involved in adherence and invasion are mostly related to the GBS interaction with the host's extracellular matrix components (ECM) or ligands to host tissues and cells such as collagen, fibrinogen laminin, fibronectin, glycosaminoglycan and integrins. The virulence factors that are anchored to the bacterial cell wall include serine rich repeat (Srr), fibrinogen binding protein (Fbs), bacterial adhesin (BibA), pili, alpha C protein and streptococcal fibronectin binding protein A (SfbA) (Mu et al., 2014; Sheen et al., 2011; Buscetta et al., 2014; Santi et al., 2007; Maisey et al., 2008; Baron et al., 2007).

The binding regions of Srr-1 and Srr-2 were discovered to bind to immobilised fibrinogen via dock, lock and latch (DLL) mechanisms (Seo et al., 2013; Wang et al., 2014). Srr-1 and Srr-2 were also required for GBS adhesion to human vaginal (VK2/E6E7), ectocervical (Ect1/E6E7), and endocervical (End1/E6E7) epithelial cell lines (Sheen et al., 2011; Wang et al., 2014). Srr-1 was also shown to bind to keratin-4 for adhesion to human vaginal epithelial cells (Sheen et al., 2011). Srr-1 was also necessary for GBS persistence in the vagina following the inoculation of these bacterial cells into the vaginal vault (Sheen et al., 2011; Wang et al., 2014).

FbsC also known as the bacterial surface adhesion of GBS (BsaB) is required for binding of GBS to immobilised fibrinogen, fibronectin and laminin (Buscetta et al., 2014; Jiang and Wessels, 2014). FbsC also enhanced GBS adhesion to human vaginal epithelial cell line (VK2) and biofilm formation (Jiang and Wessels, 2014). BibA is essential for GBS adhesion to human cervical (ME180) epithelial cell line (Santi et al., 2007). However, it is not clear about the host ligand that BibA interacts with for adhesion. BibA has been reported to bind to human C4-binding protein, which is one of the regulatory proteins involved in classical complement pathway and BibA specific IgG was discovered in healthy human serum (Santi et al., 2007).

Immunization of mice with serotype V GBS (GBS-V)-derived recombinant surface protein, rBibA combined with different adjuvants stimulated the production of antigen-specific antibodies including IgG and IgA in vivo (dos Santos et al., 2020). From in vitro assays, serum collected from vaccinated mice augmented opsonophagocytosis of GBS-V cells by macrophages cell line and decreased the GBS-V invasion of human lung epithelial cell line in vitro (dos Santos et al., 2020). rBibA combined with different adjuvants were also shown to increase the survival rate and reduce vaginal colonization when the mice were challenged with GBS-V cells (dos Santos et al., 2020). From in vitro experiments, BibA facilitates the GBS resistance to killing by phagocytes and this promotes the bacterial survival in human blood (Santi et al., 2007).

Pili consist of three covalently linked pilin proteins that include pilus tip adhesion (PilA), backbone (PilB) and base protein (PilC) (Maisey et al., 2008). PilA was demonstrated to bind immobilized collagen type I and fibrinogen (Dramsi et al., 2012; Banerjee et al., 2011). PilA also contributes to GBS adherance of human vaginal (VK2/E6E7), ectocervical (Ect1/E6E7), endocervical (End1/E6E7) and cervical (ME180) epithelial cell lines (Sheen et al., 2011). Meanwhile in vivo mouse model of GBS vaginal colonization revealed that PilA is essential for GBS persistence in the vagina of non-pregnant mice (Sheen et al., 2011). PilB is demonstrated to mediate GBS resistance to cathelicidin antimicrobial peptide and thus allowing the GBS survival when co-cultured with human macrophages and neutrophils in vitro (Maisey et al., 2008).

Previous in vitro study revealed that the expression of adherence factors including pilus components are upregulated when GBS are grown at acidic pH as compared to neutral pH (Santi et al., 2009). Thus, it can be postulated that acidic pH in the vagina of women of childbearing age is causally related to the optimal GBS adherence to vaginal epithelial cells. Overall, in vitro and in vivo studies suggest the involvement of virulence factors discussed above in GBS cervicovaginal colonization, which occurs via adhesion of vaginal and cervical epithelial cells. These virulence factors can also potentially cause stimulation and evasion of host immune responses in the cervix and vagina.

4.2 GBS Virulence Factors That Enhance Invasion of The Cervix

PilB was also portrayed to mediate the GBS paracellular translocation through the differentiated monolayer of cervical epithelial (ME180) cell line (Pezzicoli et al., 2008). Alpha C protein interacts with host cell surface glycosaminoglycan to enhance the GBS internalization of ME180 cells (Baron et al., 2007). GBS transcytosis of ME180 cells may be mediated by interaction between alpha C protein and integrins as co-receptors (Baron et al., 2007). SfbA also interacts with fibronectin to promote GBS invasion of human vaginal (VK2/E6E7), ectocervical (Ect1/E6E7), and endocervical (End1/E6E7) epithelial cell lines (Mu et al., 2014). However, the role of SfbA in mediating GBS translocation across the membranes of these cell lines were not investigated in this study (Mu et al., 2014). It was also reported that GBS strain that established persistent infection in murine vagina invaded human cervical cells at higher rate as compared to human vaginal cells, portraying that GBS may probably establish the long-term colonization in the cervix (Patras et al., 2015). Overall, these studies suggest that PilB, alpha C protein and SfbA can possibly contribute to the GBS transition, from an asymptomatic colonizer to an invasive pathogen in the cervix, to facilitate GBS invasion of amniotic membranes and fluid.

4.3 GBS Virulence Factors That Enhance Ascending Intrauterine Infection

Ornithine rhamnolipid pigment also known as hemolytic pigment mediates the GBS hemolytic activity (Whidbey et al., 2013). This hemolytic activity is contributed by the cylE expression in cyl operon (Whidbey et al., 2013). The most studied two components regulatory system for GBS, CovR/S has been reported to control the transcription of more than 100 virulence genes, and the expression of cylE is repressed by CovR/S (Rajagopal et al., 2006). Hyper-hemolytic phenotype observed in GBS is caused by mutation or loss of function of CovR/S (Rajagopal et al., 2006; Whidbey et al., 2013). In response to pH, the regulation of virulence gene expression also involves CovR/S, via unknown mechanisms (Santi et al., 2009). Meanwhile, the expression of cyl genes was upregulated when GBS was grown in Todd Hewitt broth with neutral pH, as compared to acidic pH in vitro (Santi et al., 2009). Similarly, the increased expression of cyl genes was also reported when GBS was cultured in human amniotic fluid, in comparison to Todd Hewitt-yeast extract medium (Sitkiewicz et al.,

2009). Thus, it is hypothesized that when there is a transition from acidic pH of the vagina to near-neutral pH of the cervix and amniotic fluid, hemolytic pigment is increasingly expressed for GBS invasion of the amniotic fluid.

In comparison to wildtype GBS, covR mutant (hyper-hemolytic) GBS was demonstrated with lower persistence in the vagina of non-pregnant mice (Patras et al., 2013). These results can possibly be explained by hyper-hemolytic GBS stimulation of macrophage inflammatory protein-2 (MIP-22) and interleukin 1-Beta (IL-1β) that further enhance the infiltration of neutrophils into the mouse vagina for the bacterial clearance (Kathryn A Patras et al., 2013). Hyper-hemolytic GBS that was inoculated into the vagina of mast cell–deficient mice also exhibited higher persistence both in the lower genital tract and uterine horns when compared to wildtype mice (Gendrin et al., 2015). This observation is probably due to the hemolytic pigment-mediated degranulation of mast cells that limited the GBS vaginal colonization (Gendrin et al., 2015).

In contrast, both cylE deficient and wildtype GBS were reported to effectively colonize the vagina following the inoculation of these bacterial cells into the vaginal lumen of non-pregnant mice (Randis et al., 2014). However, the vaginal colonization of cylE deficient GBS was reduced in mice that were previously colonized with wildtype GBS, implicating that hemolytic pigment might contribute to competitive colonization advantage for GBS (Randis et al., 2014). Overall, it can be assumed that other than GBS adhesins, hemolytic pigment is also involved in GBS vaginal colonization. Vaginal inoculation of pregnant mice with cylE deficient strain resulted in lower rate of preterm delivery and intrauterine fetal demise when compared to mice infected with wildtype GBS (Randis et al., 2014). A cylE deficient strain was also reported to cause a reduction in placental inflammation as well as maternal GBS bacteremia (Randis et al., 2014).

There are many dissimilarities between human pregnancy and pregnancy in mouse model that include differences in the reproductive anatomy, placentation, onset of labor, and sensitivity to pathogens. In view of these multiple dissimilarities, pregnant non-human primates (NHP) are preferably used for studies associated to pregnancy in humans, as the closest animal model. Pregnant NHP, Macaca nemestrina inoculated with hyper-hemolytic GBS in choriodecidual space had microbial invasion of amniotic fluid cavity (MIAC), preterm labour, and fetal sepsis compared to pregnant NHP administered with both covR and cylE mutant GBS or saline (Boldenow et al., 2016). This is accompanied by the elevation of IL-1β, IL8, TNF and prostaglandins in amniotic fluid, as well as recruitment of neutrophils into the chorioamniotic membranes of pregnant NHP inoculated with hyper-hemolytic GBS (Boldenow et al., 2016). Interestingly, neutrophil extracellular traps (NETs), were observed to form in the chorioamniotic membranes during ascending GBS infection and hemolytic pigment allowed GBS to resist extracellular killing by NETs (Boldenow et al., 2016).

This is supported by in vitro experiments, showing that hyper-hemolytic GBS also enhanced the penetration of human choriomaniotic membranes in comparison to both covR and cylE mutant and wildtype GBS (Whidbey et al., 2013). Hyper-hemolytic GBS also promoted the invasion of human amniotic epithelial cells (hAECs) and the secretion of pro-inflammatory cytokines from these cells as compared to cylE mutant, both covR and cylE mutant and wildtype GBS (Whidbey et al., 2013). In vitro studies revealed that hemolytic pigment is crucial for GBS resistance to killing by neutrophils, macrophages and mast cells by causing cytotoxity of these immune cells (Boldenow et al., 2016; Gendrin et al., 2015; Liu et al., 2004). This evidence implies that hemolytic pigment is crucial for ascending intrauterine infection, inducing inflammation in the placenta, chorioamniotic membranes, amniotic fluid and fetus that eventually trigger preterm delivery.

GBS hyaluronidase (HylB), is an endoglycosidase that cleaves hyaluronic acid (HA) into disaccharides (Kolar et al., 2015; Vornhagen et al., 2016). Higher hyaluronidase activity was portrayed in GBS obtained from amniotic fluid of preterm labor women or blood of infected neonates as compared to commensal strains isolated from rectovaginal swabs of healthy women (Vornhagen et al., 2016). There are limited studies to explore the role of HylB in vaginal colonization. Meanwhile, vaginal inoculation of mice with hylB deficient GBS was depicted to cause lower rate of ascending intrauterine infection, preterm delivery and in utero fetal demise as compared to wildtype GBS (Vornhagen et al., 2016). The elevated production of pro-inflammatory cytokines detected in the uterus of mice treated with hylB deficient GBS might cause GBS clearance and thus preventing the ascending intrauterine infection (Vornhagen et al., 2016). Furthermore, in vitro and in vivo experiments portrayed that HylB caused degradation of HA into disaccharides that can block the activation of TLR2/4 signaling and thus inflammation (Kolar et al., 2015). Thus, it is plausible that Hylb is required for the dampening of immune responses in the uterus to allow for ascending intrauterine infection, preterm delivery and in utero fetal demise in mice.

Recently, pregnant NHP inoculated with hylB deficient GBS into the choriodecidual space were reported with lower incidence of MIAC, preterm labour, and fetal bacteremia as compared to NHP inoculated with isogenic hylB poficient GBS or saline (Coleman et al., 2021). Reduced infiltration of neutrophils into chorioamniotic membranes and diminished production of matrix metalloproteinase (MMPs) and prostaglandins in amniotic fluid were also documented in these NHP treated with hylB deficient GBS (Coleman et al., 2021). From in vitro experiments, HylB also contributes to the GBS resistance to killing by primary human neutrophils, perhaps by diminishing the production of reactive oxygen species from these immune cells as a result of HylB mediated dampening of TLR2/4 signaling (Coleman et al., 2021). Similarly, GBS lacking of hylB were depicted with a lower survival in macrophages in vitro (Wang et al., 2014). Overall, Hylb mediates ascending intrauterine GBS infection, to cause inflammation in chorioamnion and amniotic fluid that stimulates preterm labour.

The GBS virulence factors that contribute to vaginal colonization, invasion of cervix and ascending intrauterine infection are illustrated in Figure 1. Meanwhile the interaction between these virulence factors and host immune components are summarized in Figure 2.

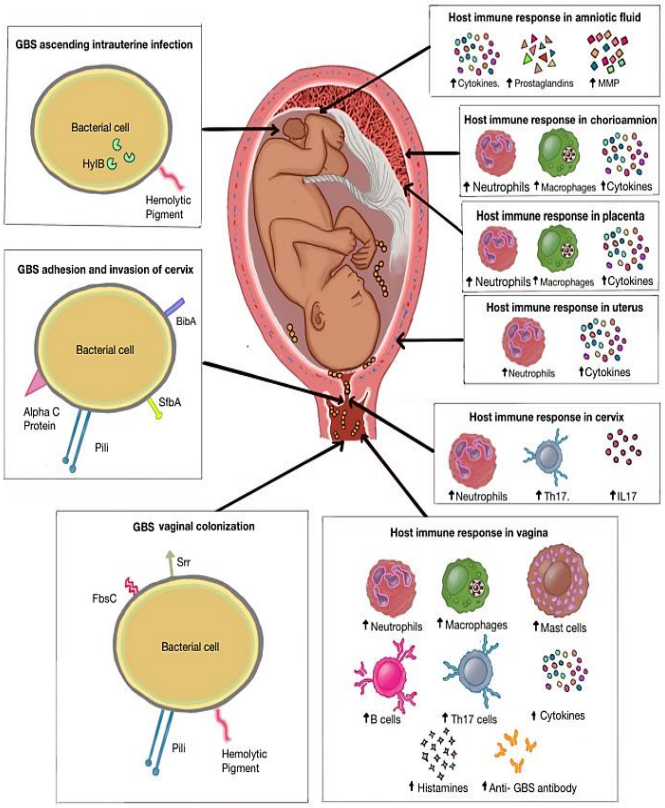

Figure 1: GBS virulence factors that are necessary for vaginal colonization, by adhering to vaginal epithelial cells include Srr, FbsC, PilA. Srr, BibA, Alpha C protein, PilB and SfbA are found to mediate GBS adhesion and invasion of cervical epithelial cells.

Hemolytic pigment and HylB are demonstrated to be important for ascending intrauterine infection. Host innate immune components that are important for immunity against GBS in vagina consist of neutrophils, macrophages and mast cells, which contribute to the synthesis of proinflammatory cytokines and histamine. B cells and Th17 cells that are responsible for the synthesis of anti-GBS antibody and IL17 cytokines respectively mediate the adaptive immune response towards GBS in the vagina. In the cervix, neutrophils and Th17 cells that contribute to the synthesis of IL17 seem to be important for GBS clearance. Infiltration of neutrophils and macrophages that contribute to production of pro-inflammatory cytokines in gestational tissues including uterus, placenta and chorioamnion are also demonstrated in response to GBS ascending intrauterine infection. Finally, the GBS invasion into the amniotic fluid triggers the synthesis of MMP and prostaglandin.

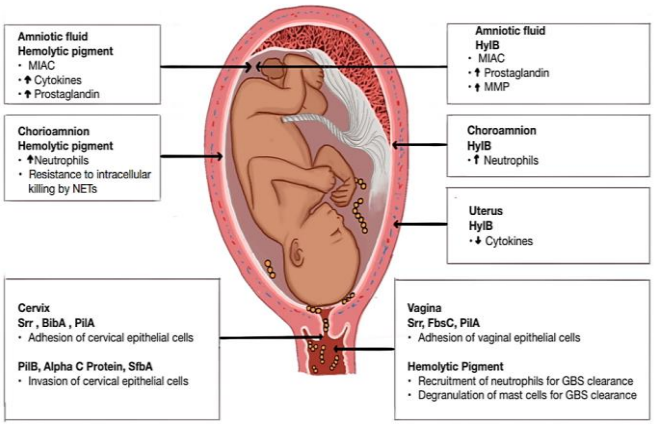

Figure 2: During vaginal colonization, GBS adhesins including Srr, FbsC and PilA bind to ligands on the surface of vaginal epithelial cells.

Hemolytic pigment mediates the recruitment of neutrophils into vagina, and the degranulation of mast cells to restrict GBS vaginal colonization. Srr, BibA and PilA are necessary for GBS adhesion of cervical epithelial cells. Alpha C protein, PilB and SfbA meanwhile are crucial for GBS invasion of the cervical epithelial cells to possibly mediate GBS transition, from an asymptomatic colonizer to an invasive pathogen and thus facilitating GBS invasion of amniotic fluid. In uterus, HylB dampens the synthesis of proinflammatory cytokines to probably allow for GBS ascending intrauterine infection. Hemolytic pigment and HylB mediate the recruitment of neutrophils into choriomanion. Hemolytic pigment allows GBS to circumvent NETs in chorioamnion, as one of the mechanisms to evade host immune response. Then both hemolytic pigment and HylB are shown to cause the GBS invasion of amniotic fluid, and these virulence factors then further trigger the synthesis of cytokines, MMP and prostaglandin in amniotic fluid.

5. Preventive Strategies For GBS Vaginal Colonization, Ascending Intrauterine Infection and Fetal Infection

5.1 Intrapartum Antibiotic Prophylaxis (IAP)

In an effort to reduce the incidence of GBS infection among pregnant mothers and neonates, Centers for Disease Control and Prevention (CDC) has established a universal culture-based screening guideline for pregnant women with gestational age of 35–37 weeks (Verani et al., 2010). IAP is administered during labour and delivery, to GBS positive women and thus limiting the use of IAP to a certain risk group (Verani et al., 2010). The incidence of early-onset neonatal GBS infections was observed to decline from 0.37 to 0.23 per 1000 live births from 2006 to 2015 due to the implementation of this IAP program in United States (Nanduri et al., 2019). However, the rate of late-onset neonatal GBS diseases was not reduced by this IAP program and there is also an apprehension over perturbed gut microbiome and antibiotic resistance in infants as a result of the common use of IAP (Nogacka et al., 2017; Tapiainen et al., 2019; Hahn et al., 2021). The development of GBS vaccine for pregnant women is crucial in reducing the rate of maternal and neonatal GBS infections especially in low-and middle-income countries where IAP program is not implemented (Berner, 2021; Vekemans et al., 2019). This approach can also be cost-effective for the healthcare system in countries where IAP program is feasible (Hahn et al., 2021).

5.2 Development of GBS Vaccine

Current vaccine candidates include trivalent CPS conjugate vaccine derived from serotypes Ia, Ib and III. In Phase II clinical trial, this vaccine is safe and well-tolerated in pregnant women, and efficient in inducing high titer of maternal antibodies that are transferred to fetus via placenta (Swamy et al., 2020). However, not all clinically-important serotypes are targeted by this vaccine, and hence a hexavalent CPS conjugate vaccine targeting serotypes Ia, Ib, II, III, IV, and V is developed. In Phase ½ clinical trial, the safety, immunogenicity and efficiency of this vaccine have been demonstrated in healthy non-pregnant individuals (Absalon et al., 2021). However, the prevalence of GBS serotypes varies in different geographical regions and in order to circumvent the host immunity, GBS may switch and replace their capsular serotypes post-vaccination.

Alternatively, N-terminal domains of Alpha C and Rib proteins are observed to be safe and highly immmunogenic in non-pregnant healthy individuals in Phase I clinical trial (Fischer et al., 2021). Meanwhile other GBS adhesins and invasins including pilus, latch domain of Srr-1 and BibA are studied in pre-clinical phase (dos Santos et al., 2020; Edwards et al., 2016; Lin et al., 2018). Hemolytic pigment and HylB can also be potentially targeted using the therapeutic measures, to prevent ascending intrauterine GBS infection (Boldenow et al., 2016; Coleman et al., 2021).

6. Conclusion

In low-and-middle income countries, the lack of availability of IAP program contributes to the increased GBS burden among pregnant women and their neonates. In countries where IAP program is implemented, the rate of early onset neonatal infection is reduced, but not the late onset neonatal infection. Thus, the development of GBS vaccine is seen to be crucial especially in low-and-middle income countries. GBS vaccine can also potentially be cost-effective for the healthcare system when executed in addition to IAP program. In this review, emphasis is given to the interaction between host immune factors and GBS virulence factors in the gestational tissues that allows the organism to evade the local host immune responses leading to ascending infection of the pregnant female genital tract to trigger preterm delivery and fetal infection. However, further research is needed to understand these complicated mechanisms that may contribute to GBS transition from a commensal organism to a pathogen in pregnant women. This knowledge is also crucial to elucidate the preventive strategies, either by targeting the GBS virulence factors using vaccines or therapeutic measures, that can be implemented in addition to or as replacement to IAP.

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References

Absalon, J., Segall, N., Block, S.L., Center, K.J., Scully, I.L., Giardina, P.C., Peterson, J., Watson, W.J., Gruber, W.C., Jansen, K.U., Peng, Y., Munson, S., Pavliakova, D., Scott, D. A., Anderson, A.S., 2021. Safety and immunogenicity of a novel hexavalent group B streptococcus conjugate vaccine in healthy, non-pregnant adults: a phase 1/2, randomised, placebo-controlled, observer-blinded, dose-escalation trial. Lancet Infect. Dis., 21 (2), Pp. 263–274.

Agrawal, V., Hirsch, E., 2012. Intrauterine infection and preterm labor. Semin Fetal Neonatal Med., 17 (1), Pp. 12-19.

Baker, J.A., Lewis, E.L., Byland, L.M., Bonakdar, M., Randis, T.M., Ratner, A.J., 2017. Mucosal vaccination promotes clearance of Streptococcus agalactiae vaginal colonization. Vaccine, 35 (9), Pp. 1273-1280.

Banerjee, A., Kim, B.J., Carmona, E.M., Cutting, A.S., Gurney, M.A., Carlos, C., Feuer, R., Prasadarao, N.V, Doran, K.S., 2011. Bacterial Pili exploits integrin machinery to promote immune activation and efficient blood-brain barrier penetration. Nat Commun., 2 (462), Pp. 1-11.

Baron, M.J., Filman, D.J., Prophete, G.A., Hogle, J.M., Madoff, L.C., 2007. Identification of a glycosaminoglycan binding region of the alpha C protein that mediates entry of group B Streptococci into host cells. J. Biol. Chem., 282 (14), Pp. 10526–10536.

Berner, R., 2021. Group B streptococcus vaccines: one step further. Lancet Infect. Dis., 21 (2), Pp. 158-160.

Bianchi-Jassir, F., Seale, A.C., Kohli-Lynch, M., Lawn, J.E., Baker, C.J., Bartlett, L., Cutland, C., Gravett, M.G., Heath, P.T., Ip, M., le Doare, K., Madhi, S.A., Saha, S.K., Schrag, S., Sobanjo-Ter Meulen, A., Vekemans, J., Rubens, C.E., 2017. Preterm Birth Associated with Group B Streptococcus Maternal Colonization Worldwide: Systematic Review and Meta-analyses. Clin. Infect. Dis., 65 (2), Pp. 133–142.

Boldenow, E., Gendrin, C., Ngo, L., Bierle, C., Vornhagen, J., Coleman, M., Merillat, S., Armistead, B., Whidbey, C., Alishetti, V., Santana-Ufret, V., Ogle, J., Gough, M., Srinouanprachanh, S., MacDonald, J.W., Bammler, T.K., Bansal, A., Denny Liggitt, H., Rajagopal, L., Adams Waldorf, K. M., 2016. Group B Streptococcus circumvents neutrophils and neutrophil extracellular traps during amniotic cavity invasion and preterm labor. Sci. Immunol., 1 (4), Pp. 1-29.

Buscetta, M., Papasergi, S., Firon, A., Pietrocola, G., Biondo, C., Mancuso, G., Midiri, A., Romeo, L., Teti, G., Speziale, P., Trieu-Cuot, P., Beninati, C., 2014. FbsC, a novel fibrinogen-binding protein, promotes

Streptococcus agalactiae-host cell interactions. J. Biol. Chem., 289 (30), Pp. 21003–21015.

Carey, A. J., Tan, C. K., Mirza, S., Irving-Rodgers, H., Webb, R. I., Lam, A., Ulett, G.C., 2014. Infection and Cellular Defense Dynamics in a Novel 17β-Estradiol Murine Model of Chronic Human Group B Streptococcus Genital Tract Colonization Reveal a Role for Hemolysin in Persistence and Neutrophil Accumulation. J. Immunol., 192 (4), Pp. 1718-1731.

Coleman, M., Armistead, B., Orvis, A., Quach, P., Brokaw, A., Gendrin, C., Sharma, K., Ogle, J., Merillat, S., Dacanay, M., Wu, T.Y., Munson, J., Baldessari, A., Vornhagen, J., Furuta, A., Nguyen, S., Adams Waldorf, K.M., Rajagopal, L., 2021. Hyaluronidase impairs neutrophil function and promotes group b streptococcus invasion and preterm labor in nonhuman primates. MBio, 12 (1), Pp. 1-18.

dos Santos, N.F.B., da Silva, L.R., Costa, F.J.M.D., de Mattos, D.M., de Carvalho, E., Ferreira, L.C. de S., Ferreira, R. de C.C., 2020. Immunization with a recombinant BibA surface protein confers immunity and protects mice against group B Streptococcus (GBS) vaginal colonization. Vaccine, 38 (33), Pp. 5286-5296.

Dramsi, S., Morello, E., Poyart, C., Trieu-Cuot, P., 2012. Epidemiologically and clinically relevant Group B Streptococcus isolates do not bind collagen but display enhanced binding to human fibrinogen. Microbes Infect., 14 (12), Pp. 1044–1048.

Edwards, M.S., Rench, M.A., Rinaudo, C.D., Fabbrini, M., Tuscano, G., Buffi, G., Bartolini, E., Bonacci, S., Baker, C. J., Margarit, I., 2016. Immune responses to invasive group B streptococcal disease in adults. Emerging Infect. Dis., 22 (11), Pp. 1877–1883.

Fischer, P., Pawlowski, A., Cao, D., Bell, D., Kitson, G., Darsley, M., Johansson-Lindbom, B., 2021. Safety and immunogenicity of a prototype recombinant alpha-like protein subunit vaccine (GBS-NN) against Group B Streptococcus in a randomised placebo-controlled double-blind phase 1 trial in healthy adult women. Vaccine, 39 (32), Pp. 4489-4499.

Gendrin, C., Vornhagen, J., Ngo, L., Whidbey, C., Boldenow, E., Santana-Ufret, V., Clauson, M., Burnside, K., Galloway, D. P., Waldorf, K. A., Piliponsky, A. M., Rajagopal, L., 2015. Mast cell degranulation by a hemolytic lipid toxin decreases GBS colonization and infection. Sci. Adv., 1 (6), Pp. 1-17.

Hahn, B.A., de Gier, B., van Kassel, M.N., Bijlsma, M.W., van Leeuwen, E., Wouters, M.G. A.J., van der Ende, A., van de Beek, D., Wallinga, J., Hahné, S.J.M., Jan van Hoek, A., 2021. Cost-effectiveness of maternal immunization against neonatal invasive Group B Streptococcus in the Netherlands. Vaccine, 39 (21), Pp. 2876-2885.

Jeganathan, R., Karalasingam, S.D., 2020. National Obstetrics Registry 6th Report (2018-2020). National Obstetrics Registry, Malaysia.

Jiang, S., Wessels, M.R., 2014. BsaB, a novel adherence factor of group B Streptococcus. Infect. Immun., 82 (3), Pp. 1007–1016.

Kolar, S.L., Kyme, P., Tseng, C.W., Soliman, A., Kaplan, A., Liang, J., Nizet, V., Jiang, D., Murali, R., Arditi, M., Underhill, D.M., Liu, G.Y., 2015. Group B Streptococcus Evades Host Immunity by Degrading Hyaluronan. Cell Host Microbe., 18 (6), Pp. 694–704.

Kothary, V., Doster, R.S., Rogers, L.M., Kirk, L.A., Boyd, K.L., Romano-Keeler, J., Haley, K. P., Manning, S.D., Aronoff, D.M., Gaddy, J.A., 2017. Group B streptococcus induces neutrophil recruitment to gestational tissues and elaboration of extracellular traps and nutritional immunity. Front. Cell. Infect. Microbiol., 7 (19), Pp. 1–13.

Lin, S. M., Jang, A. Y., Zhi, Y., Gao, S., Lim, S., Lim, J. H., Song, J. Y., Sullam, P. M., Rhee, J. H., Seo, H. S., 2018. Vaccination with a latch peptide provides serotype independent protection against group B streptococcus infection in mice. J. Infect. Dis., 217 (1), Pp. 93–102.

Liu, G. Y., Doran, K. S., Lawrence, T., Turkson, N., Puliti, M., Tissi, L., Nizet, V., 2004. Sword and shield: Linked group B streptococcal β-hemolysin/cytolysin and carotenoid pigment function to subvert host phagocyte defense. Proceedings of the National Academy of Sciences of the United States of America, 101 (40), Pp. 14491–14496.

Maisey, H. C., Quach, D., Hensler, M. E., Liu, G. Y., Gallo, R. L., Nizet, V., Doran, K. S., 2008. A group B streptococcal pilus protein promotes phagocyte resistance and systemic virulence. FASEB J., 22 (6), Pp. 1715-1724.

Mu, R., Kim, B. J., Paco, C., del Rosario, Y. D., Courtney, H. S., Doran, K. S., 2014. Identification of a group B streptococcal fibronectin binding protein, SfbA, that contributes to invasion of brain endothelium and development of meningitis. Infect. Immun., 82 (6), Pp. 2276-2286.

Nanduri, S. A., Petit, S., Smelser, C., Apostol, M., Alden, N. B., Harrison, L. H., Lynfield, R., Vagnone, P. S., Burzlaff, K., Spina, N. L., Dufort, E. M., Schaffner, W., Thomas, A. R., Farley, M. M., Jain, J. H., Pondo, T., McGee, L., Beall, B. W., Schrag, S. J., 2019. Epidemiology of Invasive Early-Onset and Late-Onset Group B Streptococcal Disease in the United States, 2006 to 2015: Multistate Laboratory and Population-Based Surveillance. JAMA Pediatr., 173 (3), Pp. 224-233.

Nogacka, A., Salazar, N., Suárez, M., Milani, C., Arboleya, S., Solís, G., Fernández, N., Alaez, L., Hernández-Barranco, A. M., de los Reyes-Gavilán, C. G., Ventura, M., Gueimonde, M., 2017. Impact of intrapartum antimicrobial prophylaxis upon the intestinal microbiota and the prevalence of antibiotic resistance genes in vaginally delivered full-term neonates. Microbiome., 5 (93), Pp. 1-10.

Patras, K. A., Rosler, B., Thoman, M. L., Doran, K. S., 2015. Characterization of host immunity during persistent vaginal colonization by Group B Streptococcus. Mucosal Immunol., 8 (6), Pp. 1339-1348.

Patras, Kathryn A, Wang, N.-Y., Fletcher, E. M., Cavaco, C. K., Jimenez, A., Garg, M., Fierer, J., Sheen, T. R., Rajagopal, L., Doran, K. S., 2013. Group B Streptococcus CovR regulation modulates host immune signalling pathways to promote vaginal colonization. Cell. Microbiol., 15 (7), Pp. 1154–1167.

Pezzicoli, A., Santi, I., Lauer, P., Rosini, R., Rinaudo, D., Grandi, G., Telford, J. L., Soriani, M., 2008. Pilus backbone contributes to group B Streptococcus paracellular translocation through epithelial cells. J. Infect. Dis., 198 (6), Pp. 890-898.

Rajagopal, L., Vo, A., Silvestroni, A., Rubens, C. E., 2006. Regulation of cytotoxin expression by converging eukaryotic-type and two-component signalling mechanisms in Streptococcus agalactiae. Mol. Microbiol., 62 (4), Pp. 941-957.

Randis, T. M., Gelber, S. E., Hooven, T. A., Abellar, R. G., Akabas, L. H., Lewis, E. L., Walker, L. B., Byland, L. M., Nizet, V., Ratner, A. J., 2014. Group B Streptococcus β-hemolysin/cytolysin breaches maternal-fetal barriers to cause preterm birth and Fintrauterine fetal demise in vivo. J. Infect. Dis., 210 (2), Pp. 265–273.

Rogers, L. M., Anders, A. P., Doster, R. S., Gill, E. A., Gnecco, J. S., Holley, J. M., Randis, T. M., Ratner, A. J., Gaddy, J. A., Osteen, K., Aronoff, D. M., 2018. Decidual stromal cell-derived PGE2 regulates macrophage responses to microbial threat. Am. J. Reprod. Immunol., 80 (4), Pp. 1-26.

Santi, I., Grifantini, R., Jiang, S. M., Brettoni, C., Grandi, G., Wessels, M. R., Soriani, M., 2009. CsrRS regulates group B Streptococcus virulence gene expression in response to environmental pH: A new perspective on vaccine development. J. Bacteriol., 191 (17), Pp. 5387–5397.

Santi, I., Scarselli, M., Mariani, M., Pezzicoli, A., Masignani, V., Taddei, A., Grandi, G., Telford, J. L., Soriani, M., 2007. BibA: A novel immunogenic bacterial adhesin contributing to group B Streptococcus survival in human blood. Mol. Microbiol., 633 (3), Pp. 754–767.

Seale, A. C., Bianchi-Jassir, F., Russell, N. J., Kohli-Lynch, M., Tann, C. J., Hall, J., Madrid, L., Blencowe, H., Cousens, S., Baker, C. J., Bartlett, L., Cutland, C., Gravett, M. G., Heath, P. T., Ip, M., le Doare, K., Madhi, S. A., Rubens, C. E., Saha, S. K., Schrag, S. J., Meule, A. S., Vekemans, J., Lawn, J. E., 2017. Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children. Clin. Infect. Dis., 65 (2), Pp. 200-219.

Seo, H. S., Minasov, G., Seepersaud, R., Doran, K. S., Dubrovska, I., Shuvalova, L., Anderson, W. F., Iverson, T. M., Sullam, P. M., 2013. Characterization of fibrinogen binding by glycoproteins Srr1 and Srr2 of Streptococcus agalactiae. J. Biol. Chem., 288 (50), Pp. 35982–35996.

Sheen, T. R., Jimenez, A., Wang, N. Y., Banerjee, A., van Sorge, N. M., Doran, K. S., 2011. Serine-rich repeat proteins and pili promote Streptococcus agalactiae colonization of the vaginal tract. J. Bacteriol., 193 (24), Pp. 6834–6842.

Sitkiewicz, I., Green, N. M., Guo, N., Bongiovanni, A. M., Witkin, S. S., Musser, J. M., 2009. Transcriptome adaptation of group B Streptococcus to growth in human amniotic fluid. PLoS One, 4 (7), Pp. 1-15.

Swamy, G. K., Metz, T. D., Edwards, K. M., Soper, D. E., Beigi, R. H., Campbell, J. D., Grassano, L., Buffi, G., Dreisbach, A., Margarit, I., Karsten, A., Henry,

O., Lattanzi, M., Bebia, Z., 2020. Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in pregnant women and their infants: Results from a randomized placebo-controlled phase II trial. Vaccine, 38 (44), Pp. 6930-6940.

Tapiainen, T., Koivusaari, P., Brinkac, L., Lorenzi, H. A., Salo, J., Renko, M., Pruikkonen, H., Pokka, T., Li, W., Nelson, K., Pirttila, A. M., Tejesvi, M. V., 2019. Impact of intrapartum and postnatal antibiotics on the gut microbiome and emergence of antimicrobial resistance in infants. Sci. Rep., 9 (10635), Pp. 1-11.

Vekemans, J., Moorthy, V., Friede, M., Alderson, M. R., Sobanjo-Ter Meulen, A., Baker, C. J., Heath, P. T., Madhi, S. A., Mehring-Le Doare, K., Saha, S. K., Schrag, S., Kaslow, D. C., 2019. Maternal immunization against Group B streptococcus: World Health Organization research and development technological roadmap and preferred product characteristics. Vaccine, 37 (50), Pp. 7391-7393.

Verani, J. R., McGee, L., Schrag, S. J., 2010. Prevention of perinatal group B streptococcal disease - revised guidelines from Centers for Disease Control and Prevention (CDC). Morbidity and mortality weekly report, 59(10), Pp. 1-36.

Vogel, J. P., Chawanpaiboon, S., Moller, A. B., Watananirun, K., Bonet, M., Lumbiganon, P., 2018. The global epidemiology of preterm birth. Best Pract Res Clin Obstet Gynaecol., (52), Pp. 3-12.

Vornhagen, J., Adams Waldorf, K. M., Rajagopal, L., 2017. Perinatal Group B Streptococcal Infections: Virulence Factors, Immunity, and Prevention Strategies. Trends Microbiol., 25 (11), Pp. 919-931.

Vornhagen, J., Quach, P., Boldenow, E., Merillat, S., Whidbey, C., Ngo, L. Y., Adams Waldorf, K. M., Rajagopal, L., 2016. Bacterial hyaluronidase promotes ascending GBS infection and preterm birth. MBio, 7 (3), Pp. 1-10.

Wang, N. Y., Patras, K. A., Seo, H. S., Cavaco, C. K., Rösler, B., Neely, M. N., Sullam, P. M., Doran, K. S., 2014. Group B streptococcal serine-rich repeat proteins promote interaction with fibrinogen and vaginal colonization. J. Infect. Dis., 210 (6), Pp. 982–991.

Wang, Z., Guo, C., Xu, Y., Liu, G., Lu, C., Liu, Y., 2014. Two novel functions of hyaluronidase from Streptococcus agalactiae are enhanced intracellular survival and inhibition of proinflammatory cytokine expression. Infect. Immun., 82 (6), Pp. 2615-2652.

Whidbey, C., Harrell, M. I., Burnside, K., Ngo, L., Becraft, A. K., Iyer, L. M., Aravind, L., Hitti, J., Adams Waldorf, K. M., Rajagopal, L., 2013. A hemolytic pigment of Group B Streptococcus allows bacterial penetration of human placenta. J. Exp. Med., 210 (6), Pp. 1265-1281.

Zheng, D., Liwinski, T., Elinav, E., 2020. Interaction between microbiota and immunity in health and disease. Cell Res., 30 (6), Pp. 492-506.