Prevention of perinatal group B streptococcal infections: A review with an Indian perspective

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Abstract

Group B Streptococcus (GBS) is an important cause of maternal and neonatal morbidity and mortality in many parts of the world. Asymptomatic colonisation of the vagina and rectum with Group B streptococci is common in pregnancy. Maternal colonisation of GBS can vary depending on ethnicity and geographical distribution. Vertical transmission of this organism from mother to foetus may lead to neonatal GBS disease. Intra-partum use of antibiotics in these women has led to a decrease in the rate of early onset but not late onset GBS disease. Identification of women with GBS is the key factor in the prevention of perinatal GBS disease. There are different screening strategies available to identify women at risk of perinatal GBS disease. Clinicians continue to face the challenge of choosing between preventive strategies to reduce the impact of perinatal GBS disease. Controversy exists regarding the ideal preventive strategy. In India, the mortality and morbidity associated with the GBS disease remains largely a under-recognised problem. This comprehensive review summarises the salient features of GBS disease and discusses the epidemiology, risk factors, screening strategies, intra-partum antibiotic prophylaxis with an Indian perspective and how it compares with the Western nations.

Key words: Colonisation, Group B Streptococcus, intra-partum antibiotic prophylaxis, neonatal sepsis, neonatal mortality, perinatal transmission

Introduction

Group B Streptococcus (GBS) is an important cause of maternal and neonatal mortality and morbidity in many parts of the world. In the 1970s GBS emerged as the leading infectious cause of early neonatal morbidity and mortality in the Western world.[1] The 1990s saw the widespread adoption of antibiotic prophylaxis during labour in many Western industrialised countries.[2] The recognition that maternal colonisation with the organism is the key factor in the occurrence of GBS-related neonatal morbidity and mortality is the basis for the preventive strategies. Intensified efforts were made to prevent this devastating infection by identifying and treating pregnant women who carry GBS or who are at highest risk of transmitting the organism to a newborn. The intra-partum use of antibiotics in these women has led unequivocally to a decrease in the rate of neonatal GBS disease. However, there is still controversy about its prevention. In India, the role of GBS in neonatal morbidity and mortality is largely unrecognised and underestimated.[3]

GBS Infection

GBS or *Streptococcus agalactiae* is a Gram-positive bacterium that causes invasive disease primarily in infants, pregnant or postpartum women. Infections in newborn occurring within the first week of life are designated early onset group B streptococcal (EOGBS) disease. Late onset disease develops in infants after 7 days and up to 3 months of age. The measures used to prevent EOGBS disease, however, do not prevent late onset GBS disease.[1]

Early Onset GBS Disease

Infants with early onset GBS disease generally present with respiratory distress, apnoea or other signs of sepsis within the first 24-48 hours of life.[1,4] The most common clinical manifestation of EOGBS disease are sepsis and pneumonia; less frequently meningitis. Mortality is higher among preterm infants compared with full term-infants.[1,5,6] Early onset infections are acquired vertically through exposure to GBS from the vagina of a colonised woman. Neonatal infection occurs primarily when GBS ascends from the vagina to the amniotic fluid...
after onset of labour or rupture of membranes, although GBS also can invade through intact membranes. GBS can be aspirated into the foetal lung, which in turn can lead to bacteraemia. Infants also can become infected with GBS during passage through the birth canal. Infants who are exposed to the organism through this route can become colonised at mucus membrane sites in the gastrointestinal or respiratory tracts but these colonised infants most commonly remain healthy.[1]

Late Onset GBS Disease

Late onset disease (7-90 days) occurs less frequently than EOGBS. Maternal obstetric complications are uncommon with late onset GBS disease. Transmission can be either horizontal (from other infected infants or healthcare workers) or vertical (from mother due to close proximity).[3] The two most common clinical manifestations of late onset disease are meningitis and bacteraemia. The initial signs usually are fever, lethargy, irritability, poor feeding and tachypnoea.[3] The mortality rate for late onset neonatal disease is 2-6%, which is significantly lower than the rate of 10% for early onset infections. However, this rate has not declined in the Western countries despite the implementation of prophylactic measures.[9,10]

Epidemiology and Burden of Disease

GBS is the leading infectious cause of morbidity and mortality among infants in the Western hemisphere. In the United States, 10-35% of pregnant women are asymptomatic carriers of GBS in the genital and gastrointestinal tract at time of delivery.[3,11] At birth, 50-65% of infants who are born to colonised mothers have positive GBS cultures from mucus membranes and skin (external ear canal, throat, umbilicus and anorectal sites).[3,12] Approximately 98% of colonised newborns remain healthy, but 1-2% develop invasive disease.[3] In the United States, the overall incidence of neonatal GBS infection was 1.7 cases per 1000 live births prior to the introduction of intra-partum prophylaxis. As a result of preventive efforts, incidence of GBS has declined dramatically to 0.34-0.37 cases per 1000 live births in the recent years, 2006-2008.[11] The current US guidelines advise routine screening for GBS carriage between 35 and 37 weeks gestation and all women colonised with GBS at 35-37 weeks of gestation or labouring before this time should be offered intra-partum antibiotic prophylaxis (IAP) usually in the form of high dose intravenous benzyl penicillin or ampicillin. IAP has been shown to significantly reduce the risk of culture positive early onset but not late onset GBS disease.[11] However, a Cochrane review concluded that while IAP for colonised mothers reduced the incidence of EOGBS disease, it has not been shown to reduce all causes of mortality or GBS-related mortality.[13] The incidence of EOGBS disease in the UK in the absence of systematic screening or widespread IAP is 0.5 per 1000 births, which is similar to that seen in the USA after universal screening and IAP, despite comparable vaginal carriage rate.[13] In view of this, the UK national screening committee, in November 2008 recommended that routine screening using bacteriological cultures or near patient testing techniques should not be introduced into UK practice.[13,14]

Burden of Disease in India

In India, the spectrum of GBS disease remains a largely under recognised problem. Puerperal sepsis has been described for centuries, and ancient Indian texts in 1500 BC have recorded that good hygiene leads to a reduction in perinatal disease.[11] Epidemiological studies in India have shown lower colonisation and infection rates in general.[3,15,16] However, on closer analysis, taking into consideration use of adequate culture techniques and microbiological media, some of the GBS colonisation rates reported from India and other developing countries are similar to those reported in the United States.[3,15]

A study was conducted in 507 pregnant women in India of different parities, trimesters of pregnancy and age groups to determine the colonisation rate of GBS either in throat or vagina or from both sites.[16] Incidence of carriage rate in throat was 4.73%, in vagina 9.66% and in both sites 12.03%. In this study isolation rate of the organism was greatly enhanced using two selective media for isolation compared with using single selective medium.[3,16] Similarly another study showed the overall carriage rate in pregnant women to be 16%.[3,17] Colonisation rates in infants born to asymptomatic maternal carriers of GBS are 53-56% and are consistent with rates reported in other parts of the world.[3,17,18]

Despite significant GBS colonisation rates, reports of invasive neonatal GBS disease in India are infrequent. During a 10-year study between 1988 and 1997, in a perinatal centre in Vellore, India, with 60,119 live births, GBS was isolated from blood cultures of only 10 babies, giving an incidence of neonatal GBS infection of 0.17 per 1000 live births.[3,19] However, this number represents only the cases occurring among deliveries in a tertiary care hospital located in a predominantly rural community.

The sample registration system (SRS), which is the largest demographic survey in India, in its latest report for the year 2010 estimated the infant mortality rate (IMR) at 47 deaths per 1000 live births.[20] According to National Neonatal Perinatal Database of India 2002-2003,[21] the most common primary cause of neonatal deaths was perinatal asphyxia (28.8%). Other major causes were septicemia/meningitis (18.6%), extreme prematurity (26.3%) and congenital malformations (9.2%) and the most frequent causes of neonatal sepsis are Klebsiella pneumoniae, Staphylococcus aureus and Escherichia coli. According

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to National Family Health Survey (NFHS-3) 2005-2006, in India about 60% of women give birth at home and therefore the true incidence of invasive GBS disease in the newborn is largely unknown. In addition, blood cultures from ill neonates are not always done in many rural primary healthcare centres, which may contribute to the underestimation of the number of GBS cases. Pre-term births and still births are also usually not investigated, and thus the total burden of perinatal GBS disease remains unrecognised. However, the estimated incidence of neonatal GBS infection in India can be calculated from Indian epidemiological data reporting maternal and infant GBS colonisation rates as 10% and 50%, respectively. Since about 2% of colonised neonates develop true infection, the incidence of neonatal GBS infection in India may be calculated as approximately 1 per 1000 live births. Bearing in mind the above incidence and current Indian demographic data, the total number of newborn infants with GBS infection may be calculated. According to Census India 2011, the population count in the year 2011 was approximately 1210 million (1210,193,422), and birth rate was 20.6 births per 1000 population per year, and the projected total number of GBS infection in newborn infants in India may be as high as 24,203 cases per year.

**Risk Factors for EOGBS Disease**

Maternal intra-partum GBS colonisation is the primary risk factor for early onset disease in infants. In the USA approximately 10-30% of pregnant women are colonised with GBS in the vagina or rectum.[11,24]

In the absence of any intervention, an estimated 1-2% of infants born colonised mothers develop EOGBS infection. GBS colonisation during pregnancy can be transient, intermittent or persistent.[25,26]

Although some women with GBS colonisation during a pregnancy will be colonised during subsequent pregnancies, a substantial proportion will not.[27,28]

The gastrointestinal tract serves as the primary reservoir for GBS and is the likely source of vaginal colonisation. Heavy colonisation, defined as culture of GBS from direct plating rather than from selective broth only, is associated with higher risk of early onset disease.[29,30] GBS identified in clean catch urine specimens during any trimester is considered a surrogate for heavy maternal colonisation and also is associated with a higher risk of early onset GBS disease.[31] In addition to maternal colonisation with GBS other factors that increase the risk for early onset disease include gestational age <37 completed weeks, longer duration of membrane rupture >18 hours or intra-partum temperature of >38°C, young maternal age, Black race and low maternal levels of GBS-specific anti-capsular antibodies.[3] Previous delivery of an infant with invasive GBS disease is a risk factor for early onset disease in subsequent deliveries.[3] Of note, women who had one of these risk factors but who had negative prenatal screening cultures were at relatively low risk for early onset GBS disease.

**Population-based Screening Approaches**

Several screening strategies have been proposed to prevent early onset GBS disease.

**Universal prenatal screening**

The 2010 Centers for Disease Control and Prevention (CDC) guidelines[1] recommended bacteriological screening for all pregnant women and the use of IAP for all screen positive women, regardless of the presence or absence of other risk factors for EOGBS disease. This involves taking low vaginal and endoanal swabs from all pregnant women between 35 and 37 weeks of gestation. This relatively late gestation is necessary because the positive and negative predictive values of swabs taken more than 5 weeks before delivery are insufficiently high in most populations to guide treatment. Since the site of colonisation does not influence the decision to use IAP, screening can be performed by passing a swab into the lower part of the vagina then passing the same swab into the anus before placing it in culture medium. Separate swabs may also be used, but both swabs should then be placed into the same culture medium so that a single bacteriological report is generated. Studies have shown that, with appropriate instructions, most pregnant women can take their own swabs, improving the acceptability of the procedure without affecting its sensitivity. For screening to be effective, a method of culture must be employed that is both sensitive and specific. Standard bacteriological swabs plated directly on to agar fail to detect GBS in up to 50% of colonised women. In contrast, by placing swabs directly into a selective enriched broth, the assay sensitivity can be increased dramatically.[1,32]

All women carrying GBS and all women who labour before swabs are taken are offered antibiotic prophylaxis. Women who do not have swabs taken, or for whom results are not available at the time of labour, are offered antibiotic prophylaxis if they have any of the clinical risk factors listed in Table.[33] Bacteriological screening is estimated to result in 26.7% of women in the USA being offered IAP and to reduce the incidence. Of early onset GBS disease by 86%. On the basis of one large, non-randomised population-based study, the 2010 CDC guidelines concluded that the universal screening was superior to risk factor approach and CDC now recommends bacteriological screening for all women.

**Risk factor-based screening**

Risk factors for EOGBS are well established and have been confirmed in case-control studies; Table 1.
Table 1: Risk factors for early onset group B streptococcal disease; from Oddie and Embleton

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth &lt;37 weeks</td>
<td>10.4</td>
<td>3.9-27.6</td>
</tr>
<tr>
<td>Preterm birth &lt;34 weeks</td>
<td>33.6</td>
<td>4.0-283.3</td>
</tr>
<tr>
<td>Rupture of membranes &gt;18 hours</td>
<td>25.8</td>
<td>10.2-64.8</td>
</tr>
<tr>
<td>Preterm prolonged rupture of membranes</td>
<td>30.3</td>
<td>6.3-144.5</td>
</tr>
<tr>
<td>Intra-partum fever &gt;38°C</td>
<td>10.0</td>
<td>2.4-40.8</td>
</tr>
<tr>
<td>Any antenatal maternal culture of GBS</td>
<td>17.7</td>
<td>1.9-163.5</td>
</tr>
<tr>
<td>Previously affected child</td>
<td>Presently quantified</td>
<td></td>
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GBS: Group B Streptococcus

risk-based strategy requires women with any one of these risk factors to be given IAP. This strategy could deliver a clear reduction in neonatal morbidity and mortality. Mathematical modelling in the USA suggests that this approach will result in approximately 25% of women being offered IAP with a decrease in the incidence of EOGBS disease of 50-68.8%. Therefore, even rigorous application of the risk-based strategy cannot reduce the incidence of EOGBS by more than 50-70%. While this approach has many advocates 30-40% of babies with EOGBS are born to women with no identifiable risk factors. This experience in USA has led CDC to publish guidelines recommending universal bacteriological screening for all pregnant women.

Combining universal screening and the risk-based strategy

The Canadian Task Force on Preventive Health Care has shown that by adopting a universal screening but then only offering IAP to women who test swab-positive and who have additional risk factors for EOGBS disease, the number of women treated with penicillin in labour can be reduced to at least as 3.4% with an estimated reduction in the incidence of EOGBS disease by 51%. Although this approach is likely to cause less morbidity in labouring women by reducing antibiotic usage, it still has the financial and organisational obstacles inherent in implementing a universal antenatal screening programme. Because of these limitations, this approach is rarely encountered in US or UK practice.

Indian perspective for screening strategy

The issue of GBS screening is a relatively new concept for India. Currently there are no antenatal screening policies followed in India. With some studies in India showing GBS colonisation rates similar to Western countries, we need to draw our attention to a group of women whose neonates are at high risk of GBS neonatal infection.

In India where there are around 28,800,000 births per year as per Census 2011, universal screening for GBS may be difficult to implement, from a logistic as well as cost-effective viewpoint. The organisational challenge of obtaining and processing swabs from a large number of women and ensuring that results are available to care providers during labour would be considerable. Furthermore, the cost implications of universal prenatal screening would be significant even though the reduction in neonatal morbidity may offset these costs to some degree.

According to NFHS-3, 2005-2006 summary of findings, only 39% of deliveries take place in a healthcare facility. In this group, a strategy based on identifying maternal risk factors [Table 1] and offering IAP to women with risk factors could potentially be used to reduce the incidence of EOGBS in India. Continued efforts in improving primary healthcare, health education and awareness regarding neonatal sepsis is more likely to reduce the number of births that take place at home. As per NFHS-3, more than one-third deliveries were assisted by traditional birth attendants. Educating traditional birth attendants at identifying the women with risk factors for neonatal GBS disease and referring them for hospital deliveries could increase the chance of offering IAP to at risk women. Until there is evidence available from comparative studies of various preventive strategies to determine the optimal strategy suitable for Indian population, the risk-based strategy could potentially be used.

Intra-partum Antibiotic Prophylaxis

Penicillin remains the agent of choice for IAP. According to RCOG green top guideline no 36, 2nd ed., it is recommended that 3 g intravenous benzyl penicillin be given as soon as possible after the onset of labour and 1.5 g 4th hourly until delivery. Clindamycin 900 mg should be given intravenously 8th hourly to those allergic to benzyl penicillin. Current clindamycin resistance rates in England and Wales stands at 10% and thus there is a chance that clindamycin might be less effective. However, in India the clindamycin resistance is unrecognised and therefore difficult to estimate the effectiveness of clindamycin in penicillin allergic women. An alternative agent in the presence of clindamycin resistance is vancomycin. However, the dosage regimens are based on tradition rather than evidence. Broad spectrum antibiotics such as ampicillins should be avoided if possible, as concerns have been raised regarding increased rates of Gram-negative neonatal sepsis. To optimise the efficacy of IAP, the first dose should be given at least 2 hours prior to delivery. There is evidence that benzyl penicillin levels in cord blood exceed the minimum inhibitory concentration for GBS as early as 1 hour after maternal administration, but it is not known how this relates to neonatal colonisation or disease. Oral antibiotics for IAP are not recommended because of variable absorption in labour. In theory, the widespread use of IAP can lead to the pregnant woman

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developing a reaction to the antibiotic. Although true allergic reactions probably occur in less than 1%, anaphylaxis has been reported in women receiving IAP for GBS and might be expected to arise in 1/100,000 women treated. Widespread use of IAP could lead to an increase in the incidence of early onset non-GBS sepsis in neonates, negating any beneficial effects. Clinicians might also expect to encounter an increase in the prevalence of drug-resistant bacteria causing disease and therefore close surveillance should be kept of the range of bacteria causing neonatal disease.

Management of Newborn Infant

Combining infant antimicrobial prophylaxis with IAP reduces the rate of EOGBS disease in both term and preterm infants when compared with strategy of no intervention. But such routine neonatal prophylaxis has not gained wide support and its benefit remain uncertain. In a UK study of invasive GBS disease, 89% of early onset cases were identified on day 1. Of those developing clinical features on day 1, 97.6% were noted by 12 hours of age. More recent UK data from infection surveillance network showed that 94% of early onset cases occurred on day 1. The majority of early onset cases in these studies presented with sepsis (79.4%), 11.8% had meningitis, 7.8% had pneumonia and 1% focal infection. The Royal College of Obstetricians and Gynaecologists advise that infants who are at risk of EOGBS should be observed for the first 12-24 hours after birth with regular assessments of general well-being, feeding, heart rate, respiratory rate and temperature. Babies with clinical signs and symptoms compatible with sepsis should be evaluated and commenced on antibiotics. There is no good evidence to support routine blood tests to aid decision making about the management of these infants.

Obstetric Management

The risk of foetal infection in women with intact membranes who are not in labour is low. In view of this, antibiotic cover for GBS need not be administered routinely to women undergoing an elective caesarean section, even in the presence of GBS colonisation. There is no present evidence to suggest that antenatal vaginal examination, membrane sweeping or insertion of prostaglandin suppositories for labour induction increase the rate of transmission of GBS from mother to the foetus. There is insufficient data to support or discourage the use of foetal scalp electrodes or foetal scalp blood pH determinations in women known to be GBS colonised.

The Future

Rapid detection of GBS colonisation

Maternal GBS colonisation may be of transient or intermittent pattern and therefore a test to detect GBS colonisation during the intra-partum period could be more advantageous compared with the earlier antenatal screening test. This would more accurately reflect the GBS colonisation status of the woman in labour. Ideally, the use of a highly sensitive and specific test with rapid turnaround time can assess intra-partum GBS colonisation and hence guide IAP. Studies have shown that the rapid tests including florescence in situ hybridisation, latex agglutination test, optical immunoassays and enzyme immunoassays were not sensitive and specific enough to replace the established culture method. Recently, molecular testing methods have been developed, including DNA probes and nucleic acid amplification tests (NAAT) such as polymerase chain reaction (PCR). However, these assays are not currently available commercially, and therefore their benefit remains to be determined.

GBS vaccines

Maternal immunisation against GBS prior to or during pregnancy has the potential to prevent foetal colonisation and thereby eliminating EOGBS disease. Human isolates of GBS express a capsular polysaccharide (CPS), a major virulence factor that helps the microorganism to evade host defence mechanisms. At least eight different GBS serotypes exist, based on specific structure of CPS and embedded proteins. Clinical trials of conjugate vaccines prepared with purified CPS types 1a, 1b, 2,3,5 have demonstrated that these preparations are safe and immunogenic. However, as expected, these preparations do not offer protection against other GBS serotypes. Epidemiological surveillance of serotype distribution in the population is critical for vaccine studies. The cost of developing and implementing a vaccine strategy is considerable and probably not a feasible strategy for the developing countries in the near future.

Conclusion

The IMR in India is decreasing over the past few years and is currently 47 deaths per 1000 live births. The most common cause of neonatal deaths was perinatal asphyxia. Other major causes include sepsicaemia/ meningitis, extreme prematurity and congenital malformations and the most frequent causes of neonatal sepsis are Klebsiella pneumoniae, Staphylococcus aureus and Escherichia coli. It is possible that the role of GBS as a cause of neonatal sepsis has been underestimated in India. It could be due to lack of appropriate screening strategies. Detection of early onset infections may be obscured by the large proportion of deliveries that take place outside health centres. Even for infants born in hospital, bacteriological procedures are not routine in many parts of India. Continued surveillance and more detailed studies are essential in the understanding of the epidemiology and spectrum of disease caused by the GBS. Whether to implement universal screening strategy or clinical risk-based strategy depends on the local incidence of
EOGBS disease, the prevalence of clinical risk factors in EOBGS disease and the current obstetric practice. There is a need to carry out comparative studies of various preventive strategies to determine the optimal strategy suitable for Indian population. Until there is evidence available from comparative studies of various preventive strategies, the risk-based strategy could potentially be used as it is cost effective and feasible for the Indian population compared with other strategies.

References

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