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Epidemiology of Group B Streptococcus Infections among Neonates and Young Infants: A Review

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Background

Globally, prematurity, birth asphyxia, and neonatal sepsis are three leading causes of neonatal deaths. Sepsis is also a leading cause of deaths among post-neonatal or young infants [<2 months] age group [1]. Based on date of neonatal infections, the neonatal sepsis has been categorized as two types: early [EONS] and late onset neonatal sepsis [LONS] that happen within 0-6 and 7-27 days after birth, respectively [2]. Streptococcus agalactiae or Group B streptoccous [GBS] is the main microorganism that is responsible for the EONS followed by some other microorganisms including *Escherichia Coli*, *Enterococci.* Although the major responsible organisms for LONS or sepsis in 'young infants' are substantially different compared to the EONS, GBS is also one of the main organisms of this [3, 4]. This paper describes the epidemiological facts related to 'GBS', the micro-organism which causes EONS and one of the leading 'killer' infectious agents in neonates and young infants. In addition, it discusses the current knowledge gaps about GBS, so that the future efforts could be directed to reduce these gaps.

Short Description of GBS

GBS is a gram-positive, beta-hemolytic, facultative anaerobic and coagulase-negative bacterium. This 'B' antigen is present on the cell-wall [4]. The bacterial capsule is composed of polysaccharides. It could form ten distinctive serotypes based on the composition of the capsular polysaccharides' antigens: 1a, 1b, II, III, IV, V, VI, VII, VIII, and IX. Although 'Serotype-III' is the commonest isolated organism, there have been regional differences in strains of bacteria which are primarily associated with infection among neonates as well as maternal colonization [5-9]. These substantial differences in distribution of serotypes indicate that more rigorous efforts would be required on a regional basis to fight against this infectious agent like other preventive services targeted to reduce neonatal deaths.

Similar to neonatal sepsis, infection of GBS has largely been classified as two types based on its day of onset, early onset [EOD] and late onset disease [LOD][4, 5]. The EOD and LOD occur in '0-6' and '7-89' days after birth, respectively [10, 11]. It could be present among one-third of the adults without producing any clinical symptoms; however, it can also infect them. Although the current incidence, consequence [except pregnant women] or burden of this infection among adults is insignificant compared to its severity in neonates, it has also been considered as a 'growing problem' in causing disease among adults [12,13].

Virulence Factors

The main virulence factor of the GBS is the capsular polysaccharide; this is associated with severity and types of GBS infection [10, 12]. In addition, surface proteins such as protein C and 'rib' protein have association with virulence of this microorganism. The capsular polysaccharides is not only associated with infection but also associated with resistance to antibiotics [4].

Clinical Manifestations

Overall, following clinical illnesses have been found as the manifestations of the GBS in neonates and young infants: sepsis, meningitis, pneumonia, cellulitis, osteomyelitis, septic arthritis, endocarditis, and epiglottitis [4, 14]. The vast majority of the diseases predominantly occur in early neonatal period [i.e., the first week of life] where sepsis is the commonest syndrome; the illness usually develops immediately after birth [10]. Manifestations of early neonatal GBS infections are typical to the symptoms of any other EONS; that include fever [axillary temperature above >99.5°F], hypothermia [axillary temperature <95.9°F], respiratory distress, convulsion, poor feeding, reduced movement or lethargy. Manifestations other than the sepsis are typically found during the late neonatal period. In most cases, clinical symptoms or signs of the EODs appear within first twenty-four hours of life. The other syndromes that mentioned here without sepsis largely occur as manifestations of LODs. However, the complications of the LODs are more severe compared to the EODs [7, 10].

Complications of GBS

The complications of neonatal infections due to GBS include cerebral palsy, learning difficulties, blindness, hearing loss, growth retardation, and death. Pre-term, low-birth weight or babies born with premature rupture of membrane have higher incidence of complications and mortality than term babies. The

mortality rate could be as high as 30% among pre-term babies without treatment [10, 15].

In addition to its association with neonatal infections, the GBS has also been associated with higher likelihood of other maternal or pregnancy complications including abortion, still-births, premature rupture of membrane, pre-term births and/or low-birth weight [6, 10, 11, 16, 17].

Incidence and Trends

The real global burden of GBS disease among young infants is not yet known; it has some limitations based on the availability of data from developing countries [5,18]. Most of the reports about its global burden come from systematic reviews and meta-analysis or other types of global reports that are largely 'estimates', not the real or exact reports. Considering underreporting and limitations of data, it was estimated that the mean global incidence could be 2.0 per 1,000 LB [19]. Another systematic review and meta-analysis conducted by Edmond et al. Found an overall global incidence of 0.53 per 1,000 LB in infants below three months of age; the incidence rates in Europe and the Americas were similar, 0.57 [95% confidence interval [CI]: 0.44-0.71], and 0.67 [95% CI: 0.54-0.80] per 1,000 LB, respectively. The GBS incidence estimates from other parts of the world largely varied from 0.02 [95% CI: -0.03 to 0.07] per 1,000 LB in South-East Asia to 1.21 [95% CI: 0.50 to 1.91] per 1,000 LB in Africa [5].

The current estimates of its trends also vary between developed and developing countries. Regarding this, the similar trends in decline of this infection were observed in the United States [US] and Europe. This is largely due to administration of intra-partum antibiotic prophylaxis and this administration correlates with the period of reduction of this infection among neonatal and young infants age group in these parts by reducing mostly EOD [4,20]. One report showed that, the incidence in the US declined from 1.7 cases per 1,000 LB in 1990 to 0.4 cases per 1,000 LB in recent years; however, it remained one of the leading causes of neonatal mortality and morbidity in the US. The estimated incidence of EOD and LOD were 0.25 and 0.26 per 1,000 LB in 2010, respectively [10]. Although the overall incidence for EODs remained nearly same as the LODs, its incidence declined more than 80% compared to its 1990 level [5]. Despite the existence of racial disparity in GBS incidence, it declined among both Whites and Blacks. Over the past several years, this has largely been in a 'plateau phase' with the current estimated rate [4,20].

However, similar to differences in reports of developed and developing countries, prevalence estimates also vary between hospital-based and community-based studies in developing countries. This difference might also be due to study design. A recent multi-country hospital-based observational study conducted in Panama, Dominic Republic, Hong Kong and Bangladesh, found an overall incidence of 2.35 [95% CI: 1.74 to 3.81] cases per 1,000 LB in Dominic Republic; however, the incidence was '0' per 1,000 LB in Bangladesh [21]. It could be underestimated considering a large number of deliveries occur at home or by unskilled attendants in Bangladesh. Another study that investigated prevalence of GBS colonization in umbilicus of children in rural Bangladesh found an overall incidence of 6.3%; finding of this community-based study is substantially different from the previously mentioned hospital-based study [7].

The estimates about its incidence in developing countries have to be discussed in the context of the potential limitations of the current best available estimates [18]. In developing countries, most of the child-births take place [~90%] at home and where most of the deaths occur during early neonatal days specifically on the first day of the life of newborns babies [22]. There could a large variation in home delivery or delivery by skilled attendants in these countries that might limit the evidence [23, 24]. Approximately 98% of the neonatal deaths occur in these countries, and almost 50% of these deaths occur within first-two days of life. On the other hand, the first day of life is the critical period when most of the clinical manifestations of this infection occur [22, 25]. These could be largely under-estimated in developing countries due to these under-reporting or lack of estimates in community-based studies [18].

Like many other infectious diseases, maternal GBS colonization with superadded human immunodeficiency virus [HIV] infection have association with higher likelihoods of neonatal GBS infection compared to the mothers who did not have HIV co-infection [26]. They also have higher probability of complications related to GBS compared to GBS-negative mothers [26, 27].

Case-Fatality Ratio

The overall global case-fatality ratio of the GBS infections was 9.6% [95% CI: 7•5–11•8]. Analogous to its incidence, the case-fatality ratio for EODs was nearly two-times higher compared to the LODs, 12.1% [95% CI: 6.2–18.3] and 6.8% [95% CI: 4.3-9.4], respectively. Furthermore, the case-fatality ratio varies between developed and developing countries; this ratio is highest in Africa, 22.0% [95% CI: 12.0-32.0%] whereas in Europe it is 7.0 [95% CI: 4.0-10.0%] [5].

The case-fatality ratio in the US declined from 55% in 1970 to 15% in 1980 [20]. The current case–fatality ratio in the US is comparable to the rate of Europe [less than 10%] due to similar diagnostic and preventive efforts targeted to reduce its incidence and severity among young infants age group [5]. Although the initial estimates of its burden as a cause of neonatal sepsis were largely based on the studies or reports of developed countries of the Americas and Europe, a number of recent studies also demonstrated that it is one of the leading causes of neonatal sepsis in African countries [5, 15, 26, 28]. These rates in African countries parallel to the rates of Europe or North America prior to implementation of the intra-partum antibiotic prophylaxis [5]; that shed lights on its universal importance as a potential pathogen to be targeted to reduce incidence and complications associated with neonatal sepsis.

Transmission

The transmission mainly occurs vertically for EOD. Although the mechanism of infection in LODs remains unclear, it could be a late manifestation of the vertical transmission as premature babies were predominantly associated with higher likelihood of the LODs [3, 11]. It could also be a type of 'horizontal infection' due to hospital-acquired infection or transmission from other carriers [29]. Maternal colonization with GBS during pregnancy period is primarily associated with the vertical transmission of this bacterium to the newborns. The primary site of colonization is the gastrointestinal tract of humans; from there, it colonizes within the genitourinary tract of pregnant women and can transmit from this space to the newborns specifically if there is a 'prolonged premature rupture of membrane' or have other high-risk conditions. Prolonged rupture of membrane could transfer the bacteria to amniotic fluids; infants get the organism from the infected amniotic fluids or can acquire it in the birth cannel during the process of delivery [12]. This mechanism is highly supported by other aspects as greater risks of infection with higher concentration of maternal GBS colonization and symptoms usually appear among the vast majority [nearly 90%] of the infected cases within first day after birth. These mechanisms resemble many other vertically transmitted infections [3,6].

Studies found that, GBS could be isolated from two-thirds of the anorectal swabs of male partners of the GBS colonized women. This is an indication that GBS could also be a sexually transmitted infection [30,31].

Risk Factors for Transmission

As previously stated the maternal intra-partum GBS colonization is the main risk factor for its transmission. Pregnant woman who became colonized with GBS could have more than twenty-five times of higher likelihood of delivering a newborn with GBS infection than a woman without GBS colonization during this period. Up to one-third of pregnant women could be colonized with GBS during their pregnancy period, specifically in vaginal canal and rectum [11, 28]. Although maternal GBS colonization in index pregnancy does not have any significant correlation with GBS colonization in subsequent pregnancies, any mother who has delivered a GBS infected baby have higher likelihood of delivering GBS-positive babies in their subsequent pregnancies. In addition to these, although studies reported that a significant proportion of GBS negative mother [i.e., mothers who were not identified as colonized with GBS during screening at their pregnancy period] could deliver GBS infected babies, the exact mechanism of this infection without maternal colonization is unknown [12,14].

Moreover, pre-term-birth and/or low-birth weight babies have higher chance of GBS infection than their term or normal weight counter-parts. These two high risk groups also have higher likelihood of other types of infections due to immune-suppression [32]. Similar to neonatal immune-suppression, maternal immune-suppression or lower level of antibody against the capsular polysaccharides of the GBS is associated with higher incidence of GBS disease in their offspring [4, 10, 12, 33].

Prolonged rupture of membranes [for >4 hours] is another risk factor for this infection in newborns, specifically for pre-term babies; it is highly likely to be transmitted from colonized parts of maternal body to the delivering baby during this prolong period [12, 26]. Additionally, maternal intra-partum fever, chorioamnionitis, endometritis, urinary tract infections and frequent vaginal examinations during pregnancy period have higher incidence of GBS transmission to the offspring [5, 11, 12, 20, 26, 28]. Other risk factors that were revealed include young maternal age [<20 years] maternal ethnicity [African-American race] and maternal co-infection with HIV [12,26].

Laboratory Diagnosis

Diagnosis of the GBS colonization among pregnant women is important to direct its preventive efforts; it is of particular importance to identify women by screening who should be the potential candidates for the intra-partum antibiotic prophylaxis to reduce the transmission from those women to their offspring. Moreover, improper antibiotic administration without the mothers who are not at higher risk can induce antibiotic resistance, hypersensitivity or other adverse reactions among mother and their babies [34,35]. The main diagnostic procedure is its culture of vaginal-rectal specimens. So far, two approaches have largely been used to diagnose women with colonization of this organism to diagnose who would require an intra-partum antibiotic prophylaxis: risk-based and culture-based screening. Risk-based screening is done among women with pre-term delivery [gestational age <37 weeks], intra-partum fever [temperature ≥100.4 º F], or prolong rupture of membrane [for ≥18 hours]. The Centers for Disease Control and Prevention [CDC] currently recommends the culture-based screening of all women. Studies from the USA reported that culture-based screening have higher probability of detecting high-risk mothers [up to 78%] who could potentially transmit the organism to their newborns compared to the risk-based screening [up to 41%] [36-38]. The culture-based screening is done to diagnose GBS colonization among all women in late trimester mainly during 35-37 weeks of gestation [34,35].

The GBS bacteriuria is also a marker of maternal heavy GBS colonization and is associated with higher likelihood of disease among newborns; this is identified by culture of the urine of women. It can be isolated from urine of 2-7% of pregnant women [37-39]. This is also done by culture.

Identification of GBS in neonates is primarily done after clinical signs and symptoms of neonatal sepsis. This includes blood culture. In clinical meningitis, cerebro-spinal fluid [CSF] culture is also recommended. Latex agglutination of the CSF can also detect this [15]. The organism could not be isolated from blood cultures of a significant proportion [20-30%] of newborns with meningitis; in those cases, it is detected from the CSF. Blood culture could be negative among newborns delivered by mothers

who were exposed to antibiotics during intra-partum period. In addition, complete blood count [CBC] can show a higher proportion of white blood cells [WBC] in blood [35]. A higher sensitivity of clinical symptoms compared to blood tests has been observed. The Nuclic Acid Amplification Tests [NAAT] and Polymerase Chain Reaction [PCR] can also detect it [34].

Prevention

Prevention of neonatal GBS infection is possible as previously stated due to use of intrapartum prophylaxis, early diagnosis and treatment of mothers. However, the prevention has several limitations as well as potential area of future investigations.

It was previously mentioned in this discussion that identification of high-risk mothers who are colonized with GBS and provision of intra-partum antibiotics during late trimester largely reduces its incidence among newborns. In addition to this, CDC recommends administering intra-partum antibiotic in any high-risk woman even without known colonization status [34]. Maternal GBS bacteriuria in last trimester of pregnancy is also another indication for intra-partum antibiotic prophylaxis as this usually occurs with higher likelihood of incidence of this disease.

Prevention of GBS in pre-term babies is challenging as the GBS colonization status is not known when the delivery takes place before 37 weeks of gestation. Moreover, administering antibiotic in these high-risk babies could result in other severe diseases including necrotizing enterocolitis and cerebral palsy [40,41].

The antibiotics that have been found effective against GBS among colonized pregnant women are penicillin, ampicillin, vancomycin, and cefazolin [12, 40, 41]. Intra-venous administration of one of these antibiotics could reduce the incidence by 80% among the babies of high-risk mothers. Although intra-partum antibiotic is highly effective against EOD, it is not effective enough to prevent LODs, specifically to prevent meningitis caused by GBS [12,41].

Unfortunately, there is no vaccine currently available against this organism. The preventive methods against this organism is a procedure comparable to the 'test and treat strategy' of the HIV infection [42]; that is mainly to screen all mothers to identify the high-risk groups [i.e., women who are susceptible to infections] as it is already stated that beneficial effects of all currently available preventive efforts largely depend on screening pregnant women to identify the high risk group [9,36].

Treatment

The treatment of this infection in children is similar to any other sepsis treatment. Clinical symptoms do not differ between antibiotic exposed infants and infants who were not exposed to any antibiotics during intra-partum period [43,44]. Intra-venous antibiotics are the main treatment in addition to other supportive treatment as per the symptoms and/or complications. It is better to administer antibiotic according to culture and antibiotic sensitivity patterns of the blood and/or CSF. The drugs that are used for intra-partum antibiotic prophylaxis are also indicated for neonatal treatment including penicillin, cefazolin, and vancomycin [34]. Currently, the WHO recommends prescribing inject able ampicillin and gentamicin to all high-risk neonates [45].

Knowledge Gaps and Challenges [And Hopes]

Most of the current gaps have already been mentioned. Vaccine is the first priority of the future research gaps. However, there are several issues about developing an effective vaccine against GBS. First of all, any vaccine which is given to someone takes a period of time to develop immunity against it; so administering vaccine to newborn is not possible as the vast majority of cases occur within the first day of their life. Due to this cause, the vaccine has to be developed for mothers to prevent maternal to fetal transmission. Nevertheless, the geographical variation of the strains that prevent colonize mothers could be a potential barrier for producing one universal single vaccine [9,12,21]. Moreover, the cost of a vaccine could be another potential barrier as a large number of neonatal deaths occur in developing countries and most of the births in these countries still take place at home [23,24]. Even if the production-cost is managed with the foreign help, another barrier would be to send vaccine to those women who are highly at risk of transmitting infection and not to send to those who are not at risk of this infection [19].

However, the preventive effects of antibodies against capsular polysaccharides indicate that the vaccine could be effective against it; similar to many other diseases that transmit vertically or that can be prevented in neonates by immunizing mothers [14,46]. For instance, globally more than 90% of the deaths due to neonatal tetanus cases were prevented with successful implementation of maternal tetanus immunization [47]. Furthermore, an inverse 'dose-response relationship' was observed between maternal anti-capsular antibody level and neonatal GBS sepsis [14]. Recently, Phase-II trial of a potential GBS polysaccharide-protein conjugate vaccine [GBS-CV] was successfully completed. The safety and efficacy of this GBS-CV vaccine was at the desired level [19,47]. Although that vaccine was effective only against a certain number of strains, the cost-effectiveness study is not yet done [19,47].

Secondly, although we know about its actual burden in neonates or young infants developed countries, we are not yet confirmed about actual disease burden in developing countries [5,12]. Like the disease burden, we don't know the antimicrobial susceptibility pattern or disease strains in many developing countries; without knowing the antimicrobial susceptibility pattern it could lead an over-prescription of GBS-resistant antibiotic besides the risks of adverse drug reactions [19]. It is also important to estimate the proportion of high-risk mothers in developing countries; this is still unknown – this estimation is required to utilize the current preventive and diagnostic methods [19]. Future research should focus more in estimating the burden and best mechanism to identify these high-risk infants and

mothers in developing countries as most of the neonatal deaths occur in these countries [25].

We already know the mechanism how GBS causes sepsis among neonates or the mechanism how it is transmitted from mother to their offspring; however, several mechanisms are yet to be identified to establish the causal pathways. Studies revealed association of GBS with stillbirths and pre-term births; the mechanism that how it is associated with these condition or whether it is a 'reverse causality' issue is yet to be known [10,11,17]. Understanding these mechanisms could be helpful to reduce the huge burden of preterm births or still births in developing countries, as these two are higher in developing countries compared to developed countries [1]. Furthermore, the effective methods to reduce LODs are still unknown [10].

Conclusions

In this paper, the epidemiology of GBS among neonates and young infants was discussed. It is evident from the discussion that this infection is largely preventable and curable; preventing and treating this infection can reduce a large proportion of additional neonatal deaths. In addition, this paper sheds lights on the future research implications to fill the existing gaps in knowledge; filling these gaps could be significantly useful to achieve the neonatal mortality targets of sustainable development goals to decline from its current static level.

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